Neurodevelopmental disorders (ESSENCE):

Early detection and outcome in adulthood

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Memento mori

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ABSTRACT

Objectives: Examine outcomes in adulthood for a group of individuals diagnosed with fetal alcohol spectrum disorders (FASD), and for another group during childhood diagnosed with attention-deficit/ hyperactivity disorder (ADHD) with concurrent developmental coordination disorder (DCD). In addition, to also examine the usefulness of a parental screening questionnaire for concerns regarding neurodevelopmental problems (NDPs) in 11-year-old children.

Methods and results: Papers I-III reported on two population-based cohorts, and paper IV on a school-based cohort, all three conducted in a Swedish setting. In **paper I**, 37 adoptees diagnosed with FASD in childhood were reassessed as young adults by a multidisciplinary team. At a median age of 22 years (range 18-28), a majority were dependent on social support, had a psychiatric disorder (most commonly ADHD) and exhibited stunted growth and a declining intellectual quotient compared with childhood. In **paper II**, a group with ADHD+DCD (n=62), an index comparison group without neurodevelopmental disorders (n=51) and a registry-matched group (n=360) were followed from middle childhood into young adulthood through national registers. At a median age of 30 years, the ADHD+DCD group had significantly higher rates of psychiatric diagnoses, prescriptions of psychoactive medications and occurrence of sick pension than both comparison groups, although a substantial minority in all groups did not experience any of these four adverse outcomes. **Paper III** reported on the relative contribution from symptoms at nine years of age, in predicting a score of seven adverse outcomes in adulthood for the index and comparison groups (n=60+50). The strongest predictors at age 9 were symptoms of conduct disorder, oppositional defiant disorder, ADHD and motor dysfunction. Combining the six strongest predictors (adding depressive symptoms and autistic traits) explained 40% of the variance in the adverse outcome score. In **paper IV**, 11-year-old children attending regular school (n=223) participated in a NDP work-up, and parents completed the ESSENCE-Q screening questionnaire (range 0-24) for early concerns regarding NDPs. A cutoff of ≥3 had the highest accuracy (78%) with a negative predictive value of 82% in detecting clinically impairing NDPs.

Conclusions: Outcome of NDDs in adulthood is variable, and prognosis is informed by both etiological aspects and symptom load in childhood. Active ascertainment of children with clinically impairing NDPs is feasible with a parental screening questionnaire, although preferably in conjunction with other screening methods.

Keywords: attention-deficit/hyperactivity disorder, developmental coordination disorder, fetal alcohol spectrum disorders, ESSENCE-Q

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SAMMANFATTNING PÅ SVENSKA

Bakgrund: Mer kunskap behövs om förloppet från barndom till vuxen ålder för personer med utvecklingsneurologiska/neuropsykiatriska funktionsnedsättningar. Avhandlingen syftade till att följa förloppet för nu vuxna individer som i barndomen diagnostiserats med fetala alkoholspektrumstörningar (FASD, studie I), aktivitets- och uppmärksamhetsstörning (ADHD) i kombination med motorisk koordinationsstörning (DCD, studie II, III), samt att pröva ett screening-instrument för utvecklingsneurologiska problem (studie IV).

Metod och resultat: I studie I-III rekryterades deltagare från en helpopulation, studie IV från hela skolklasser. I **studie I** undersöktes 37 adopterade individer med FASD (medianålder 22, 18 till 28 år). Majoriteten behövde socialt stöd för sitt fungerande i vardagen, hade psykiatriska diagnoser (ADHD vanligast), samt hade en hämmad kroppslig tillväxt och lägre allmän begåvningsnivå som vuxna än de haft som barn. I **studie II** följdes en grupp med ADHD+DCD (62 individer), en ursprunglig jämförelsegrupp (51 individer) samt en registerdragen jämförelsegrupp (360 individer) från barndom till ung vuxen ålder genom nationella register för sjukvård, demografi och kriminalitet. Vid 30 till 31 års ålder hade gruppen med ADHD+DCD i signifikant högre grad haft psykiatrisk kontakt och medicinering och högre förekomst av sjukpension än bägge jämförelsegrupper. En betydande minoritet hade ej erfarit något av de negativa utfallen. **Studie III** undersökte hur olika symtomområden som kartlades vid 9 års ålder påverkade prognosen för negativt utfall i vuxen ålder för gruppen med ADHD+DCD och jämförelsegruppen (totalt 110 individer). Graden av trotssyndrom, uppförandestörning, ADHD, motoriska svårigheter, depression och autistiska drag var starkast förknippade med prognosen. Tillsammans kunde de sex symtomområdena förklara 40% av spridningen i utfall i vuxen ålder. I **studie IV** deltog 223 11-åriga skolbarn i en utvecklingsneurologisk bedömning samtidigt som föräldrar fyllde i formuläret ESSENCE-Q (0-24 poäng) om tidiga symptom. En handlingsgräns ≥3 hade högst precision (balans mellan sant positiva och falskt negativa) och ett negativt prediktivt värde om 82% (andelen för vilka avskriven misstanke om utvecklingsneurologiska problem som motiverar kontakt med sjukvården var korrekt).

Betydelse: En majoritet av individerna med FASD hade stort stödbehov även som vuxna. Prognosen vid ADHD+DCD var för många god och kunde delvis förklaras av graden av symptom inom flera angränsande problemområden, såsom uppmärksamhet, motorik, trots. Formuläret ESSENCE-Q är användbart för att identifiera utvecklingsneurologiska problem hos 11-åriga skolbarn, ger en fingervisning om svårighetsgraden, men behöver vid screening kombineras med andra metoder.

LIST OF PAPERS

This thesis is based on the following papers, referred to in the text by their Roman numerals.

I. Landgren, V., Svensson, L., Gyllencreutz, E., Aring, E., Grönlund, M. A., & Landgren, M. Fetal alcohol spectrum disorders from childhood to adulthood: A Swedish population-based naturalistic cohort study of adoptees from Eastern Europe. BMJ Open, 2019; 9(10), e032407.

II. Landgren, V., Fernell, E., Gillberg, C., Landgren, M., & Johnson, M. Attention-deficit/hyperactivity disorder with developmental coordination disorder: 24-year follow-up of a population-based sample. BMC Psychiatry, 2021, 21(1), 161.

III. Landgren V., Fernell E., Gillberg C., Landgren M., & Johnson M. Deficits in attention, motor control and perception childhood to age 30 years: prospective case–control study of outcome predictors. BMJ Open. 2022 Mar 1;12(3):e054424.

IV. Landgren V., Svensson L., Knez R., Theodosiou M., Gillberg C., Fernell E., Landgren M., Johnson M. The ESSENCE-questionnaire for neurodevelopmental problems - a Swedish school-based validation study in 11-year-old children. Accepted for publication in Neuropsychiatric disease and treatment

CONTENT

ABBREVIATIONS

ADHD	Attention-deficit/hyperactivity disorder
ARND	Alcohol-related neurobehavioral disorder
CGI-S	Clinical global impression - severity
DAMP	Deficits in attention motor control and perception
DCD	Developmental coordination disorder
DSM	Diagnostic and statistical manual of mental disorders
ESSENCE	Early symptomatic syndromes eliciting neurodevelopmental clinical examinations
FAS	Fetal alcohol syndrome
FASD	Fetal alcohol spectrum disorders
ICD	International classification of diseases
IQ	Intellectual quotient
NDD	Neurodevelopmental disorder
NDP	Neurodevelopmental problem
PFAS	Partial fetal alcohol syndrome
WHO	World health organization

1 INTRODUCTION

Although the medical practice of today has ancient roots, current theories of disease and diagnostic constructs are not as old. This recency is particularly evident for the medical specialty of psychiatry. In order to give a more comprehensive overview of the research context for this thesis, the introduction will provide a brief history and description of the subject at study, covering development of important concepts (The content of the ideas conceived in the mind) and their designated terms (The words or symbols designated to convey concepts) (Gunnell, 1998). This will be followed by a short overview of the literature of longitudinal studies and early detection of neurodevelopmental disorders (NDDs).

1.1 NEURODEVELOPMENTAL DISORDERS

According to the international classification of diseases, 11th edition (ICD-11),

> *"Neurodevelopmental disorders are behavioral and cognitive disorders that arise during the developmental period that involve significant difficulties in the acquisition and execution of specific intellectual, motor, language, or social functions" (World Health Organization, 2020)*

Conceptual development

Congenital intellectual disability has been recognized as a mental disease for many centuries, but with little detail or differentiation. The first recorded definition of NDDs as a medical concept in the present sense outlined in ICD-11 can be traced to the 19th century French physician Étienne Jean Georget (1796-1828) (G. E. Berrios & Porter, 1995; Morris-Rosendahl & Crocq, 2020). He operated in a new era where empirical symptom-based disease classification was promulgated by prominent scientists at the time, drawing on the influential work of the Swedish physician and botanist Carl von Linné (1707-1778) and the Scottish physician William Cullen (1710-1790) in particular. (Munsche, 2012; World Health Organization, No date).

The commencement of this era is attributed to the English physician Thomas Sydenham (1624-1689). Sydenham diverged from a resignation with regard to the understanding of human disease reigning by that time, in which it was perceived as ambiguous and irregular. He argued that diseases could be

categorized similar to the way botanists classify plants (Faber, 1923; Walker, 1990). Notably, he delineated gout from rheumatism, and is the source of the eponym Sydenham's chorea. His approach gradually supplanted previous humoral concepts of disease and emphasized empiricism and meticulous systematizing of observations.

An hierarchical taxonomy of plants was applied to human disease by the French physician François Boissier de Sauvages de Lacroix (1706-1767), categorizing them in classes – orders – genera – species. Inspired by de Sauvages, Linné himself lectured on, and published *genera morborum* (Linné, 1759). The work covered disease concepts with short definitions. Both Latin and Swedish terms were used to designate the concepts *"…upon the request of several people"*.

Among the eleven classes encompassing 325 species in total, traces of symptoms consistent with NDDs could be found, at least in the species *"morosis"* and *"amentia"* in particular (everyday Swedish terms translated to English are below included in brackets):

The species of *"morosis"* resided in the class of *"quietales"* (peaceful diseases), which covered loss of sensory faculties, memory, hunger, thirst or libido. It was categorized in the third order, "*privativi"* (disease of deprivation/loss), after the orders *"defectivi"* (waning) and *"soporosi"* (soporific/sedating)

- *"morosis – dumbness [brist på inbillningskraft – lack of imaginative capacity]"*

The species of *"amentia"* was found in the class of "*mentales – mental disease"*, that comprised three orders; *"ideales"* (concerning the ability to think), "*imaginarii"* (imagined) and *"pathetici"* (affect laden). In the order of "*ideales"*, Linné described four chronic diseases;

- *"amentia - chronic madness, universal, harmless [hufwudswag - feeble mindedness]"*
- *"mania – chronic madness, universal, with rage [ursinnig -enraged]"*
- *"vesania – chronic madness, partial, harmless [förryckt - crazy]"*
- *"melancholia – chronic madness, partial, gloomy, pondering [hiertängslan - apprehension]"*

Translations of student annotations from lectures indicate that *mania* was separated from *amentia* by presence of combativeness and frenzy, and *vesania* separated from both by being restricted and not affecting all mental capacities

(Uddenberg, 2012). This implied that amentia and mania entailed more profound impairments for the patient.

Cullen separated congenital, acquired and senile forms of *amentia* (*"congenital", "acquisita" and "senilis"*) (Munsche, 2012). Although the diagnoses may seem imprecise, there are also contemporary clinical descriptions from these times aligning well with current clinical NDDs. For instance, the German physician Adam Weikard (1742-1803) in his influential psychiatry textbook described *"attentio volubilis"* (eng; "rolling/spinning attention"):

> *"Every humming fly, every shadow, every sound, the memory of old stories will draw him off his task to other imaginations. Even his imagination, if and when it is copious, entertains him with a thousand minor subjects… An inattentive person won't remark anything but will be shallow everywhere" (Barkley & Peters, 2012)*

Weikard attributed attentional deficits to the environment, whereas Alexander Crichton (1763-1856) considered them innate or acquired (Crichton, 2008). Crichton's thoughts have been considered influential on French psychiatry, in which Georget developed the classification further. Georget drew on the influential work of Carl von Linné (1707-1778) and William Cullen (1710-1790) in particular.
He distinguished two groups of mental illness where "*lack of* ***development*** *of intellectual faculties*" of various degrees of severity was emphasized. He also considered the conditions not to be diseases strictly speaking as they were not acquired but of innate origin, akin to congenital malformations. In this sense, Georget honed in on the modern concept of NDDs (Morris-Rosendahl & Crocq, 2020).

The birth of modern nosology

William Farr (1807-1883) was a medical statistician in the founding years of the General Register Office of England and Wales, an institution devoted to population statistics, including causes of death (World Health Organization, No date). He found the disease classification of Cullen still in use largely unrevised and therefore no longer up-to-date with medical progress. He instead aspired for better classifications of diseases and proposed an arrangement of classification under five groups: epidemic diseases, constitutional (general) diseases, local diseases according to anatomical site, developmental diseases,

and diseases that are the direct result of violence (World Health Organization, No date). In addition to causes of death, this allowed for more statistics of diagnoses for prognosis and choosing intervention, key aspects of the medical diagnosis. Its utility was quickly recognized in western Europe and the United States, and following decennial revisions in international meetings, responsibility for revising it was assumed by the World Health Organization (WHO) in 1948, thenceforth referred to as "*international classification of diseases*" (ICD), the leading medical classification system to this day.

With WHO at the helm, the ICD-6 released in 1948 included non-fatal diseases, with a new chapter devoted to psychiatric conditions. However, it was not until the ninth edition (ICD-9) in 1978, the words *"developmental disorder"* was ascribed to conditions distinct from mental retardation (World Health Organization, 1978). In the section of mental disorders in ICD-9, "*pervasive developmental disorder/autism"* was found among psychotic conditions, and *hyperkinetic syndrome of "childhood/attention deficit disorder"* was found among non-psychotic mental disorders, alongside specific delays in development (coordination and specific learning disorders). It was also the first version of ICD to have a diagnosis for suspected damage of the fetus from maternal prenatal alcohol consumption, under the section of etiologies to complications of pregnancy. Figure 1 depicts the timeline for the introduction of diagnostic concepts and terms studied in this thesis.

