Intellectual Disability and coexisting Autism and ADHD in Down syndrome - a population-based study

ULRIKA WESTER OXELGREN
The thesis investigated associated neurodevelopmental/neuropsychiatric aspects in a population-based cohort of 60 children and adolescents (5–17 years) with Down syndrome (DS). Forty-one subjects were comprehensively assessed by a clinical research team; 17 (41%) and 14 (34%) met DSM criteria for autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD), respectively. Forty-nine subjects had a formal cognitive test and 11 had clinical assessments due to profound intellectual disability (ID). Mild ID (IQ 50–70) was found in 9% of the teenagers (13–18 years) and in 35% of the younger (5–12 years) children. Corresponding figures for severe ID (IQ <50) were 91% and 65%, respectively. The ID was more severe in individuals with coexisting ASD.

Levels and profiles of autistic symptoms, according to ADOS Module-1, were analysed. Children with DS and ASD, with different levels of ID, had significantly more symptoms within all autism domains, than those with DS only – a difference which remained when subgroups with severe ID were compared. A considerable proportion of subjects with DS had ASD in addition to ID, but there was a group with DS and severe ID without ASD. The autism profiles of children with DS and ASD were similar to those of children with idiopathic autism. The commonly used investigation tools used to diagnose ASD in the study, seemed to be appropriate in this patient group.

An intervention programme, including education for parents and school staff, adapted to the specific needs of schoolchildren with DS and ASD was performed and evaluated. Although the studied group comprised older children and adolescents, most of whom with severe or profound ID, they could achieve goals and skills previously not managed. In addition, the parents’ views on the intervention were encouraging.

In conclusion, there is a need of awareness of the increased prevalence of ASD and ADHD in children with DS. We suggest that screening for ASD and ADHD should be implemented for children with DS at the age of 3–5 years and at early school years, respectively. We also suggest that children with DS should be re-evaluated regarding level of ID before entering secondary school.

Keywords: Down syndrome, intellectual disability, autism spectrum disorder, attention-deficit/hyperactivity disorder, autism phenotype, autism intervention.
To the children and teenagers who participated in this study
List of Papers

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


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<th>Full Form</th>
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<tr>
<td>AAC</td>
<td>Augmentative Alternative Communication</td>
</tr>
<tr>
<td>ABA</td>
<td>Applied Behavioural Analysis</td>
</tr>
<tr>
<td>ABAS-II</td>
<td>Adaptive Behavior Assessment System-II</td>
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<tr>
<td>ADHD</td>
<td>Attention-Deficit/Hyperactivity Disorder</td>
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<tr>
<td>ADI-R</td>
<td>Autism Diagnostic Interview-Revised</td>
</tr>
<tr>
<td>ADOS</td>
<td>Autism Diagnostic Observation Schedule</td>
</tr>
<tr>
<td>ASD</td>
<td>Autism Spectrum Disorder</td>
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<tr>
<td>DISCO</td>
<td>Diagnostic Interview for Social and Communication Disorders</td>
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<td>DS</td>
<td>Down Syndrome</td>
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<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
</tr>
<tr>
<td>EIBI</td>
<td>Early Intensive Behavioral Intervention</td>
</tr>
<tr>
<td>ESSENCE</td>
<td>Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations</td>
</tr>
<tr>
<td>FSI</td>
<td>Family Strain Index</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International Classification of Diseases-10</td>
</tr>
<tr>
<td>ID</td>
<td>Intellectual Disability</td>
</tr>
<tr>
<td>IDD</td>
<td>Intellectual Developmental Disorder</td>
</tr>
<tr>
<td>IQ</td>
<td>Intelligence Quotient</td>
</tr>
<tr>
<td>PECS</td>
<td>Picture Exchange Communication System</td>
</tr>
<tr>
<td>SCQ</td>
<td>Social Communication Questionnaire</td>
</tr>
<tr>
<td>SDQ</td>
<td>Strengths and Difficulties Questionnaire</td>
</tr>
<tr>
<td>SNAP-IV</td>
<td>Swanson, Nolan, and Pelham-IV</td>
</tr>
<tr>
<td>TEACCH</td>
<td>Treatment and Education of Autistic and Communication related handicapped Children</td>
</tr>
<tr>
<td>VABS-II</td>
<td>Vineland Adaptive Behavior Scales-II</td>
</tr>
<tr>
<td>WISC-IV</td>
<td>Wechsler Intelligence Scales for Children-IV</td>
</tr>
<tr>
<td>WPPSI-III</td>
<td>Wechsler Preschool and Primary Scale of Intelligence-III</td>
</tr>
</tbody>
</table>
There is a specialized outpatient clinic for children with Down syndrome (DS) in Uppsala County. While working at this clinic for many years I have met all the children with DS in the county and I have had the opportunity to follow them from birth to adulthood. I have worked with excellent colleagues at the University Children’s Hospital and devoted professionals in the rehabilitation teams in our county. I have also had the opportunity to coordinate the work of the National medical guidelines for children with Down syndrome in Sweden.