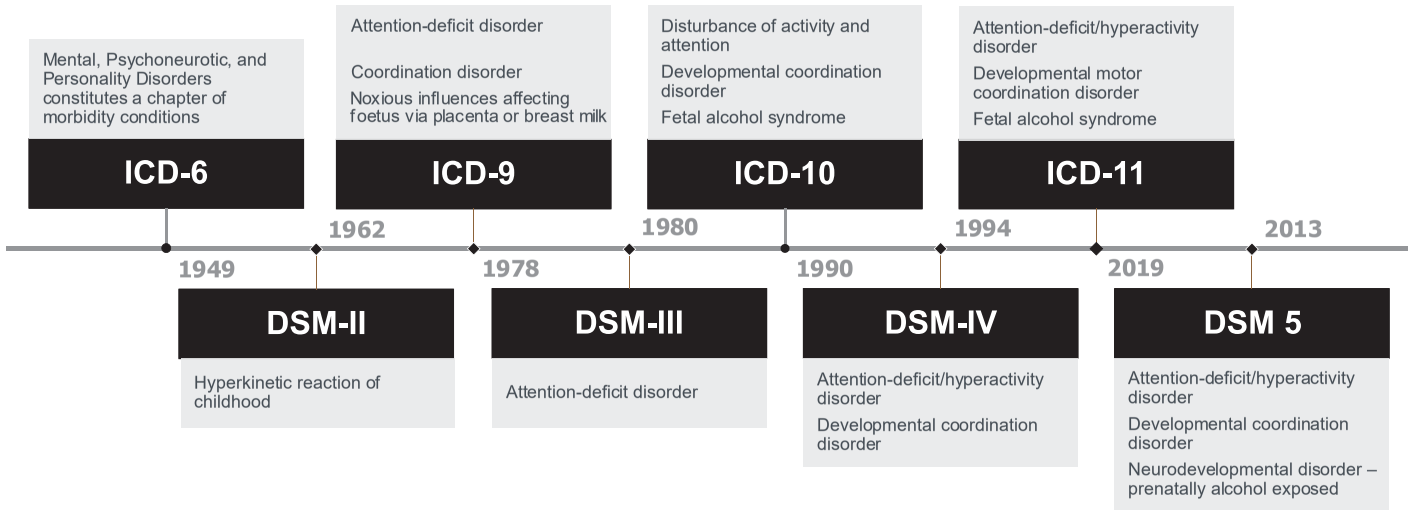

Figure 1. Timeline for the introduction of diagnoses in the international classification of diseases (ICD) and diagnostic and statistical manual for mental disorders (DSM)

Figure 2. The characteristic facial features of the fetal alcohol syndrome, short distance between the palpebral fissures (1), smooth philtrum (2) and thin vermilion border of the upper lip (3). Illustration: Freja Gyllencreutz

Fetal alcohol spectrum disorders (FASD)

The suspicion of teratogenic effects from alcohol on the developing fetus has waxed and waned throughout history (Warren & Hewitt, 2009). Dissuasion of alcohol consumption during pregnancy appears for instance in the book of Judges of the Bible, where an angel appears to Manoah and his wife, saying:

> *''Behold, thou shall conceive, and bear a son, and now drink no wine or strong drink...'' (Judges 13:7)*

In the "London Gin Epidemic" of the 18th century, the royal college of physicians expressed their concern with regard to effects on children from the rampant alcohol consumption in the population. They stated to the House of Commons:

> *''...the frequent use of several sorts of distilled Spirituous Liquors…[is] too often the cause of weak, feeble, distempered children, who must be instead of an advantage and strength, a charge to their Country.'' (Warren & Hewitt, 2009)*

On the contrary and rather unwittingly, intravenous alcohol drip was used in 20th century obstetric wards for anaesthetic purposes and halting of premature labor, with protocols aiming at a blood alcohol concentration of 1.5‰ (Abel, 1981). The modern "rediscovery" of the teratogenicity of alcohol comes from a French line of research in the 20th century. Starting with the thesis of Jacqueline Rouquette, and subsequently a clinical report from Lemoine and colleagues, the adverse effects from prenatal alcohol exposure were reconnected with child development (Lamache, 1967; Lemoine, Haroossseau, Borteryu, & Menuet, 1968; Rouquette, 1957).

The *fetal alcohol syndrome* (FAS) became an established clinical entity in the field of pediatric dysmorphology with the reports from the American dysmorphologists Smith & Jones (Jones & Smith, 1973; Jones, Smith, Ulleland, & Streissguth, 1973). They described a distinct pattern of malformations; growth restriction and microcephaly in tandem with the facial characteristics; short palpebral fissures, hypoplastic midface, smooth philtrum and thin vermilion of the upper lip (Figure 2).

ICD-9 listed alcohol under "Noxious influences affecting foetus via placenta or breast milk" whereas the more precise concept *foetal alcohol syndrome* occur for the first time in ICD-10, sorted under the chapter heading "congenital malformation syndromes due to known exogenous causes".

The American Psychiatric Association has published the influential "*diagnostic and statistical manual of mental disorders"* (DSM) in five editions since 1952. In the DSM-III and later editions, the manual maintains a general agnostic stance with regard to the etiology of conditions. There has sometimes been exceptions, such as for drug-related disorders, withdrawal syndromes, deliria and catatonia due to "a medical condition", and cognitive disorder due to human immunodeficiency virus infection. In DSM-IV, Rett syndrome, a behavioral phenotype syndrome characterized by early regression, was given prominence in being listed among pervasive developmental disorders alongside e.g., autism (American Psychiatric Association (APA), 1994). A strong association of Rett syndrome with mutations in the Methyl-CpG-binding protein 2 gene was shown in 1999 (present in 95-97% of cases), further elucidating the genetic pathomechanism of the syndrome (Neul et al., 2010). In the DSM-5, Rett syndrome was removed from the manual, and the possibility of a general "etiology specifier" for developmental disorders was added instead (American Psychiatric Association (APA), 2013).
Although FASD is not recognised as a disorder in its own right, the DSM-5 included thea general concept of *"neurobehavioral disorder- prenatally alcohol exposed"* (ND-PAE) as an area for future research. The diagnostic criteria of ND-PAE include no physical findings.

There are operationalized criteria for FASD developed in a research setting, where the key physical features described initially by Smith & Jones are still the hallmarks for delineating the full FAS (Hoyme et al., 2016). At the same time, it is recognized that prenatal alcohol exposure is associated with a spectrum of conditions. This has led to a development of the concept *fetal alcohol spectrum disorders* (FASD). The spectrum comprises FAS, facial features without associated growth restriction (partial FAS), *alcohol-related neurobehavioral disorder* (ARND) without associated facial features, *and alcohol-related birth defects* (ARBD). Mouse models have revealed a key mechanism for the facial features of FASD to be alcohol-induced apoptosis of neural crest cells, a cell population that forms large parts of the midface as well as the forebrain. This implies that the developing central nervous system is particularly sensitive to alcohol exposure (Lipinski et al., 2012; Parnell et al., 2006). Neurodevelopmental disorders are common in FASD (Aronson, Hagberg, & Gillberg, 1997; Raja Mukherjee, Layton, Yacoub, & Turk, 2011). Additionally, Kerstin Strömland, Marita Andersson-Grönlund and colleagues have highlighted the vulnerability of the developing eye, and shown the frequent concurrent ocular abnormalities in FASD (Strömland, 1985; Grönlund, 2005; Andersson Grönlund et al., 2010; Gyllencreutz 2021).

Reported prevalence of FASD varies widely across the globe (Popova, Lange, Probst, Gmel, & Rehm, 2017). The prevalence in Sweden is unknown, but empirical studies of European countries and American states have shown

rates of several percent, making FASD a leading preventable cause of developmental disabilities (May et al., 2011; Petković & Barišić, 2013; May P.A. et al., 2018; McQuire et al., 2019). Epidemiological studies indicate that there are effects from prenatal alcohol exposure detectable on a population level, where natural experiments of both reduction and increase in proxy measures of fetal alcohol exposure are associated with educational and occupational outcomes in a dose-dependent manner (Francis-Tan, Tan, & Zhang, 2018; Nilsson, 2014).

Deficits in attention motor control and perception (DAMP)

Medical history is rife with descriptions of deviant children marked by inattention (Lange, Reichl, Lange, Tucha, & Tucha, 2010). With the surge in cases of encephalitis lethargica during the influenza pandemic in the early 20th century, the pediatric medical community connected behavioral problems with residual symptoms of encephalitis (Lange et al., 2010). This spawned a growing interest in hyperactivity in children. Although the German doctors Kramer and Pollnow describe a *"hyperkinetic disease of infancy''* distinct from the post-encephalitic syndrome, or frank brain insult, the emphasis on precipitating factors remained strong (Kramer & Pollnow, 1932; Lange et al., 2010). This shifted theory from psychosocial to physiological explanations (Lange et al., 2010). Traumatic brain injury, prenatal infections and perinatal complications such as asphyxia and premature birth were all causally linked to behavioral problems, including hyperactivity.

The overarching concept"*Minimal brain damage*" (MBD) encompassed this wide range of behavioral problems (Knobloch & Pasamanick, 1959). The concept inferred an anatomical lesion, although evidence of such a process often was absent, and also despite the fact that the suggested precipitating events did not invariably lead to evident behavioral problems.

The acronym withstood, but the meaning was eventually supplanted by *"minimal brain dysfunction*" (Clements & Peters, 1962). The clinical syndrome of MBD described by Clements in the 1960's was characterized by deficits in attention, impulsivity and motor control (Clements & Peters, 1962; Lange et al., 2010), although it became somewhat of a "catch-all etiquette" (Gillberg, 2003).

Scandinavian researchers drew on the MBD-concept, and following the research of the child neurologist Bengt Hagberg, Gillberg distilled operationalized criteria for the more specified definition "*deficits in attention, motor control and perception*" (DAMP, Figure 3), which superseded MBD (Gillberg, Rasmussen, Carlström, Svenson, & Waldenström, 1982).

Deficits in attention, motor control and perception (DAMP)
was defined as the combination of:
1. cross situational impairing attention deficit (ADD), with or without impairing hyperactivity/impulsivity; and
2. impairing deficit in at least one of the following areas:
- gross motor,
- fine motor,
- perception (i.e. the experience and interpretation of sensory information)
- speech-language

Deficits are not attributable to intellectual disability and/or cerebral palsy or other major neurological impairment.
Severe DAMP was diagnosed in cases showing the combination of (1) and all of the deficits listed under (2).

Figure 3. Diagnostic criteria for deficits in attention, motor control and perception (DAMP).

With the growing influence from American psychiatry on research and nosology, the overlapping concept of attention-deficit/hyperactivity disorder (ADHD) grew in favour, and care for children with attention problems was gradually shifted from pediatrics to child psychiatry.

Attention-deficit/hyperactivity disorder (ADHD)

The American psychiatric association included the diagnosis *"Hyperkinetic reaction of childhood"* in the DSM-II, published in 1968 (American Psychiatric Association (APA), 1968). The brief description overlapped with that of MBD already present within pediatrics, ("The disorder is characterized by overactivity, restlessness, distractibility, and short attention span…") but with no reference to perceptual or motor deficits.

The psychoanalytical orientation of American psychiatry was evident from the phrasings of diagnoses in the DSM, wherein the notions *"reaction"*, and in DSM-II also *"neurosis"*, implied relational and intrapsychic processes as having primacy in the etiology and diagnosis of mental illness (Shorter, 1998). Robert Spitzer led the taskforce of DSM-III published in 1980 (American Psychiatric Association (APA), 1980). The committee had a slant toward a more medically than psychoanalytically oriented psychiatry (Shorter, 1998) and enabled a paradigm shift from previous editions, with the explicit objective

to increase the reliability of psychiatric diagnoses through operationalized diagnostic criteria (R. L. Spitzer, Forman, & Nee, 1979). The DSM-III was by design agnostic to the nature of, or etiology of most conditions (a stance sometimes designated as *"atheoretical"*), which were referred to as *"disorders"* and not *"reactions"* as in DSM-II. It was therefore seen as a "peace treaty" between medical psychiatrists and psychoanalysts. Common ground between the two sides had also come to the cost of downplaying physical examination and elicited signs as part of diagnostic criteria. Instead, criteria favored chiefly psychological concepts and behavioral descriptions from proxy persons.

In the DSM-III, operationalized criteria for *"Attention-deficit disorder"* (ADD) subtyped as with or without hyperactivity were presented. In subsequent revisions (DSM-III-R), the subtyping was removed, and the name changed to *Attention-deficit/hyperactivity disorder* (ADHD). In the sequel of DSM-IV released in 1994, subtypes reemerged in three forms (inattentive type, hyperactive-impulsive type, and a combined type), with the wording in 2013 changed from *"type"* to *"presentations"* in DSM-5.

It was not until DSM-5 that ADHD was listed as a neurodevelopmental and not a behavioral disorder. The exclusion criterion of autism was also removed (ADHD could not be diagnosed in patients with autism in earlier versions of the DSM), even though the co-existence of ADHD and autism had been well documented since long (Ehlers & Gillberg, 1993). From DSM-III to DSM-5, the symptom list has remained virtually unchanged, but rather been expanded from 14 to 18 items. In addition to existing items covering hyperactivity, impulsivity and inattention, the added items emphasize difficulties with long-term persistence in goal-directed behavior of everyday life.

In parallel, the ICD-9 released in 1975 introduced the conceptual variation *"attention deficit disorder"* under the label *"Hyperkinetic syndrome of childhood"*. With ICD-10, the concept was rephrased *"Disturbance of activity and attention"* and located, among *"hyperkinetic disorders"*. Interestingly, the release of ICD-10 was followed by a "Bluebook" of prototypical descriptions and diagnostic guidelines for mental disorders (World Health Organization, 1992). Operationalized criteria were presented for some disorders (e.g., Schizophrenia) but not for hyperkinetic disorders. With ICD-11, the terminology converges with that of DSM-5, describing three "presentations" of attention deficit hyperactivity disorder (inattentive, hyperactive-impulsive, and combined).

Developmental coordination disorder (DCD)

Already in the emergence of the MBD-concept, fine or gross coordination deficits were considered hallmarks in its identification (Clements & Peters, 1962; Magnus Landgren, 1999; Wender, 1973). Coordination deficits has been designated with many different terms in the literature (e.g., minimal brain dysfunction, minimal neurological dysfunction, dyspraxia, physical awkwardness, clumsiness syndrome, specific motor development disorder, motor delay), and a lack of terminological consistency and consensus may have contributed to the underidentification and possibly underappreciation of its implications (Henderson & Henderson, 2003; Kirby, Sugden, & Purcell, 2014).

Coordination deficits is only recently acknowledged in the large classification systems. Both ICD-6 and ICD-7 mention several specific deficits with arithmetics, reading and articulation, but it was not until ICD-9 that the concept of psychomotor deficits was introduced, under the label "*coordination disorder"*. In ICD-10 it was renamed to "*developmental coordination disorder"*.

The DSM-I and II covered learning and speech disturbance among special symptom reactions that may occur on their own, tucked away in a brief section at the end of the manuals. Overall, the DSM-I through III pays little attention to motor coordination. Although it theoretically could be encompassed under *"other psychomotor disorder"* in DSM-II, a label for coordination deficits was absent in DSM-III, and resurfaced first with DSM-IV and DSM-5 as *"developmental coordination disorder"*. The criteria are based on history-taking, and provides no bedside tests or operationalization on how to assess the criteria.

ESSENCE

In 1978, Spitzer and colleagues presented the research domain criteria for establishing valid psychiatric diagnoses, proposing that there were about 24 valid diagnostic entities in psychiatry (R. L. Spitzer, Endicott, & Robins, 1978). Rather surprisingly, DSM-III, whose task force was headed by Spitzer two years later, contained 265 disorders and has amounted to almost 300 in the DSM-5.

Authors of the DSM-text have assured the provisional nature of the diagnoses, that they do not reflect discrete natural entities, and likely will be revised (American Psychiatric Association (APA), 1994). Yet, an *"insidious reification"* - the treatment of an abstract or obscure phenomenon as a discrete natural entity - has been inescapable (Kendell & Jablensky, 2003). This suggests that psychiatric disorders have increasingly been perceived as distinct entities, in spite of lacking empirically verified natural boundaries between most of them.

In a research context, continuity and symptom overlap across neurodevelopmental disorders in particular too often have been ignored (Lichtenstein, Carlström, Råstam, Gillberg, & Anckarsäter, 2010; Waterhouse, London, & Gillberg, 2016). This has led to a focus on optimal diagnostic symptom load cutoffs, discouraged multiple diagnoses and encouraged diagnosis-specific research enterprises. In effect, this has perpetuated the reification and hampered progress.

In a clinical context, it has fostered diversification of increasingly diagnosis-specific guidelines, clinics and social services tied to specific disorders that are unrepresentative of the extent to which neurodevelopmental problems and disorders co-occur (Gillberg, 2010; Neville, 2013; Thapar, Cooper, & Rutter, 2017).

In response to the above, the concept of ESSENCE (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations) was coined. ESSENCE is not a diagnosis, but rather a general notion that contains the interconnectedness and clinical characteristics of NDDs (Figure 4). It stresses that:

i. Initial symptoms of NDDs are unspecific, and of early onset (e.g., disrupted sleep, feeding problems),
ii. They generally evoke parental concern and elicit contact with various single health care professionals (nurse, speech therapist) although the input from a team of professionals would be appropriate,
iii. Eventually, symptom patterns align with specific NDD(s),
iv. Co-existing NDDs oscillating around the diagnostic cutoff is the rule, rather than an exception,
v. Because children with NDDs are at elevated risk of complications from medical conditions, and that behavioral phenotype and epilepsy syndromes have similar early unspecific symptoms and impairments, a vigilance for the detection and familiarity with such conditions is needed from the investigating physician.
vi. The initial presentation should therefore generally prompt a comprehensive assessment of all developmental areas, requiring the involvement of a team of health care professionals.

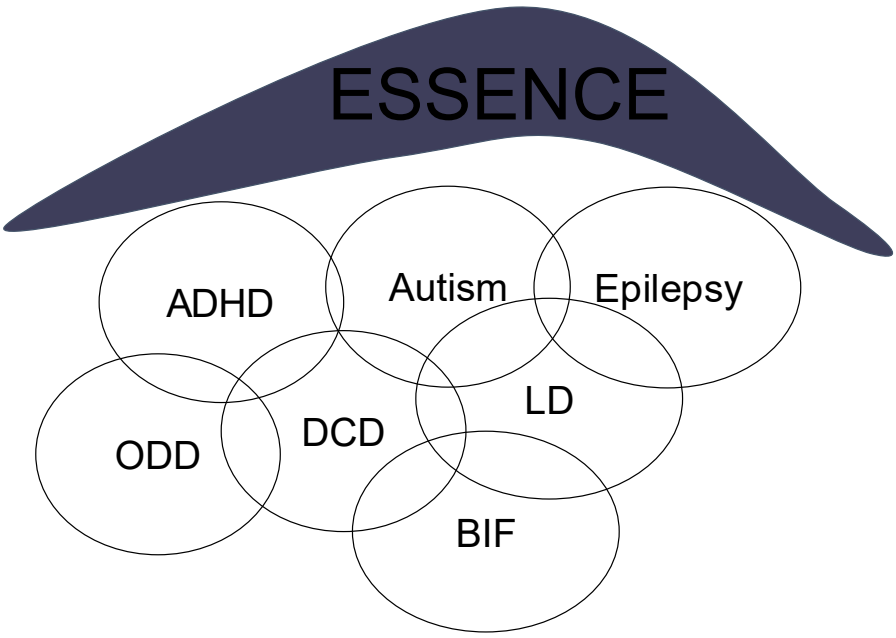

Figure 4. A non-exhaustive enumeration of conditions encompassed under the umbrella concept "Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations" (ESSENCE). ADHD, attention-deficit/hyperactivity disorder; DCD, developmental coordination disorder; ODD, oppositional defiant disorder; LD, language disorder; BIF, borderline intellectual functioning.

Nosological confusion

The biopsychosocial model of disease was coined by Roy Grinker (1900-1993) and proposed by George Engel (1913-1999) as a "*blueprint for research, a framework for teaching, and a design for action in the real world of health care"* (Engel, 1977). Engel emphasized the importance of considering all three aspects - biological, psychological and social – of the patient (Engel, 1977). Although considered helpful in reminding clinicians of the psychosocial aspects of clinical practice, critics such as Nassir Ghaemi argue that it paved the way for individualized treatment as practically speaking doing whatever one wants to do, without evidence-based support (N. Ghaemi, 2019; S. N. Ghaemi, 2009), and an unwarranted premise that "more is better". Rather, the biopsychosocial model should be replaced with methodological and explanatory pluralism, where the best solution or explanation takes precedence over other competing perspectives, Ghaemi argues (S. N. Ghaemi, 2009; Kendler, 2005). In Kenneth Kendlers words:

> *"Multiple explanatory perspectives can be adopted in our attempts to understand most natural phenomena. Furthermore, for any given phenomenon, these perspectives will differ in their informativeness and efficiency"*

The intersection of three perspectives

In this thesis, developmental deviations (problems with attention in particular) are approached at different levels of explanation. Consequently, in the studies different features are given prominence. The diagnosis of ADHD was conceived as a psychiatric descriptive, atheoretical concept defined by *psychological and behavioral criteria*, whereas FASD was a prenatally acquired syndrome, delineated from genetic syndromes, defined by a pattern of dysmorphological traits discerned upon *physical examination* connected to a specific *etiology* in a pediatric context. The DAMP-concept springs from a pediatric approach and incorporates both behavioral aspects and *neurological examination* findings. The ESSENCE-concept encompasses a range of areas where clinically relevant symptoms and impairments are recognized and contextualized with the environment and developmental trajectory of the child in a pediatric context.

1.2 LONGITUDINAL STUDIES

Fetal alcohol spectrum disorders

Although FASD became a clinical entity in pediatric literature in the 1970's, few longitudinal studies on the trajectory of FASD into adulthood have been conducted. Lemoine followed a case-series of individuals prenatally exposed to alcohol into adulthood and described them as having persisting behavioral problems and microcephaly, but attenuated dysmorphology and growth restriction compared with childhood (Lemoine et al., 1968). Ann Streissguth, a pioneer in research and development of services for families and children affected by prenatal alcohol exposure, reported on a clinic-based cohort. They were similarly marked by behavioral problems, but also unstable social environment and frequent out-of-home placements (Streissguth et al., 1991). The authors commented that effects from innate deficits and adverse postnatal environment are hard to disentangle. Spohr and colleagues performed follow-up assessments in young adulthood of a clinic-based cohort (N=37) of German individuals diagnosed with FASD. They concluded that:

> *"Despite substantial efforts at rehabilitation, only a very small group of patients was able to live a normal adult life" (Spohr, Willms, & Steinhausen, 2007)*

From Sweden there has emanated a registry-based follow-up of children diagnosed with FASD at the pediatric clinic of Gothenburg (N=75), showing a markedly increased rate of low educational attainment, sick pension, psychiatric inpatient care, as well as frequent prevalence of out-of-home placements in childhood (Rangmar et al., 2015).

Attention-deficit/hyperactivity disorder

A major meta-analytical study into the long-term course of ADHD by Faraone et al found only one clinical cohort followed beyond 30-years of age (Faraone, Biederman, & Mick, 2006). Importantly, persistence of the disorder was highly influenced by theoretical assumptions as to how "persistence" of ADHD should be assessed. Results were different depending on whether studies used the same diagnostic criteria as in childhood, other/fewer criteria due to a natural evolution of the symptom profile with age, or relied primarily on indirect evidence of impairment (e.g., financial difficulties, criminal convictions). The study showed a trend in age-dependent decline of overt

symptoms which was by some taken as evidence that ADHD in adults was increasingly rarer with age. A later study of childhood ADHD followed into the fourth decade of life found persisting ADHD in around 20% of probands (n=135) and 5% in the comparison group (n=136) (Klein et al., 2012). In a recent major consensus declaration article on ADHD, vague statements about adult prevalence estimates and non-existent discussion of prognostic indicators illustrate that clear scientific consensus regarding persistence and prevalence of ADHD in adulthood is lacking (Faraone et al., 2021).

Results from three large cohort studies have suggested that there are variants of adult-onset ADHD without childhood symptoms, adding further fuel to the fire (Agnew-Blais et al., 2016; Caye, 2016; Moffitt et al., 2015). When applying a binary definition (either you "have it" or you do not), the authors showed that the groups with ADHD in childhood and ADHD in adulthood only in a minority of cases comprised the same individuals. Other prospective studies support alternative explanations for the apparent "adult-onset" cases of ADHD.

First, symptoms of ADHD in adulthood for many may be better explained by substance use disorders or other psychiatric disorders, if they are scrutinized critically (Sibley et al., 2018).

Second, studies applying dimensional perspectives of ADHD rather than viewing it as a binary condition have shown that many with apparent adult-onset symptoms have had evidence of other neurodevelopmental problems in childhood. These may have overshadowed "sub-threshold" concurrent attention deficits that have become increasingly apparent with age (Taylor, Larsson, Gillberg, Lichtenstein, & Lundström, 2019).

Third, studies with repeated assessments have shown that symptoms of ADHD vary over time, and contribute to conflicting binary classifications of ADHD (Cooper et al., 2018; Sibley et al., 2022). Adolescent-onset symptoms in particular, are more likely to be transient.

Fourth, the female preponderance in purportedly adult-onset ADHD points toward a problematic male-normativity regarding the definitions of ADHD, that may not adequately detect the female phenotype of ADHD and cause a diagnostic delay (Cooper et al., 2018; Kopp, 2010; Taylor et al., 2019).

Studies of predictors of ADHD persistence have used mainly retrospective studies and clinic-based cohorts (Caye, Swanson, et al., 2016; Cherkasova, Sulla, Dalena, Pondé, & Hechtman, 2013; Mohr-Jensen & Steinhausen, 2016). Co-occurring oppositional defiant disorder (ODD), conduct disorder (CD), low IQ and male sex appears associated with persistence and/or adverse outcome in adulthood, but there is a lack of prospective studies with broad assessment programs addressing the question.

Developmental coordination disorder

Contemporary research emphasizes co-occurring NDDs to be the rule for children with DCD, although "pure" forms exist (Kirby et al., 2014). This makes the parsing of effects from DCD from co-existing NDDs a challenge, because impact from co-occurring disorders or traits are not adjusted for. With these caveats, there is some support for the claim that DCD is associated specifically with internalizing symptoms, executive problems and sedentary behavior in childhood and adolescence (Li, Graham, & Cairney, 2018). Notably, individuals with below average motor skills seem to be at increased risk of victimization from bullies in childhood (Bejerot, Ståtenhag, & Glans, 2022; Kirby et al., 2014) The assertion that children "grow out of it" has not earned support. Although task-specific training improves motor ability, the deficits make motor skill acquisition more tedious, and less generalizable to other areas than for typically developing peers (Kirby et al., 2014).

Of note is the approach to retrospective ascertainment of DCD-type problems in adults with the Adult Developmental Coordination Disorder/ Dyspraxia Checklist (ADC) (Kirby, Edwards, Sugden, & Rosenblum, 2010). It appears that problems associated with DCD in adulthood are similar to those in adolescence, with the addition of occupational dissatisfaction and unemployment (Kirby, Williams, Thomas, & Hill, 2013). One of few prospective longitudinal studies into adulthood is the study by Rasmussen and Gillberg (Rasmussen & Gillberg, 2000), wherein participants with either or both ADHD and DCD were re-examined at 22 years of age. The high rate of neurodevelopmental "co-morbidity" reiterates that studies of DCD that fail to take this aspect into account will be misrepresentative.

1.3 EARLY DETECTION OF NEURODEVELOPMENTAL DISORDERS

Child health care services conduct developmental check-ups by a nurse and/or a physician with the purpose of detecting significant developmental deviations. There are a host of instruments developed to improve the screening for NDDs, and in the majority of screen-positive children NDDs are ascertained in subsequent investigations (Barnevik Olsson, Carlsson, Westerlund, Gillberg, & Fernell, 2013; Gillberg, 2010; Marlow, Servili, & Tomlinson, 2019; Miniscalco, Nygren, Hagberg, Kadesjö, & Gillberg, 2006).

Nonetheless, when taking the incidence of NDDs across the entire childhood age span (0-18) into account, the performance of the screening procedures in preschool children may be slightly exaggerated. Although symptom onset in general (or by definition) can be traced back to preschool years, a majority of those receiving a NDD diagnosis in regular care are not identified and diagnosed prior to school entry. For example, in a Swedish nationwide twin study, 74 individuals received an ADHD diagnosis as adults, 394 between the ages of 12-18 and 194 prior to age 12 (Taylor et al., 2019), and a Swedish population-based study of children only, found the mean age at diagnosis of ADHD to be 12 years (Bahmanyar, Sundström, Kaijser, von Knorring, & Kieler, 2013). Similarly, a nation-wide Danish register study found that the incidence rate for ADHD and Asperger's syndrome peaked for boys at age 8 and 14, and for girls at age 17 and 16 respectively, whereas peak incidence rate of childhood autism was age 5 for boys and evenly distributed between ages 2-17 for girls (Dalsgaard et al., 2020). The majority of cases are thus diagnosed in school-age years.

This pattern is in part inescapable, since deficits in some higher-order neurodevelopmental functions cannot be recognized before they are challenged (e.g., reading comprehension) or even expected to be developed (e.g., abstract reasoning and executive function). The completion of basic education is a key factor for employment and stable establishment in the job market (Statistics Sweden, 2014). The identification of factors interfering with school performance such as NDDs is therefore warranted.

Although there are numerous measures available for screening purposes in school-aged children, few short instruments have the aim to cover the full range of NDDs, but are rather focused on specific disorders (Marlow et al., 2019; Mulraney et al., 2021). Using the ESSENCE-Q for screening in the community or in referred children of preschool-age has shown promising results (Hatakenaka et al., 2016, 2020; Hatakenaka, Ninomiya, Billstedt, Fernell, & Gillberg, 2017; Stevanovic et al., 2018). This warrants further study of the instrument in other age-groups.

2 AIM

The overarching aim of the thesis is to describe the trajectory into adulthood for fetal alcohol spectrum disorders (FASD) and ADHD with coexistent DCD, and to test the utility of parental screening for ESSENCE in childhood.

The thesis comprises four studies with the following specific aims:

I – Describe medical and psychosocial aspects of outcome in adulthood for participants diagnosed with FASD in childhood
II – Describe medical and psychosocial aspects of outcome in adulthood for participants diagnosed with ADHD + DCD in childhood in relation to a comparison group
III – Determine the relative association between clinical characteristics in childhood and outcome in adulthood for participants with ADHD + DCD and a comparison group.
IV – Report the prevalence and predictive validity of caregiver-rated ESSENCE-Q for clinically relevant neurodevelopmental symptoms/problems in 11-year-old children

3 PARTICIPANTS AND METHODS

3.1 STUDY DESIGNS AND SETTINGS

The four papers are based on studies of three cohorts recruited in western Sweden. A summary table of study designs and outcomes are provided in table 1. **Paper I** reports outcome of FASD in young adulthood in a prospective, *population-based* longitudinal design with clinical follow-up. **Paper II** and **III** cover outcome of ADHD with coexisting DCD with a likewise *population-based* longitudinal design with registry-based follow-up. **Paper IV** describes the prevalence of ESSENCE and the utility of screening in a cross-sectional population-based cohort with a *school-based* study design.

Table 1. Summary table of study design for the four thesis papers.

	Paper			
	I	II	III	IV
Year of birth	1990-1995	1986-1987	1986-1987	2007-2008
Recruitment	Population-based	Population-based	Population-based	School-based
Baseline assessment years	2000-2002	1992-1993	1995-1996	2017-2018
Follow-up year/years	2014-2018	2017	2017	2017-2018
Follow-up method	Face-to-face	Registry-based	Registry-based	Face-to-face
Key outcomes	Diagnostic status, IQ	Composite psychosocial outcome (four)	Composite psychosocial outcome (seven)	ESSENCE-status

3.2 STUDY POPULATIONS

Paper I; All adoptees born in eastern Europe between 1993-1997 and adopted to western Sweden had been invited (along with their parents) to participate in the original study (Magnus Landgren et al., 2006). Out of 99 eligible participants, 71 underwent a multidisciplinary assessment by a pediatrician, psychologist, ophthalmologist and orthoptist at a mean age of 7.5 years. The 37 that had been diagnosed with FASD were invited to participate in a follow-up assessment (M. Landgren, Svensson, Stromland, & Andersson Gronlund, 2010).

Paper II; 570 of 589 (97%) eligible children took part in a study of a population-based school-entry screening program for DAMP at 6.5 years of age (Magnus Landgren, Pettersson, Kjellman, & Gillberg, 1996). Screen-positive participants underwent a multidisciplinary diagnostic assessment by a pediatrician, psychologist and a speech-language therapist. With enrichment of the sample from adjacent communities applying the screening procedure, the diagnostic assessments showed that 62 participants met criteria for DAMP (ADHD + DCD). A population-matched comparison group (n=51, PM group) was randomly selected from screen-negative individuals in the population and assessed in the same way (M. Landgren, Kjellman, & Gillberg, 2000). In the follow-up study a registry-drawn comparison group (n=310, RM group) matched on age, sex and region was added for comparison.

Paper III; 110 of the 113 initial participants described in paper II had been reassessed at 9 years of age with a similar procedure.

Paper IV; 223 of 348 (64%) eligible 11-year-old children in two consecutive academic years from eight schools in western Sweden agreed to participate. Participants underwent a physical exam, psychological testing, parental- and teacher rating scales, review of medical records and a maternal interview.

3.3 DIAGNOSTIC CRITERIA

For **paper I**, FASD was diagnosed according to the criteria by Hoyme et al (Hoyme et al., 2005). Through operationalized criteria, *Fetal alcohol syndrome* required a) ≥2 of the three characteristic facial features (short palpebral fissures <10th centile, thin vermilion border, smooth philtrum, both rated as 4 or 5 with the lip/philtrum guide) in conjunction with b) evidence of growth restriction (length or weight <10th centile) and c) deficient brain growth (structural brain abnormalities or head circumference <10th centile). *Partial fetal alcohol syndrome* required characteristic facial features with ≥1 sign of growth restriction, together with neurobehavioral impairment defined as evidence of behavioral or cognitive abnormalities that cannot be attributed to

environmental factors or genetic predisposition. *Alcohol related neurodevelopmental disorder* was diagnosed when there was confirmed alcohol exposure in tandem with either deficient brain growth or neurobehavioral impairment. *Alcohol related birth defect* was diagnosed when there was confirmed alcohol exposure, characteristic facial features, in conjunction with ≥1 of listed birth defects associated with alcohol exposure.

For **papers II and III**, cases were included as having DAMP (Fig 2) along with comparison groups assessed without evidence of a NDD. Today, the diagnosis of DAMP corresponds to a diagnosis of ADHD in combination with DCD (although the clinical gestalt often includes language problems and autistic traits). In DSM-5, a diagnosis of ADHD requires symptom onset <12 years of age, cross-situational symptoms (6 of 9 symptoms) of inattention and/or hyperactivity/impulsivity, whereas DCD is defined as acquisition and execution of coordinated motor skills below the expected given the chronological age. Both ADHD and DCD require symptom onset in the developmental period causing impairment in daily life, and that symptoms are not better explained by other reasons (e.g., intellectual impairment, affective syndrome or pure oppositional behavior for ADHD, and intellectual disability or a neurological condition for DCD).

In **paper IV**, the presence and severity of neurodevelopmental problems (NDPs) were assessed. No diagnostic interviews could be performed, but classification of prominent symptom areas were made on clinical gestalt when possible, in line with the LEAD framework proposed by Spitzer (longitudinal, expert, all data) (Robert L. Spitzer, 1983).

3.4 OUTCOME MEASURES

In **paper I**, a multidisciplinary team, which included a physician, neuropsychologist, ophthalmologist and orthoptist assessed participants in young adulthood. The physician performed a physical exam, took a brief history and administered the MINI Neuropsychiatric interview, and assessed ADHD-symptoms supported by the Adult ADHD Self-report scale (Kessler et al., 2005; Sheehan et al., 1998). The neuropsychologist administered the Leiter-R battery and the Adaptive Behavior Assessment System II (ABAS-II) (Harrisson & Oakland, 2003; Roid & Miller, 1997) The ophthalmologist and orthoptist assessed visual acuity, refraction, strabismus and structural abnormalities by visual inspection, fundoscopy and optic coherence tomography.

For **paper II and III**, national registers, covering diagnoses in specialty care, medication prescriptions, criminal convictions and use of social welfare

benefits were used to define outcomes. In paper II a composite outcome of four binary endpoints (1. Psychiatric disorder according to International classification of diseases 10th edition [ICD-10], 2. Psychotropic medication prescription [Class N01-N07 according to the Anatomic Therapeutic Chemical classification system [ATC], 3. A criminal conviction, 4. Occurrence of sick pension) was constructed in order to facilitate comparison with a previous study of a cohort with similar characteristics (Rasmussen & Gillberg, 2000).

In **paper III**, the composite outcome from study II was expanded with three binary endpoints (education level and occupation level below the 10th centile, and need for social benefits above the 90th centile compared to a registry-drawn reference population) rendering a possible score range of 0-7.

For **paper IV**, we argued that assessment width and the global judgment of functional deficits, symptom severity and impairment were more important than diagnostic precision. The wide range of information sources (physical exam and interview maternal interview, neuropsychological assessment, medical chart review, parent and teacher rated questionnaires, national tests 3rd grade) were summarized in a case-conference. At this conference all information was evaluated with respect to the need of a clinical work-up, and with regard to clinically relevant problems encompassed under the ESSENCE-umbrella.

With regard to the need of a clinical work-up, cases were rated as follows: 0= No indication of ESSENCE, 1= Slight ESSENCE cannot be ruled out, 2= ESSENCE is likely and warrants thorough work-up, but a specific diagnostic category cannot be determined, 3= ESSENCE is confirmed and consistent with specific NDD(s). The case-conference was validated against a panel of physicians experienced with work-ups of NDD, who independently assessed a subset of the same participants. Lastly, we weighed each participant's symptom severity and functional impairment according to the Clinical Global Impression-Severity scale (CGI-S, range 1-7, 1=no indications of NDPs, 7=very severely impaired with multiple NDDs) in order to describe the clinical relevance of the problems detected (Busner & Targum, 2007). In our experience, a CGI-S rating of 1-3 would not necessitate a work-up in regular health care, whereas a rating of 4-7 would likely have symptoms/impairments warranting clinical attention and likely diagnosis.

3.5 STATISTICS

Descriptive statistics were applied in all papers with the indices deemed appropriate according to sample size and visual distribution of the variables. For some variables this meant the mean and standard deviation (SD), and for some the median and interquartile range (IQR). An $\alpha = 0.05$ was considered significant in statistical null-hypothesis testing. Statistics applied in the four papers differed considerably.

In **paper I**, few analyses were conducted. Only a paired *t*-test was applied to compare IQ at baseline with follow-up.

In **paper II**, binary proportions were compared with pairwise $\chi 2$-tests. Since the study included three groups, analyses of continuous variables and time-to-event variables were conducted in two steps. First, an overall test of difference between the groups was made with the Kruskal-Wallis test and overall log-rank test for ordinal and time-to-event variables respectively. If significant, pairwise comparisons with the Mann-Whitney U test for continuous or ordinal variables and the log-rank test for time-to-event variables were performed. As the specific endpoints may be difficult to interpret for the general reader, we converted differences to standardized mean differences (i.e., Cohen's *d*) to improve interpretability.

The multiple analyses performed in this study put the study at risk of producing false "positive" results (type II error). This was mitigated to some extent by applying two-step analysis (minimizing the need for additional analyses if the overall test proved insignificant) and the use of two comparison groups. In line with Benjamini and Hochberg, we argued that if the direction of results were similar for the whole family of tests (and also robust against *p*-value adjustment for multiplicity of comparisons when applicable), this argued against the finding being spurious/false positive (Benjamini & Hochberg, 1995).

Paper III modelled the extent to which clinical variables ("predictors") in childhood could predict outcomes in adulthood, using linear regression. Unlike correlation (e.g. Pearson or Spearman correlation), which is a measure of the strength of association between two variables, the family of regression analyses (including linear regression) model the extent to which the outcome can be predicted, given values of the predictor (Vittinghoff, 2012). The degree to which the predictor statistically "explains" variation in the outcome, is expressed as R^2 ("R-squared"), taking values from 0-1, and therefore sometimes expressed as percentage (0-100%). Both simple (one predictor) and multiple (multiple predictors) linear regression were used. The multiple linear regression reflects the joint strength of several predictors in explaining the outcome.

Among important constraints for interpreting the model is the issue of *multicollinearity*, meaning that some predictors are correlated. This renders the individual contributions from the predictors in the model uninterpretable, but does not invalidate its overall performance. When analysing relatively small samples, the adding of predictors may lead to *overfitting*, inflating the R^2. This means that the multiplicity of predictors "outweighs" the data size, and fits the outcome values of the particular data set "too well". If the sample would have been larger, or if the model is applied to a new data set, R^2 shrinks considerably because results were due to overfitting and are therefore not generalizable. Practical implications of this were highlighted in a recent review of prediction models regarding COVID-19, where authors judged all studies to be at high or unclear risk of bias, commonly due to model overfitting and lack of model validation (Wynants, 2021). To test the robustness of a regression model the *predicted* R^2 can be calculated. It simulates analyses, removing one data point at a time from analysis. If the accuracy of the model is dependent on few observations, the predicted R^2 will shrink, and the reliability of the model estimate diminishes.

Paper IV evaluated the classification capacity of the ESSENCE-Q instrument in distinguishing participants with impairing neurodevelopmental problems from those without such problems. Having a binary outcome allows for evaluating *sensitivity* (true positive rate), *specificity* (true negative rate) and *accuracy* (proportion accurately classified, [true positive + true negative / all positive and negative]) of the test at specific cutoffs The *area under the curve* (AUC), provides a summary statistic of the overall classification capacity of all ranges of a test, and is often reported in tandem with a *Receiver Operating Characteristic* (ROC) curve. Importantly, the AUC and ROC-curve provide no guidance on how to use a test. The AUC can indicate the value of the test over that of chance alone (An AUC-value of 0.50 means that on average the test is equivalent to the tossing of a coin, and a value of 0.99 means that the test performs extremely well). The ROC-curve allows for a more intuitive direct interpretation of the strengths and weaknesses of a test (e.g., if test results in a certain range have high sensitivity or specificity, as opposed to in other ranges). There are few "perfect" tests in the world of medicine, but imperfect tests can be of great value, if used appropriately.

First, the selection of which patients to test are paramount for any diagnostic test. Even very sensitive tests (e.g., 99% sensitivity and 99% specificity) can have low *predictive value* in a population with low prevalence of the disease due to a high proportion false positives. For a disease prevalent in 1% of 10 000 tested individuals, such a test would detect 99 of 100 true positive to the "cost" of 100 false positive cases, making interpretation ambiguous, since only 50% of those with a positive test would actually have the disease. For example, screening for prostate cancer with prostate surface antigen blood tests in men

(purported sensitivity of 21%, specificity 94%) is subject to debate due to the rate of false positive cases and consequences of undergoing unnecessary, costly and potentially harmful procedures in the ensuing diagnostic odyssey required after testing positive (Ankerst & Thompson, 2006). On the contrary, infant screening tests for phenylketonuria, a rare metabolic disorder, is routinely conducted, due to excellent test characteristics (Sensitivity of 99.2%, Specificity of 99.9%) and neglible harm from false positive testing (confirmatory non-invasive tests can rule out disease) (Hanley et al., 1997).

Second, the probability of disease differs depending on the results of a test. This is reflected in the terms *positive* and *negative likelihood ratio* (LR+ = True positive/False positive, LR- = True negative / False negative), which combines the test characteristics at a specific cutoff/value into a ratio. For example, a Mini-Mental Status Examination (MMSE, range 0-30) test result of 26 or more has a LR+ of 0.1, whereas a result <20 has a LR+ of 14 for clinical dementia (McGee, 2018). This means that the post-test probability of disease is impacted differently by whether the result on the MMSE is above 26, or <20.

The application of tests across the lines described above is in actual fact a formalized framework of the clinical reasoning applied by physicians in everyday practice. In the mind of the physician, information gathered in the process of clinical decision-making ultimately ends in a probabilistic answer to the question "Does the patient have the disease, in the light of the series of tests and findings elicited?". If sufficiently probable, the decision is communicated in a dichotomized "Yes" or "No" and acted on accordingly. Reasoning in conditional probabilities in this way is described as bayesian reasoning, which is attributed to the vicar and scientist Thomas Bayes (Gill, Sabin, & Schmid, 2005).

3.6 ETHICS

All studies that the papers are based on were approved by the regional ethical review board in Gothenburg.

Since **paper I** concerns individuals affected by prenatal alcohol exposure who were assessed in childhood, they may not be aware of their prior study participation and potential status as exposed to alcohol prenatally. The study invitation may therefore have confronted them with this possibility, in addition to their adoption history, and may have caused distress. On the contrary, many participants and their families expressed relief in being listened to and in receiving information that they had been missing previously, i.e., an explanation as to why they were experiencing so much hardship, in spite of being told at adoption that they were perfectly healthy children and that life would pan out as for children in general.

Paper II and III are studies based on registry-data for which the ethical review board approved a waiver of consent. Informed consent is a cornerstone of ethical research practice, wherein participants can choose freely, without implicit personal risk or pressure affecting their decision. However, there is research that cannot be undertaken if informed consent is required. The Swedish ethics review act (SFS 2003:460) acknowledges this in § 21, stating that (i) if the research provides knowledge unattainable with consent, (ii) is in the interest for the research participant or other citizens with similar ailments and (iii) that the research poses minimal risk for harm or distress to the participant, research without explicit consent may be considered (Riksdagsförvaltningen, 2003).

Experience from previous population-based studies has revealed a high risk for attrition among individuals with the highest psychiatric morbidity, possibly due to lack of personal resources, energy or motivation and being "tired of investigations" (Stormark, Heiervang, Heimann, Lundervold, & Gillberg, 2008). This leads to the paradox that the most afflicted individuals in most need of benefit from research are most prone to non-participation. By the registry-based study design we therefore believe the research is being done in accordance with all aspects of § 21 of the Swedish ethics review act, and hopefully may serve the purpose of improving knowledge and interventions.

Paper IV concerns children, a vulnerable population. Study participation and questions about health may cause distress for some individuals. However, we know by clinical experience that children generally participate gladly in health exams, something we were reminded of when doing the assessments. On the contrary, we also know that a substantial number of children experience distress from adverse social circumstances, academic failure and the school environment itself. Unlike adults, children do not have the choice to discontinue or to not show up if their school environment makes them disharmonious; school is mandatory. The fact that 4% of children experience bullying and 15% find school participation meaningless is a societal failure (Folkhälsomyndigheten, 2018). Children with ESSENCE are at increased risk of academic failure and school-related problems, and it may go unaddressed for years. One could argue that not studying this in order to improve detection and early mitigation strategies is an unethical error of omission on the side of society.

4 RESULTS

4.1 PAPER I

Of 99 children adopted to western Sweden from eastern Europe between 1993-1997, 71 had previously participated in the initial study, and 37 were diagnosed with FASD. Of the 37 adoptees with FASD, 36 (15 females) were evaluated at a median age of 22 years (range 18–28) and a mean follow-up time of 15.5 years (range 13–17).

Of 33 participants completing the psychiatric interview, any psychiatric disorder was ascertained in 29 individuals (88%), 23 (70%) had ADHD, three or more disorders had been diagnosed in 16 individuals (48%), 7 (21%) had a history of suicide attempt and 9 (26%, 6 women, 3 men) reported sexual victimization. At baseline, the mean IQ was 86, and at follow-up in adulthood it was 68 (one-sample t-test mean difference: 18.9; 95% CI 12.7–25.0, n=29). Dependency on social support was reported by 20 of 36 individuals (56%). Median score on the clinical global impression-severity instrument was 6, which means “severely ill”.

Out of 32 participants assessed, 20 (69%) had gross motor coordination abnormalities, high blood pressure was measured in 9 (28%) and ophthalmological abnormalities were found in 29 of 30 participants (97%). Growth restriction in height and head circumference of approximately -1.8 standard deviations persisted into adulthood for participants with fetal alcohol syndrome (n=21).

The results indicate that FASD confers morbidity in multiple areas that persist into adulthood, warranting planning for habilitation across the lifespan.

4.2 PAPER II

For the three groups (ADHD+DCD n=62, PM group n=51, RM group n=310) outcomes were collected at an age of 30-31 years, covering 9693 person-years in total. Five participants were deceased, one in the ADHD+DCD group, and two each in the two comparison groups. The composite outcome (any psychiatric disorder, prescription, sick pension or criminal sentence) occurred at a higher rate in the ADHD+DCD (~60%) group than in both comparison groups (vs PM group ~35%, p=0.0115, vs RM group ~40%, p=0.0054) although ~40% in the ADHD+DCD group did not experience the outcome. Analyzed separately, the ADHD+DCD group had higher rates of psychiatric diagnoses, psychotropic medication prescriptions and occurrence of sick pension than both comparison groups, whereas rates of criminal convictions did not differ. Participants with ADHD+DCD were most commonly prescribed antidepressants (17, 27%) and anxiolytics (14, 23%) and only six (10%) had been prescribed stimulants. Rates of pain diagnoses and analgesic prescriptions were similar across all groups. The ADHD+DCD group had lower education attainment, more unemployment and dependency on social benefits than both comparison groups.

A higher proportion of individuals with ADHD+DCD experienced unfavorable outcomes as adults than a non-clinical comparison group and the general population in the same county born the same years. The relative impact of neuromotor function and inattention on outcome should be evaluated.

4.3 PAPER III

Participants of the original study group had been reassessed at age 9 years (n=110; 60 children with ADHD+DCD and 50 children in the comparison group). At that time the assessments included examinations of neuropsychiatric symptoms, continuous performance test results and measures of motor function. These clinical variables were used as predictors and national registers data up to 30-31 years of age were used as outcomes. The predictors were used in linear regression models with an outcome score (range 0-7) consisting of seven binary endpoints (low educational attainment, low occupation level, psychiatric disorder, psychotropic medication prescription, sick pension, high dependence on social benefits and criminal conviction). When applicable, strong predictors in the outcome score were analyzed on each outcome as a continuous variable when applicable (not applicable for sick pension).

Three of the 110 participants were deceased. The strongest predictors at age 9 for the adverse outcome score in adulthood were motor coordination problems, symptoms of conduct disorder, oppositional defiant disorder, and ADHD, all with an R^2 around 25%, followed by autistic traits (R^2=15%) and depressive symptoms (R^2=8%). When these predictors were combined in a multivariable model, the adjusted R^2 was 40%. Intellectual quotient did not increase the R^2. Analyses stratified by group status (ADHD+DCD and comparison group) and sex were similar, except in females, where a strong association of autistic traits with adverse outcome was found (n=20, R^2=50%), although this finding did not withstand sensitivity analyses for generalizability (predicted R^2=0%).

Several neurodevelopmental symptoms in addition to ADHD severity at age 9 years accounted for the variance in adverse outcome in adulthood. The full amount of neurodevelopmental symptoms irrespective of whether a diagnostic threshold is reached have prognostic implications and should inform both research and clinical practice.

4.4 PAPER IV

Out of 343 eligible children, 223 enrolled, of whom 173 (50% of all eligible) had a parent-rated ESSENCE-Q and were included in the study. At least one of the 12 possible concerns was reported as "Yes" by parents of 36% of participants. Based on the information sources (physical exam and maternal interview, neuropsychological assessment, medical records, parent and teacher rated questionnaires, national tests in 3rd grade), case conference assessments and CGI-S ratings indicated that in 101 (57%) participants a work-up was warranted (i.e., ESSENCE-problems likely and warrant some clinical investigation), and 64 (37%) had clinically impairing NDPs (i.e., a CGI-S rating of 4-7, meaning that symptoms/impairments warrant clinical attention and likely a diagnosis). The AUC of the ESSENCE-Q in detecting need for work-up was 0.70 (95% confidence interval [CI] 0.63-0.77), and the AUC in detecting participants with clinically impairing NDPs was 0.82 (95% CI 0.76-0.88). ESSENCE-Q ratings correlated positively with CGI-S scores (r=0.48, p<0.05). An ESSENCE-Q cutoff of ≥3 had the highest accuracy (78%) with a negative predictive value of 82% for ruling out clinically impairing NDPs. Among participants with ratings >6 there were very few false positive cases, which was reflected in positive likelihood ratios >10 and positive predictive values of 86% or more in this range.

This study of the ESSENCE-Q in 11-year-old children suggests it might be an acceptable instrument for screening of NDPs in children in middle school. High ESSENCE-Q ratings were predictive of NDPs warranting clinical attention, but detection accuracy of the instrument indicates that it needs to be combined with other methods for screening purposes in this age-group. Furthermore, the large attrition rate and the selection of the schools included might have contributed both to overestimation of NDP prevalence rates and to the less-than perfect negative predictive values.

5 DISCUSSION

This thesis demonstrates the heterogenous presentation in childhood, as well as outcome in adulthood of conditions characterized by neurodevelopmental deviations. In **paper I**, a majority of participants with FASD experienced adverse outcomes in adulthood, as reflected in dependence on support and psychiatric morbidity. In **paper II**, adverse outcomes in a composite score occurred more frequently in those with ADHD+DCD, although 40% of them did not experience any of the adverse outcomes. **Paper III** showed that symptom severity across several symptom areas in addition to that of ADHD alone jointly explained almost 40% of the variance in an extended adverse outcome score. **Paper IV** found that high scores in the ESSENCE-Q rated by caregivers were predictive of, and correlated positively with clinically impairing neurodevelopmental problems in 11-year-old children.

5.1 PAPER I

Echoing previous authors in the field, the disentangling of hereditary, prenatal and postnatal contributors to outcome in FASD is a challenge (Spohr et al., 2007; Streissguth et al., 1991). In this regard, a strength of study I is that all participants were a population-based, non-referred sample of adoptees. This avoided referral bias, and the effect from parental and social instability in childhood from time of adoption was substantially reduced. Even so, the optimized environment did not suffice to prevent development of substantial morbidity and impairments. The social catastrophe preceding adoptions for many of the participants, including frequent separations, neglect, parental unemployment and substance misuse, implies a "triple hit" from not only post- and prenatal suboptimalities, but likely also hereditary liabilities for psychiatric disorders.

The surprising finding of significantly lower non-verbal IQ at follow-up, coupled with stunted growth parameters and neurological abnormalities is not the expected trajectory for intelligence in the general population, which tends to be more stable over time (Deary, Whalley, Lemmon, Crawford, & Starr, 2000; Larsen, Hartmann, & Nyborg, 2008). Cognitive development occuring at a slower rate is a pattern previously reported in cohorts of individuals with Down's syndrome, (Patterson, Rapsey, & Glue, 2013; Wester Oxelgren et al., 2019). The finding of arrested cognitive development from an IQ in the normal range at baseline, and whether it is characteristic of FASD, warrants further study.

Neurodevelopmental symptoms at baseline for cohorts of study I and II-III were in many regards comparable, including symptoms of inattention, motor

coordination problems and oppositional defiant behaviors to varying degrees (M. Landgren et al., 2010; V. Landgren, Fernell, Gillberg, Landgren, & Johnson, 2022). In contrast, impairments in the groups as a whole seemed to increase with age for those with FASD, whereas they decreased for those with ADHD+DCD. This implies that the diagnosis of FASD may contain important information regarding prognosis, a key feature of a diagnosis (Heckers & Kendler, 2020).

Limitations of the study are the small sample size, heterogeneity in quality of postnatal rearing environment before adoption, possible selection effects paving the way for international adoption, and differences in the timing of adoptions, that reduce the extent to which hereditary, pre- and postnatal factors can be weighed in contributing to outcomes. Age at adoption in the original study of adoptees (N=76) ranged from 5 months to 7 years, covering a critical period of neurological and psychological development (Magnus Landgren et al., 2006). There are two cohorts worth mentioning in conjunction with this study with regard to the role of the rearing environment.

The longitudinal English and Romanian adoptees study was able to shed some light on the role of early childhood deprivation. It was framed as a *natural experiment*, occurring with the fall of the Ceausescu regime in Romania (Sonuga-Barke et al., 2017). Although there is no clear definition of natural experiment, the main theme generally is that "treatment"/exposure allocation has occurred independently of the researchers (Craig et al., 2012). The power of randomization lies in the (give or take) even distribution of known and (most importantly) *unknown* characteristics of the participants that may confound or interact with effects from the exposure/intervention (Collins, Bowman, Landray, & Peto, 2020). Thus, some dust from the "magic of randomization" is imparted on the natural experiment allowing for estimation of causal inference, as compared with observational studies however carefully planned, that cannot eliminate the risk of misinterpretation due to confounding - unless the putative effect is very large. Such exceptions are the study showing a strong association between tobacco smoking and lung cancer, and more recently a case-control study convincingly suggesting a causal role of Epstein-Barr virus in precipitating multiple sclerosis (Doll & Hill, 1956; Bjornevik et al., 2022). With the fall of the Romanian regime, a wave of international adoptions from children living in orphanages with poor living standards ensued, some of whom received new families in the UK. Since the timing of the adoption was largely determined by the fall of the regime, authors argued that orphanage exposure could be considered a natural experiment. However, it is not entirely clear whether the choice of who was adopted internationally, and importantly, the length of stay in the orphanage was completely at random. The large-scale system of orphanages in Romania was a consequence of social engineering policy capitalizing on a high fertility rate due to prohibited

abortion and poverty, summed up in the cynical saying at the time *"The State wanted children, let the State look after them"* (Popescu, Muntean, & Juffer, 2020). Children were routinely assessed by staff and purposely transferred between orphanages with poor staffing and resourcing. In instances of developmental delays, they were kept for a longer time, and children with disabilities were transferred to special institutions (Popescu et al., 2020). It is therefore unclear whether differences in psychiatric morbidity reported by Sonuga-Barke et al between those with and without prolonged institutional stay can be attributed to the institutionalization only, or whether there are confounding contributors inflating the difference, as implied by the higher rate of extremely low birthweight among those with prolonged institutional care. Authors report no formal dysmorphological assessment or assessment of reasons for the children's out-of-home placements, although for most parents it was due to extreme poverty (Rutter, 1998).

The second rather exceptional study is the Bucharest early intervention project, a randomized controlled trial comparing early foster care placement with institutional care in Romania (Nelson et al., 2007). By invoking clinical equipoise, 68 children from six institutions in Romania were randomized at a mean age of 21 months to foster care or continuing institutional care. A non-randomized group of never institutionalized children was also recruited. Of note is that 51 were excluded from the study prior to randomization for medical reasons, including genetic syndromes and fetal alcohol syndrome. Institutionalized children scored lower than the foster care group on measures of development and intelligence at 42 and 54 months, with standardized effect sizes in the range of 0.5. Up to 16-years of age, the degree of psychopathology (primarily externalizing symptoms) was significantly higher in the institutionalized children group (the majority not remaining institutionalized at this timepoint) compared with the foster care group, an effect exacerbated by lower birth weight and male sex (Wade, Fox, Zeanah, & Nelson, 2018). Early environmental deprivation seems to imprint lasting effects on mental health into late adolescence, primarily expressed as externalizing symptoms. Authors do not report on the subscales driving this effect, although most subscales covered severity of interpersonal deficits (oppositional defiant, conduct, overt aggression, relational aggression, and attention-deficit/hyperactivity disorder).

Other studies, albeit not randomized, have not as consistently replicated this effect. Mukeheerje and colleagues did not find increased rates of NDDs in patients with FASD exposed to maltreatment vs those not (R Mukherjee, Cook, Norgate, & Price, 2019). A Swedish twin-study did find only slightly higher symptoms of NDDs in twins exposed to maltreatment vs those not (Dinkler et al., 2017). For FASD there are clearly clinical findings that may be specifically attributable to alcohol exposure, such as birth defects, growth restriction and ocular abnormalities (Aring et al., 2021; Gomez et al., 2020; Hoyme et al.,

2016). There are psychiatric behavioral or neurodevelopmental patterns common in FASD, but whether they are specific to alcohol exposure or postnatal deprivation is less clear.

On the one hand, Rutter and colleagues argue for a "deprivation-specific psychological pattern" characterized by quasi-autism (characterized by low social reciprocity, awareness, interaction and empathy coupled with obsessional interests, but with little of stereotypical behavior), disinhibited attachment (lack of normal social boundaries, engaging with strangers) inattention/overactivity, and cognitive impairment (Rutter et al., 1999, 2010). Put differently, participants have been described in psychiatric terms as having a:

> *"deprivation-related ADHD [with a…characteristic pattern of comorbidities marked by persistently high disinhibited social engagement, autism spectrum disorder, callous unemotional traits and low [self-reported] conduct disorder" (Kennedy et al., 2016)*

On the other hand, the same phenomena appear to be described in FASD, albeit in less psychiatric terms. In a review of neurobehavioral characteristics of FASD, Kable emphasizes deficits in executive function and marked social interaction problems.

> *"…individuals with PAE [prenatal alcohol exposure] demonstrate difficulties in planning and organization, or cognitive inflexibility…[executive function] problems have been found to be greater than expected based on IQ… Because of problems with impulse control, individuals with PAE are often clinically described as breaking rules or cheating at games, confabulating or telling lies, or stealing…Clinical observations reveal symptoms such as being overly friendly with strangers, socially immature, having difficulty understanding social consequences or reading social cues, or being naïve and gullible. Individuals with PAE have difficulty making and keeping friends, or have superficial friendships, often choosing unsuitable peers as friends." (Kable et al., 2016)*

The behavioral patterns described are almost indistinguishable from those of children exposed to prolonged institutional deprivation. Taken together, early childhood deprivation has significant developmental effects interacting with hereditary and prenatal effects for children with FASD that all need to be taken into consideration. While recognizing the impact of the environment, disorders primarily understood as being constitutional, such as NDDs, should not be overlooked, but rather be actively pursued in patients exposed to environmental deprivation or neglect.

International experts as well as the WHO advocate for educating health care professionals in both prevention and diagnosis of FASD (Jonsson, Salmon, & Warren, 2014; Pan American Health Organization, 2020). On the contrary, researchers engaged in the Swedish health technology assessment review of FASD have discouraged clinicians from diagnosing FASD (Helgesson et al., 2018; SBU, 2016). The authors' argue that disadvantages with diagnosing FASD include stigmatization of children and their mothers, parental feelings of guilt, and speculates on a potential drift of resources being tied to diagnoses rather than specific needs. Furthermore, the assuming of a strong causal link from alcohol to impairments in all conditions described under the FASD-umbrella concept is deemed unwarranted. At the same time, they acknowledge that the emergence of future research may change the current view. Few children in Sweden are diagnosed with FASD. In Swedish citizens born between 1987-2012, 107 individuals (0.004%) had been diagnosed with FAS between 2001-2013 (SBU, 2016). It seems unlikely that future research in Sweden will emerge if the identification of the condition is discouraged further.

5.2 PAPER II AND III

Outcomes in adulthood aligned surprisingly well with previous clinic-based cohorts, showing that impairments are reduced for a large proportion diagnosed with ADHD in childhood (Caye, Spadini, et al., 2016). Prognosis prediction has proven difficult for psychiatric conditions. Cross-sectional clinical data explaining 40% of the variance in long-term outcome as shown in study III is however not negligible. For comparison, a long-term follow-up of participants with schizophrenia found that 25% of the variance in outcome could be explained by baseline predictors, including clinical characteristics (Harrow, Jobe, & Tong, 2021).

There is an ongoing debate within psychiatric research regarding the utility of defining a *p*-factor of psychopathology, akin to the *g*-factor of intelligence (Fried, Greene, & Eaton, 2021; Lahey et al., 2012; Pettersson, Larsson, D'Onofrio, Bölte, & Lichtenstein, 2020). In view of the fact that diverse cognitive abilites are correlated, and predictive of a host of later outcomes (e.g., health and education), the concept of a latent, underlying *g*-factor explaining the association across cognitive abilities was proposed already in the early 20th century (Deary, 2012).

With regard to *p*, critics have called for a clearer definition (is *p* a measure of liability for, or severity of psychiatric conditions?) and argue that *p* does not account for more than the sum of its constituents (Fried et al., 2021). The underlying data often consists of the presence of psychiatric disorders of

several kinds, which by nature are crude binary measures (Pettersson et al., 2020). Failure to account for subsyndromal symptoms, and underrecognized conditions (e.g., DCD and borderline intellectual functioning) is therefore an inherent limitation of current *p*-factor models. Whether *p* will prove to be more than the sum of its parts is an open question. Practically speaking, *p* is restating the (not so surprising) fact that psychopathology of various kinds is correlated and that the sum of problems is predictive of future outcomes.

Clinically, it supports a psychiatric practice that makes broad diagnostic assessments in order to inform both intervention and prognosis. Judging from study III, it is reasonable to incorporate neurodevelopmental aspects in such assessments, whose contributions may be underestimated, especially since *p* is derived from register-based studies. As mentioned in study III, the positive predictive value of a diagnosis in the national patient register is in general adequate (Ludvigsson et al., 2011), but the negative predictive value (that the absence of a diagnosis in the register is true) is very poor for neurodevelopmental conditions such as DCD and borderline intellectual functioning. When prevalence in the registers is compared with the expected prevalence rates from studies of DCD, they differ by a factor of several hundred.

5.3 PAPER IV

The validity of the ESSENCE-Q in predicting clinically impairing NDPs proved to be in the range of other measures, with the caveat that the vast majority of previous studies have been validated against specific NDDs such as ADHD and autism, and not the full range of NDDs (Marlow et al., 2019; Mulraney et al., 2021).

The predictive validity is always constrained by the inherent limitations of the measure it is derived from. For example, blood tests measuring cardiac necrosis will in some scenarios never detect myocardial infarction before an electrocardiogram can, because when the first electrophysiological abnormalities present on the electrocardiogram, necrosis has not occurred. With regard to the ESSENCE-Q, it has inherent limitations by virtue of being a rating scale dependent on the judgment of the rater. Because no single informant can be expected to be the perfect arbiter of a psychiatric diagnosis, any screening by proxy will be imperfect, irrespective of whether the assessor is a teacher, parent or a clinician.

Just as anthropometric measures and biochemical assays have different cutoffs and reference values depending on the population (e.g., age-groups, sex), techniques used (e.g., reference values and cutoffs for measurement of myocardial infarction is dependent on the substrate [whole blood or plasma]

molecule isoform [Troponin T or I], assay technique [type of antibody used]) and differences between laboratories, the same goes for rating scales in psychiatry. In this vein, the study provides empirical support to the use of the ESSENCE-Q in 11-year-old children, and a sense of how to interpret any given score on the measure in this age group.

6 FUTURE PERSPECTIVES

It may well be so that the diagnostic constructs studied in this thesis will be obsolete and replaced by different or refined concepts in a generation or two. Nosological quagmire seems to be the defining characteristic of psychiatry as a medical discipline since its inception. If we were to rerun the history of psychiatry, as Kendler framed it,

> *"Unlike the elements in the periodic table, our current menu of psychiatric disorders would not likely be consistently rediscovered" (Kendler, 2016)*

Taking a closer look at medical diagnoses that have withstood the test of time, been refined and more precise than they were a 100 years ago, they follow a similar pattern. First they are defined by symptoms or findings, then clustering in syndromes with modest specificity, then further teased apart by tests that elucidate a pathophysiological fingerprint, and lastly by an etiological explanation. Examples pertaining to psychiatry following this pattern have been general paralysis of the insane/tertiary syphilis, gastric ulcer and a host of genetic conditions such as Rett-, 22q11-deletion-, Fragile X- and Down's syndrome (Daey Ouwens et al., 2015; Overmier & Murison, 2013; Windsperger & Hoehl, 2021). In these instances the discovery of a pathomechanism or etiology has reframed the key aspects of the diagnoses to pivot around the mechanism rather than the pattern of symptoms. With this follows almost invariably that care for patients identified with the diagnosis depart from psychiatry to other medical specialties, however important the psychiatric or psychological aspects of the illness still may be. It is therefore important that psychiatry as a medical discipline and research endeavor remains open to applying multiple levels of explanations to the clinical needs of patients, defending both the medical narrative, as well as the psychological approach increasingly reflected in diagnostic criteria and psychotherapeutic interventions for psychiatric disorders in the last 50 years (G. Berrios, 2016; German E Berrios & Marková, 2017; Kendler, 2005).

Regarding **paper I**, the diagnosis of FASD will possibly remain a diagnostic construct since linkage to etiology entails lasting validity to a larger extent than

that of purely symptom-based diagnoses. At its core, it is an etiological syndrome delineated by a characteristic set of features distinct from other kinds of syndromes, and the "likely" exposure to alcohol. Future studies of the factors that buffer or exacerbate effects of exposure may yield therapeutic options, which is indicated by the interaction of alcohol exposure and nutritional factors in causing the FASD-phenotype (Naik, Lee, Wu, Washburn, & Ramadoss, 2022). There are also research lines indicating that computer-assisted analyses may be useful in identifying syndromes with dysmorphological traits, including FASD (Pantel et al., 2020; Valentine et al., 2017).

Primary prevention of FASD is an obvious aim for future research, but the means for achieving this aim needs to be manifold and include a harm reduction approach on a societal level ("What Is Harm Reduction?," n.d.).

With regard to papers **II-IV**, the concepts of ADHD, DCD and NDPs are, by virtue of being symptom-based, likely to be changed as future diagnostic paradigms "stack the deck" of symptoms and signs. Even though diagnostic labels may change, the presenting symptoms and deficits on which the reports are based will not. The continuation of meticulous empirical descriptive studies with a broad approach therefore form the basis from which new theories and interventions can emerge, although they themselves may not be transformative.

Paper IV shows that NDPs as reported by parents and identified by clinicians are not rare, but rather a part of the human predicament for a substantial proportion of individuals. Awareness of the neurodevelopmental perspective on individual strengths and difficulties need to spread from research desks and clinics and inform all structures of society and facilitate more diverse ways for individuals to prosper and find their place in the world.

7 RELATED PUBLICATIONS NOT INCLUDED IN THIS THESIS

Gyllencreutz, E., Aring, E., Landgren, V., Svensson, L., Landgren, M., and Andersson Grönlund, M. 2020. Ophthalmologic Findings in Fetal Alcohol Spectrum Disorders – A Cohort Study From Childhood to Adulthood. *American Journal of Ophthalmology* 214 (June): 14–20.

Gyllencreutz, E., Aring, E., Landgren, V., Svensson, L., Landgren, M., and Andersson Grönlund, M. 2020. Thinner Retinal Nerve Fibre Layer in Young Adults with Foetal Alcohol Spectrum Disorders. *British Journal of Ophthalmology*, July 3: bjophthalmol-2020-316506.

Gyllencreutz, E., Aring, E., Landgren, V., Landgren, M., & Grönlund, M. A. (2022). Visual perception problems and quality of life in young adults with foetal alcohol spectrum disorders. *Acta Ophthalmologica* 100, e115–e121.

Aring, E., Gyllencreutz, E., Landgren, V., Svensson, L., Landgren, M., Andersson Grönlund, M. 2021. The FASD Eye Code: A Complementary Diagnostic Tool in Fetal Alcohol Spectrum Disorders. *BMJ Open Ophthalmology* 6 (1): e000852

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REFERENCES

Abel, E. L. (1981). A critical evaluation of the obstetric use of alcohol in preterm labor. *Drug and Alcohol Dependence*, *7*, 367–378.

Agnew-Blais, J. C., Polanczyk, G. V., Danese, A., Wertz, J., Moffitt, T. E., & Arseneault, L. (2016). Evaluation of the Persistence, Remission, and Emergence of Attention-Deficit/Hyperactivity Disorder in Young Adulthood. *JAMA Psychiatry*, *73*, 713.

American Psychiatric Association (APA). (1968). *Diagnostic and statistical manual of mental disorders* (Second edition). APA.

American Psychiatric Association (APA). (1980). *Diagnostic and statistical manual of mental disorders* (Third edition). Washington, DC: APA.

American Psychiatric Association (APA). (1994). *Diagnostic and statistical manual of mental disorders* (Fourth edition). Washington, DC: APA.

American Psychiatric Association (APA). (2013). *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition). Washington, DC: APA.

Andersson Grönlund, M., Landgren, M., Strömland, K., Aring, E., Svensson, L., Tuvemo, T., & Hellström, A. (2010). Relationships between ophthalmological and neuropaediatric findings in children adopted from Eastern Europe. *Acta Ophthalmologica*, *88*, 227–234.

Ankerst, D. P., & Thompson, I. M. (2006). Sensitivity and specificity of prostate-specific antigen for prostate cancer detection with high rates of biopsy verification. *Archivio Italiano Di Urologia, Andrologia: Organo Ufficiale [Di] Societa Italiana Di Ecografia Urologica E Nefrologica*, *78*, 125–129.

Aring, E., Gyllencreutz, E., Landgren, V., Svensson, L., Landgren, M., & Grönlund, M. A. (2021). The FASD Eye Code: A complementary diagnostic tool in fetal alcohol spectrum disorders. *BMJ Open Ophthalmology*, *6*, e000852.

Aronson, M., Hagberg, B., & Gillberg, C. (1997). Attention deficits and autistic spectrum problems in children exposed to alcohol during gestation: A follow-up study. *Developmental Medicine & Child Neurology*, *39*, 583–587.

Bahmanyar, S., Sundström, A., Kaijser, M., von Knorring, A.-L., & Kieler, H. (2013). Pharmacological treatment and demographic characteristics of pediatric patients with Attention Deficit Hyperactivity Disorder, Sweden. *European Neuropsychopharmacology*, *23*, 1732–1738.

Barkley, R. A., & Peters, H. (2012). The Earliest Reference to ADHD in the Medical Literature? Melchior Adam Weikard's Description in 1775 of "Attention Deficit" (Mangel der Aufmerksamkeit, Attentio Volubilis). *Journal of Attention Disorders*, *16*, 623–630.

Barnevik Olsson, M., Carlsson, L. H., Westerlund, J., Gillberg, C., & Fernell, E. (2013). Autism before diagnosis: Crying, feeding and sleeping problems in the first two years of life. *Acta Paediatrica*, *102*, 635–639.

Bejerot, S., Ståtenhag, L., & Glans, M. R. (2022). Below average motor skills predict victimization from childhood bullies: A study of adults with ADHD. *Journal of Psychiatric Research*, *153*, 269–275.

Benjamini, Y., & Hochberg, Y. (1995). Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society. Series B (Methodological)*, *57*, 289–300.

Berrios, G. (2016). An erudite encounter with: German Berrios. *Australian & New Zealand Journal of Psychiatry*, *50*, 927–928.

Berrios, G. E., & Porter, R. (1995). *A History of Clinical Psychiatry: The Origin and History of Psychiatric Disorders*. Athlone Press.

Berrios, German E, & Marková, I. S. (2017). Historical and conceptual aspects of motor disorders in the psychoses. *Schizophr. Res.*, 7.

Bjornevik, K., Cortese, M., Healy, B. C., Kuhle, J., Mina, M. J., Leng, Y., … Ascherio, A. (2022). Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. *Science*, *375*, 296–301.

Busner, J., & Targum, S. D. (2007). The Clinical Global Impressions Scale. *Psychiatry (Edgmont)*, *4*, 28–37.

Caye, A., Rocha, T. B.-M., Anselmi, L., Murray, J., Menezes, A. M. B., Barros, F. C., … Rohde, L. A. (2016). Attention-Deficit/Hyperactivity Disorder Trajectories From Childhood to Young Adulthood: Evidence From a Birth Cohort Supporting a Late-Onset Syndrome. *JAMA Psychiatry, 73,* 705–712.

Caye, A., Spadini, A. V., Karam, R. G., Grevet, E. H., Rovaris, D. L., Bau, C. H. D., … Kieling, C. (2016). Predictors of persistence of ADHD into adulthood: A systematic review of the literature and meta-analysis. *European Child & Adolescent Psychiatry*, *25*, 1151–1159.

Caye, A., Swanson, J., Thapar, A., Sibley, M., Arseneault, L., Hechtman, L., … Rohde, L. A. (2016). Life Span Studies of ADHD—Conceptual Challenges and Predictors of Persistence and Outcome. *Current Psychiatry Reports*, *18*, 111.

Cherkasova, M., Sulla, E. M., Dalena, K. L., Pondé, M. P., & Hechtman, L. (2013). Developmental Course of Attention Deficit Hyperactivity Disorder and its Predictors. *Journal of the Canadian Academy of Child and Adolescent Psychiatry*, *22*, 47–54.

Clements, S. D., & Peters, J. E. (1962). Minimal brain dysfunctions in the school-age child. Diagnosis and treatment. *Archives of General Psychiatry*, *6*, 185–197.

Collins, R., Bowman, L., Landray, M., & Peto, R. (2020). The Magic of Randomization versus the Myth of Real-World Evidence. *New England Journal of Medicine*, *382*, 674–678.

Cooper, M., Hammerton, G., Collishaw, S., Langley, K., Thapar, A., Dalsgaard, S., … Riglin, L. (2018). Investigating late-onset ADHD: A population cohort investigation. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *59*, 1105–1113.

Craig, P., Cooper, C., Gunnell, D., Haw, S., Lawson, K., Macintyre, S., … Thompson, S. (2012). Using natural experiments to evaluate population health interventions: New MRC guidance. *Journal of Epidemiology and Community Health*, *66*, 1182–1186.

Crichton, A. (2008). An Inquiry Into the Nature and Origin of Mental Derangement: On Attention and Its Diseases. *Journal of Attention Disorders*, *12*, 200–204.

Daey Ouwens, I. M., Lens, C. E., Fiolet, A. T. L., Ott, A., Koehler, P. J., & Verhoeven, W. M. A. (2015). Clinical Presentation of General Paralysis of the Insane in a Dutch Psychiatric Hospital, 1924-1954. *European Neurology*, *74*, 54–59.

Dalsgaard, S., Thorsteinsson, E., Trabjerg, B. B., Schullehner, J., Plana-Ripoll, O., Brikell, I., … Pedersen, C. B. (2020). Incidence Rates and Cumulative Incidences of the Full Spectrum of Diagnosed Mental Disorders in Childhood and Adolescence. *JAMA Psychiatry*, *77*, 155–164.

Deary, I. J. (2012). Intelligence. *Annual Review of Psychology*, *63*, 453–482.

Deary, I. J., Whalley, L. J., Lemmon, H., Crawford, J. R., & Starr, J. M. (2000). The Stability of Individual Differences in Mental Ability from Childhood to Old Age: Follow-up of the 1932 Scottish Mental Survey. *Intelligence*, *28*, 49–55.

Dinkler, L., Lundström, S., Gajwani, R., Lichtenstein, P., Gillberg, C., & Minnis, H. (2017). Maltreatment-associated neurodevelopmental disorders: A co-twin control analysis. *Journal of Child Psychology and Psychiatry*, *58*, 691–701.

Doll, R., & Hill, A. B. (1956). Lung Cancer and Other Causes of Death in Relation to Smoking. *Br Med J*, *2*, 1071–1081.

Ehlers, S., & Gillberg, C. (1993). The Epidemiology of Asperger Syndrome. *Journal of Child Psychology and Psychiatry*, *34*, 1327–1350.

Engel, G. L. (1977). The need for a new medical model: A challenge for biomedicine. *Science (New York, N.Y.)*, *196*, 129–136.

Faber, K. (1923). *Nosography in Modern Internal Medicine*. Paul B. Hoeber, Inc.

Faraone, S. V., Banaschewski, T., Coghill, D., Zheng, Y., Biederman, J., Bellgrove, M. A., … Wang, Y. (2021). The World Federation of ADHD International Consensus Statement: 208 Evidence-based

conclusions about the disorder. *Neuroscience & Biobehavioral Reviews*.
Faraone, S. V., Biederman, J., & Mick, E. (2006). The age-dependent decline of attention deficit hyperactivity disorder: A meta-analysis of follow-up studies. *Psychological Medicine*, *36*, 159–165.
Folkhälsomyndigheten. (2018). *Varför har den psykiska ohälsan ökat bland barn och unga i Sverige?* (No. 18023–2; p. 113).
Francis-Tan, A., Tan, C., & Zhang, R. (2018). School spirit: Exploring the long-term effects of the U.S. temperance movement on educational attainment. *Economics of Education Review*, *62*, 162–169.
Fried, E. I., Greene, A. L., & Eaton, N. R. (2021). The p factor is the sum of its parts, for now. *World Psychiatry*, *20*, 69–70.
Ghaemi, N. (2019). *Clinical Psychopharmacology: Principles and Practice*. Oxford University Press.
Ghaemi, S. N. (2009). The rise and fall of the biopsychosocial model. *British Journal of Psychiatry*, *195*, 3–4.
Gill, C. J., Sabin, L., & Schmid, C. H. (2005). Why clinicians are natural bayesians. *British Medical Journal*, *330*, 1080–1083.
Gillberg, C. (2003). Deficits in attention, motor control, and perception: A brief review. *Archives of Disease in Childhood*, *88*, 904–910.
Gillberg, C. (2010). The ESSENCE in child psychiatry: Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations. *Research in Developmental Disabilities*, *31*, 1543–1551.
Gillberg, C., Rasmussen, P., Carlström, G., Svenson, B., & Waldenström, E. (1982). Perceptual, motor and attentional deficits in six-year-old children. Epidemiological aspects. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *23*, 131–144.
Gomez, D. A., May, P. A., Tabachnick, B. G., Hasken, J. M., Lyden, E. R., Kalberg, W. O., … Abdul-Rahman, O. A. (2020). Ocular measurements in fetal alcohol spectrum disorders. *American Journal of Medical Genetics. Part A*, *182*, 2243–2252.
Grönlund, M. A. 1959-. (2005). *Ophthalmologic characteristics andneuropediatric findings. With special emphasis on children adopted from eastern Europe*. Retrieved from https://gupea.ub.gu.se/handle/2077/16694
Gunnell, J. G. (1998). Time And Interpretation: Understanding Concepts And Conceptual Change. *History of Political Thought*, *19*, 641–658.
Gyllencreutz, E. (2021). *Fetal Alcohol Spectrum Disorders in Children and Young Adults with an emphasis on ophthalmology*. Retrieved from https://gupea.ub.gu.se/handle/2077/67132
Hanley, W. B., Demshar, H., Preston, M. A., Borczyk, A., Schoonheyt, W. E., Clarke, J. T., & Feigenbaum, A. (1997). Newborn phenylketonuria

(PKU) Guthrie (BIA) screening and early hospital discharge. *Early Human Development*, *47*, 87–96.

Harrisson, P. L., & Oakland, T. (2003). *Adaptive Behavior Assessment System—Second edition*.

Harrow, M., Jobe, T. H., & Tong, L. (2021). Twenty-year effects of antipsychotics in schizophrenia and affective psychotic disorders. *Psychological Medicine*, 1–11.

Hatakenaka, Y., Fernell, E., Sakaguchi, M., Ninomiya, H., Fukunaga, I., & Gillberg, C. (2016). ESSENCE-Q - a first clinical validation study of a new screening questionnaire for young children with suspected neurodevelopmental problems in south Japan. *Neuropsychiatric Disease and Treatment*, *Volume 12*, 1739–1746.

Hatakenaka, Y., Maeda, M., Ninomiya, H., Hachiya, K., Fernell, E., & Gillberg, C. (2020). ESSENCE-Q obtained in routine Japanese public child health check-ups may be a valuable tool in neurodevelopmental screening. *Acta Paediatrica*, *109*, 764–773.

Hatakenaka, Y., Ninomiya, H., Billstedt, E., Fernell, E., & Gillberg, C. (2017). ESSENCE-Q - used as a screening tool for neurodevelopmental problems in public health checkups for young children in south Japan. *Neuropsychiatric Disease and Treatment*, *Volume 13*, 1271–1280.

Heckers, S., & Kendler, K. S. (2020). The evolution of Kraepelin's nosological principles. *World Psychiatry*, *19*, 381–388.

Helgesson, G., Bertilsson, G., Domeij, H., Fahlström, G., Heintz, E., Hjern, A., … Hultcrantz, M. (2018). Ethical aspects of diagnosis and interventions for children with Fetal Alcohol Spectrum Disorder (FASD) and their families. *BMC Medical Ethics*, *19*, 1.

Henderson, S. E., & Henderson, L. (2003). Toward An Understanding of Developmental Coordination Disorder: Terminological and Diagnostic Issues. *Neural Plasticity*, *10*, 1–13.

Hoyme, H. E., Kalberg, W. O., Elliott, A. J., Blankenship, J., Buckley, D., Marais, A.-S., … May, P. A. (2016). Updated Clinical Guidelines for Diagnosing Fetal Alcohol Spectrum Disorders. *Pediatrics*, *138*.

Hoyme, H. E., May, P. A., Kalberg, W. O., Kodituwakku, P., Gossage, J. P., Trujillo, P. M., … Robinson, L. K. (2005). A practical clinical approach to diagnosis of fetal alcohol spectrum disorders: Clarification of the 1996 institute of medicine criteria. *Pediatrics*, *115*, 39–47.

Jones, K. L., & Smith, D. W. (1973). Recognition of the fetal alcohol syndrome in early infancy. *Lancet (London, England)*, *302*, 999–1001.

Jones, K. L., Smith, D. W., Ulleland, C. N., & Streissguth, P. (1973). Pattern of malformation in offspring of chronic alcoholic mothers. *Lancet (London, England)*, *1*, 1267–1271.

Jonsson, E., Salmon, A., & Warren, K. R. (2014). The international charter on prevention of fetal alcohol spectrum disorder. *The Lancet Global Health*, *2*, e135–e137.

Kable, J. A., O'Connor, M. J., Olson, H. C., Paley, B., Mattson, S. N., Anderson, S. M., & Riley, E. P. (2016). Neurobehavioral Disorder Associated with Prenatal Alcohol Exposure (ND-PAE): Proposed DSM-5 Diagnosis. *Child Psychiatry & Human Development*, *47*, 335–346.

Kendell, R., & Jablensky, A. (2003). Distinguishing Between the Validity and Utility of Psychiatric Diagnoses. *American Journal of Psychiatry*, *160*, 4–12.

Kendler, K. S. (2005). Toward a Philosophical Structure for Psychiatry. *Am J Psychiatry*, 8.

Kendler, K. S. (2016). The nature of psychiatric disorders. *World Psychiatry*, *15*, 5–12.

Kennedy, M., Kreppner, J., Knights, N., Kumsta, R., Maughan, B., Golm, D., … Sonuga-Barke, E. J. S. (2016). Early severe institutional deprivation is associated with a persistent variant of adult attention-deficit/hyperactivity disorder: Clinical presentation, developmental continuities and life circumstances in the English and Romanian Adoptees study. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *57*, 1113–1125.

Kessler, R. C., Adler, L., Ames, M., Demler, O., Faraone, S., Hiripi, E., … Walters, E. E. (2005). The World Health Organization Adult ADHD Self-Report Scale (ASRS): A short screening scale for use in the general population. *Psychological Medicine*, *35*, 245–256.

Kirby, A., Edwards, L., Sugden, D., & Rosenblum, S. (2010). The development and standardization of the Adult Developmental Co-ordination Disorders/Dyspraxia Checklist (ADC). *Research in Developmental Disabilities*, *31*, 131–139.

Kirby, A., Sugden, D., & Purcell, C. (2014). Diagnosing developmental coordination disorders. *Archives of Disease in Childhood*, *99*, 292–296.

Kirby, A., Williams, N., Thomas, M., & Hill, E. L. (2013). Self-reported mood, general health, wellbeing and employment status in adults with suspected DCD. *Research in Developmental Disabilities*, *34*, 1357–1364.

Klein, R. G., Mannuzza, S., Olazagasti, M. A. R., Roizen, E., Hutchison, J. A., Lashua, E. C., & Castellanos, F. X. (2012). Clinical and functional outcome of childhood attention-deficit/hyperactivity disorder 33 years later. *Archives of General Psychiatry*, *69*, 1295–1303.

Knobloch, H., & Pasamanick, B. (1959). Syndrome of minimal cerebral damage in infancy. *Journal of the American Medical Association*, *170*, 1384–1387.

Kopp, S. (2010). *Girls with social and/or attention impairments*. Retrieved from https://gupea.ub.gu.se/handle/2077/23134

Kramer, F., & Pollnow, H. (1932). Über eine hyperkinetische Erkrankung im Kindesalter. Pp. 21–40. *European Neurology*, *82*, 21–40.

Lahey, B. B., Applegate, B., Hakes, J. K., Zald, D. H., Hariri, A. R., & Rathouz, P. J. (2012). Is there a general factor of prevalent psychopathology during adulthood? *Journal of Abnormal Psychology*, *121*, 971–977.

Lamache, A. (1967). Réflexions sur la descendance des alcooliques. *Bulletin de l'Académie nationale de médecine*, *151*, 517–521.

Landgren, M., Kjellman, B., & Gillberg, C. (2000). Deficits in attention, motor control and perception (DAMP): A simplified school entry examination. *Acta Paediatrica*, *89*, 302–309.

Landgren, M., Svensson, L., Stromland, K., & Andersson Gronlund, M. (2010). Prenatal Alcohol Exposure and Neurodevelopmental Disorders in Children Adopted From Eastern Europe. *Pediatrics*, *125*, e1178–e1185.

Landgren, Magnus. (1999). *Deficits in attention, motor control and perception—DAMP. Epidemiologic, etiologic,diagnostic and learning aspects*. Göteborg. Retrieved from https://gupea.ub.gu.se/handle/2077/12426

Landgren, Magnus, Andersson Grönlund, M., Elfstrand, P.-O., Simonsson, J.-E., Svensson, L., & Strömland, K. (2006). Health before and after adoption from Eastern Europe. *Acta Paediatrica*, *95*, 720–725.

Landgren, Magnus, Pettersson, R., Kjellman, B., & Gillberg, C. (1996). Adhd, Damp and Other Neurodevelopmental/Psychiatric Disorders in 6-Year-Old Children: Epidemiology and Co-Morbidity. *Developmental Medicine & Child Neurology*, *38*, 891–906.

Landgren, V., Fernell, E., Gillberg, C., Landgren, M., & Johnson, M. (2022). Deficits in attention, motor control and perception childhood to age 30 years: Prospective case–control study of outcome predictors. *BMJ Open*, *12*, e054424.

Lange, K. W., Reichl, S., Lange, K. M., Tucha, L., & Tucha, O. (2010). The history of attention deficit hyperactivity disorder. *Attention Deficit and Hyperactivity Disorders*, *2*, 241–255.

Larsen, L., Hartmann, P., & Nyborg, H. (2008). The stability of general intelligence from early adulthood to middle-age. *Intelligence*, *36*, 29–34.

Lemoine, P., Haroossseau, H., Borteryu, J. P., & Menuet, J. C. (1968). Les Enfants de Parents Alcooliques. Anomalies Observee a Propos de 127

cas [The Children of Alcoholic Parents: Anomalies Observed in 127 Cases]. *Quest Medicale*, *21*, 476–482.

Li, Y.-C., Graham, J. D., & Cairney, J. (2018). Moderating Effects of Physical Activity and Global Self-Worth on Internalizing Problems in School-Aged Children With Developmental Coordination Disorder. *Frontiers in Psychology*, *9*, 1740.

Lichtenstein, P., Carlström, E., Råstam, M., Gillberg, C., & Anckarsäter, H. (2010). The Genetics of Autism Spectrum Disorders and Related Neuropsychiatric Disorders in Childhood. *American Journal of Psychiatry*, *167*, 1357–1363.

Linné, C. von. (1759). *Genera morborum*.

Lipinski, R. J., Hammond, P., O'Leary-Moore, S. K., Ament, J. J., Pecevich, S. J., Jiang, Y., … Sulik, K. K. (2012). Ethanol-induced face-brain dysmorphology patterns are correlative and exposure-stage dependent. *PloS One*, *7*, e43067.

Ludvigsson, J. F., Andersson, E., Ekbom, A., Feychting, M., Kim, J.-L., Reuterwall, C., … Olausson, P. O. (2011). External review and validation of the Swedish national inpatient register. *BMC Public Health*, *11*, 450.

Marlow, M., Servili, C., & Tomlinson, M. (2019). A review of screening tools for the identification of autism spectrum disorders and developmental delay in infants and young children: Recommendations for use in low- and middle-income countries. *Autism Research*, *12*, 176–199.

May, P. A., Fiorentino, D., Coriale, G., Kalberg, W. O., Hoyme, H. E., Aragón, A. S., … Ceccanti, M. (2011). Prevalence of Children with Severe Fetal Alcohol Spectrum Disorders in Communities Near Rome, Italy: New Estimated Rates Are Higher than Previous Estimates. *International Journal of Environmental Research and Public Health*, *8*, 2331–2351.

May P.A., Chambers C.D., Kalberg W.O., Zellner J., Feldman H., Buckley D., … Hoyme H.E. (2018). Prevalence of fetal alcohol spectrum disorders in 4 US communities. *JAMA - Journal of the American Medical Association*, *319*, 474–482. Embase.

McGee, S. R. (2018). *Evidence-based physical diagnosis* (4th edition). Philadelphia, PA: Elsevier.

McQuire, C., Mukherjee, R., Hurt, L., Higgins, A., Greene, G., Farewell, D., … Paranjothy, S. (2019). Screening prevalence of fetal alcohol spectrum disorders in a region of the United Kingdom: A population-based birth-cohort study. *Preventive Medicine*, *118*, 344–351.

Miniscalco, C., Nygren, G., Hagberg, B., Kadesjö, B., & Gillberg, C. (2006). Neuropsychiatric and neurodevelopmental outcome of children at age 6 and 7 years who screened positive for language problems at 30 months. *Developmental Medicine and Child Neurology*, *48*, 361–366.

Moffitt, T. E., Houts, R., Asherson, P., Belsky, D. W., Corcoran, D. L., Hammerle, M., … Caspi, A. (2015). Is adult ADHD a childhood-onset neurodevelopmental disorder? Evidence from a 4-decade longitudinal cohort study. *The American Journal of Psychiatry*, *172*, 967–977.

Mohr-Jensen, C., & Steinhausen, H.-C. (2016). A meta-analysis and systematic review of the risks associated with childhood attention-deficit hyperactivity disorder on long-term outcome of arrests, convictions, and incarcerations. *Clinical Psychology Review*, *48*, 32–42.

Morris-Rosendahl, D. J., & Crocq, M.-A. (2020). Neurodevelopmental disorders—The history and future of a diagnostic concept. *Dialogues in Clinical Neuroscience*, *22*, 65–72.

Mukherjee, R, Cook, P. A., Norgate, S. H., & Price, A. D. (2019). Neurodevelopmental outcomes in individuals with fetal alcohol spectrum disorder (FASD) with and without exposure to neglect: Clinical cohort data from a national FASD diagnostic clinic. *Alcohol*, *76*, 23–28.

Mukherjee, Raja, Layton, M., Yacoub, E., & Turk, J. (2011). Autism and autistic traits in people exposed to heavy prenatal alcohol: Data from a clinical series of 21 individuals and nested case control study. *Advances in Mental Health and Intellectual Disabilities*, *5*, 42–49.

Mulraney, M., Arrondo, G., Musullulu, H., Iturmendi-Sabater, I., Cortese, S., Westwood, S. J., … Coghill, D. (2021). Systematic Review and Meta-analysis: Screening Tools for Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry*.

Munsche, H. A. (2012). Classification Of Mental Illness In The 18th Century: A Comparison Of The Nosologies Of Carl Linnaeus, Francois Bossier De Sauvages, Rudolpho Vogel And William Cullen. *All NMU Master's Theses*, *470*, 55.

Naik, V. D., Lee, J., Wu, G., Washburn, S., & Ramadoss, J. (2022). Effects of nutrition and gestational alcohol consumption on fetal growth and development. *Nutrition Reviews*, *80*, 1568–1579.

Nelson, C. A., Zeanah, C. H., Fox, N. A., Marshall, P. J., Smyke, A. T., & Guthrie, D. (2007). Cognitive Recovery in Socially Deprived Young Children: The Bucharest Early Intervention Project. *Science*, *318*, 1937–1940.

Neul, J. L., Kaufmann, W. E., Glaze, D. G., Christodoulou, J., Clarke, A. J., Bahi-Buisson, N., … Percy, A. K. (2010). Rett Syndrome: Revised Diagnostic Criteria and Nomenclature. *Annals of Neurology*, *68*, 944–950.

Neville, B. (2013). Role of ESSENCE for preschool children with neurodevelopmental disorders. *Brain and Development*, *35*, 128–132.

Nilsson, P. (2014). Starkölsförsöket: Fr\a an fosterstadiet till vuxen \a alder. *SNS Analys*. Retrieved from https://www.sns.se/wp-content/uploads/2016/08/peter_nilsson_presentation.pdf

Overmier, J. B., & Murison, R. (2013). Restoring Psychology's Role in Peptic Ulcer. *Applied Psychology. Health and Well-Being*, *5*, 5–27.

Pan American Health Organization. (2020). *Assessment of Fetal Alcohol Spectrum Disorders: A training workbook.* S.l.: Pan American Health Organization.

Pantel, J. T., Hajjir, N., Danyel, M., Elsner, J., Abad-Perez, A. T., Hansen, P., … Mensah, M. A. (2020). Efficiency of Computer-Aided Facial Phenotyping (DeepGestalt) in Individuals With and Without a Genetic Syndrome: Diagnostic Accuracy Study. *Journal of Medical Internet Research*, *22*, e19263.

Parnell, S. E., Dehart, D. B., Wills, T. A., Chen, S.-Y., Hodge, C. W., Besheer, J., … Sulik, K. K. (2006). Maternal oral intake mouse model for fetal alcohol spectrum disorders: Ocular defects as a measure of effect. *Alcoholism, Clinical and Experimental Research*, *30*, 1791–1798.

Patterson, T., Rapsey, C. M., & Glue, P. (2013). Systematic review of cognitive development across childhood in Down syndrome: Implications for treatment interventions. *Journal of Intellectual Disability Research*, *57*, 306–318.

Petković, G., & Barišić, I. (2013). Prevalence of Fetal Alcohol Syndrome and Maternal Characteristics in a Sample of Schoolchildren from a Rural Province of Croatia. *International Journal of Environmental Research and Public Health*, *10*, 1547–1561.

Pettersson, E., Larsson, H., D'Onofrio, B. M., Bölte, S., & Lichtenstein, P. (2020). The general factor of psychopathology: A comparison with the general factor of intelligence with respect to magnitude and predictive validity. *World Psychiatry*, *19*, 206–213.

Popescu, R., Muntean, A., & Juffer, F. (2020). Adoption in Romania: Historical Perspectives and Recent Statistics. *Adoption Quarterly*, *23*, 1–26.

Popova, S., Lange, S., Probst, C., Gmel, G., & Rehm, J. (2017). Estimation of national, regional, and global prevalence of alcohol use during pregnancy and fetal alcohol syndrome: A systematic review and meta-analysis. *The Lancet Global Health*, *5*, e290–e299.

Rangmar, J., Hjern, A., Vinnerljung, B., Stromland, K., Aronson, M., & Fahlke, C. (2015). Psychosocial Outcomes of Fetal Alcohol Syndrome in Adulthood. *PEDIATRICS*, *135*, e52–e58.

Rasmussen, P., & Gillberg, C. (2000). Natural Outcome of ADHD With Developmental Coordination Disorder at Age 22 Years: A Controlled, Longitudinal, Community-Based Study. *Journal of the American Academy of Child & Adolescent Psychiatry*, *39*, 1424–1431.

Riksdagsförvaltningen. (2003). SFS 2003:460. Retrieved August 19, 2020, from https://www.riksdagen.se/sv/dokument-lagar/dokument/svensk-forfattningssamling/lag-2003460-om-etikprovning-av-forskning-som_sfs-2003-460

Roid, G., & Miller, L. (1997). Leiter International Performance Scale–Revised. *Wood Dale, IL: Stoelting*.

Rouquette, J. (1957). *Influence de I`intoxication alcoolique parentale sur le dévelopment physique et des jeune enfants* (Dissertation). Paris.

Rutter, M. (1998). Developmental Catch-up, and Deficit, Following Adoption after Severe Global Early Privation. *Journal of Child Psychology and Psychiatry*, *39*, 465–476.

Rutter, M., Andersen-Wood, L., Beckett, C., Bredenkamp, D., Castle, J., Groothues, C., … O'Connor, T. G. (1999). Quasi-autistic Patterns Following Severe Early Global Privation. *Journal of Child Psychology and Psychiatry*, *40*, 537–549.

Rutter, M., Sonuga-Barke, E. J., Beckett, C., Castle, J., Kreppner, J., Kumsta, R., … Gunnar, M. R. (2010). Deprivation-specific psychological patterns: Effects of institutional deprivation. *Monographs of the Society for Research in Child Development*, *75*, i–253.

SBU. (2016). *Fetalt alkoholsyndrom (FAS) och Fetala alkoholspektrumstörningar (FASD) – Tillstånd och insatser: En systematisk översikt och utvärdering ur ett socialt medicinskt, ekonomiskt och etiskt perspektiv* (SBU-rapport nr 258). Stockholm.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., … Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry*, *59 Suppl 20*, 22-33;quiz 34-57.

Shorter, E. (1998). *A History of Psychiatry: From the Era of the Asylum to the Age of Prozac* (1 edition). New York: Wiley.

Sibley, M. H., Arnold, L. E., Swanson, J. M., Hechtman, L. T., Kennedy, T. M., Owens, E., … Rohde, L. A. (2022). Variable Patterns of Remission From ADHD in the Multimodal Treatment Study of ADHD. *American Journal of Psychiatry*, *179*, 142–151.

Sibley, M. H., Rohde, L. A., Swanson, J. M., Hechtman, L. T., Molina, B. S. G., Mitchell, J. T., … for the Multimodal Treatment Study of Children with ADHD (MTA) Cooperative Group. (2018). Late-Onset ADHD Reconsidered With Comprehensive Repeated Assessments Between Ages 10 and 25. *American Journal of Psychiatry*, *175*, 140–149.

Sonuga-Barke, E. J. S., Kennedy, M., Kumsta, R., Knights, N., Golm, D., Rutter, M., … Kreppner, J. (2017). Child-to-adult neurodevelopmental and mental health trajectories after early life deprivation: The young

adult follow-up of the longitudinal English and Romanian Adoptees study. *The Lancet*, *389*, 1539–1548.
Spitzer, R. L., Endicott, J., & Robins, E. (1978). Research diagnostic criteria: Rationale and reliability. *Archives of General Psychiatry*, *35*, 773–782.
Spitzer, R. L., Forman, J. B., & Nee, J. (1979). DSM-III field trials: I. Initial interrater diagnostic reliability. *The American Journal of Psychiatry*, *136*, 815–817.
Spitzer, Robert L. (1983). Psychiatric diagnosis: Are clinicians still necessary? *Comprehensive Psychiatry*, *24*, 399–411.
Spohr, H.-L., Willms, J., & Steinhausen, H.-C. (2007). Fetal alcohol spectrum disorders in young adulthood. *The Journal of Pediatrics*, *150*, 175–179, 179.e1.
Statistics Sweden. (2014). *The entrance to the labour market among Upper secondary school leavers.* (Education Report 2014:7). Retrieved from https://www.scb.se/contentassets/3488dff639c84ac3b7ccde247e665301/uf0512_2014a01_br_a40br1407.pdf
Stevanovic, D., Knez, R., Zorcec, T., Anderluh, M., Kodrič, J., Petrov, P., … Gillberg, C. (2018). ESSENCE-Q: Slavic language versions for developmental screening in young children. *Neuropsychiatric Disease and Treatment*, *Volume 14*, 2141–2148.
Stormark, K. M., Heiervang, E., Heimann, M., Lundervold, A., & Gillberg, C. (2008). Predicting Nonresponse Bias from Teacher Ratings of Mental Health Problems in Primary School Children. *Journal of Abnormal Child Psychology*, *36*, 411–419.
Streissguth, A. P., Aase, J. M., Clarren, S. K., Randels, S. P., LaDue, R. A., & Smith, D. F. (1991). Fetal alcohol syndrome in adolescents and adults. *Jama*, *265*, 1961–1967.
Strömland, K. (1985). Ocular abnormalities in the fetal alcohol syndrome. *Acta Ophthalmologica. Supplement*, *171*, 1–50.
Taylor, M. J., Larsson, H., Gillberg, C., Lichtenstein, P., & Lundström, S. (2019). Investigating the childhood symptom profile of community-based individuals diagnosed with attention-deficit/hyperactivity disorder as adults. *Journal of Child Psychology and Psychiatry*, *60*, 259–266.
Thapar, A., Cooper, M., & Rutter, M. (2017). Neurodevelopmental disorders. *The Lancet Psychiatry*, *4*, 339–346.
Uddenberg, N. (2012). *Linné och mentalsjukdomarna: En kommenterad utgåva av Pehr Osbecks anteckningar om psykiatri under Linnés föreläsningar över temat Systema Morborum, läsåret 1746-1747*. Atlantis.
Valentine, M., Bihm, D. C. J., Wolf, L., Hoyme, H. E., May, P. A., Buckley, D., … Abdul-Rahman, O. A. (2017). Computer-Aided Recognition of

Facial Attributes for Fetal Alcohol Spectrum Disorders. *Pediatrics*, *140*, e20162028.

Vittinghoff, E. (Ed.). (2012). *Regression methods in biostatistics: Linear, logistic, survival, and repeated measures models* (2nd ed). New York: Springer.

Wade, M., Fox, N. A., Zeanah, C. H., & Nelson, C. A. (2018). Effect of Foster Care Intervention on Trajectories of General and Specific Psychopathology Among Children With Histories of Institutional Rearing: A Randomized Clinical Trial. *JAMA Psychiatry*, *75*, 1137–1145.

Walker, H. K. (1990). The Origins of the History and Physical Examination. In H. K. Walker, W. D. Hall, & J. W. Hurst (Eds.), *Clinical Methods: The History, Physical, and Laboratory Examinations* (3rd ed.). Boston: Butterworths.

Warren, K. R., & Hewitt, B. G. (2009). Fetal alcohol spectrum disorders: When science, medicine, public policy, and laws collide. *Developmental Disabilities Research Reviews*, *15*, 170–175.

Waterhouse, L., London, E., & Gillberg, C. (2016). ASD Validity. *Review Journal of Autism and Developmental Disorders*, *3*, 302–329.

Wender, P. H. (1973). Minimal Brain Dysfunction in Children: Diagnosis and Management. *Pediatric Clinics of North America*, *20*, 187–202.

Wester Oxelgren, U., Myrelid, Å., Annerén, G., Westerlund, J., Gustafsson, J., & Fernell, E. (2019). More severe intellectual disability found in teenagers compared to younger children with Down syndrome. *Acta Paediatrica*, *108*, 961–966.

What is harm reduction? (n.d.). Retrieved May 23, 2022, from Harm Reduction International website: https://www.hri.global/what-is-harm-reduction

Windsperger, K., & Hoehl, S. (2021). Development of Down Syndrome Research Over the Last Decades–What Healthcare and Education Professionals Need to Know. *Frontiers in Psychiatry*, *12*, 749046.

World Health Organization. (1978). *International classification of diseases* (9th revision). World Health Organization.

World Health Organization (Ed.). (1992). *The ICD-10 classification of mental and behavioural disorders: Clinical descriptions and diagnostic guidelines*. Geneva: World Health Organization.

World Health Organization. (2020). *International Classification of Diseases* (11th revision). Geneva: World Health Organization.

World Health Organization. (No date). *History of the development of the ICD*. World Health Organization.

Wynants, L. et al. (2021). Update to living systematic review on prediction models for diagnosis and prognosis of covid-19. *BMJ*, *372*, n236.