In the clinical work, I have noticed that many children with DS, in addition to intellectual disability (ID), exhibit autistic symptoms, hyperactivity and impulsiveness. Searching for scientific literature, I was surprised to find that there were very few studies concerning the prevalences of autism and attention-deficit/hyperactivity disorder (ADHD) in DS and that very little was reported about intervention for these conditions in children with DS. In 2012, we therefore set out to study these additional disorders in a group of children with DS.

I am grateful to all the families taking part in our studies for giving me and the team a possibility to investigate these issues in detail.
Introduction

Down syndrome

![Figure 2. Girl with Down syndrome](image)

Down syndrome (DS) is named after John Langdon Down. He was the first clinician to identify this specific group of patients with common characteristics in 1866 and suggested that they were responsive to treatment.

In 1958, the French geneticist and paediatrician Jerome Lejeune and colleagues discovered that the syndrome was caused by a gene defect resulting in 47 chromosomes, with three copies of chromosome 21 rather than two, namely trisomy 21.¹ Down syndrome may emerge due to classic trisomy 21 (94%), unbalanced translocation (4%), mosaicism (2%) and partial trisomy 21 (<1%) where only a part of chromosome 21 is triplicated. In trisomy 21 mosaicism the clinical picture can vary depending on the actual percentage of trisomy in different organs. The phenotype of DS depends on gene dosage effects from specific genes on chromosome 21. In partial trisomy 21 the clinical picture depends on the triplicated part of the chromosome.

Genetics

A few defined sets of dosage sensitive key genes on chromosome 21 have been linked to the phenotypic characteristics in DS. Two genes (DYRK1A and RUNX1) on chromosome 21 appear to be important for the neurodevelopment and the trisomy of these genes seems to be responsible for the intellectual disability (ID) in DS.²³ Future research on these genes may lead to
better understanding of the neurodevelopmental problems in DS and hopefully in new therapies.

The DYRK1A gene encodes an enzyme that plays a role in neurodevelopment. Several studies point to a crucial role of DYRK1A protein for brain defects in patients with DS. DYRK1A inhibition in mouse models of DS has resulted in benefits including improvement in cognitive behaviour. A clinical trial has shown that a DYRK1A inhibitor given to young patients with DS improved visual recognition memory, working memory performance as well as adaptive behaviour.4-6

![Figure 3. Karyotype with trisomy 21](image)

Prevalence and trend for survival

Down syndrome is the most common single cause of ID and occurs in 12–14 per 10,000, or in about one per 800 live births in Sweden.7 The total number of pregnancies with DS has increased due to increased maternal age, but has so far been balanced by an increase of the number of terminations of pregnancies with trisomy 21.7,8

The life expectancy of children with DS is primarily dependent on the risk of mortality in the first year of life.8,9 The fall in mortality has mainly been related to the successful surgical treatment of congenital heart disease (CHD) and to the improved treatment of congenital anomalies of the gastrointestinal tract. Both mortality and morbidity in childhood could be reduced further, and in this respect respiratory infections and neonatal problems are the most important issues to be solved.

Median survival of individuals with DS has increased considerably resulting in an increase of the total population of individuals.10 The median age at
death in individuals with DS in the United States has risen from 25 years in 1983 to 49 years in 1997\(^1\), while the median age at death in Sweden is close to 60 years.\(^8\) The longer life expectancy requires medical care for individuals with DS over their total lifespan. In this context, the importance of national medical guidelines enabling a preventive health care programme should be emphasized, both for children and adults with DS.

**Associated medical conditions**

Down syndrome is associated with many prenatal and acquired medical conditions. Cardiac and other congenital anomalies are common in DS affecting almost every second child.\(^12\) There is also an increased risk of disorders related to the central nervous system such as infantile spasm, or West syndrome, which is the most common type of seizure in infants with DS.\(^13\) Children with DS are furthermore at increased risk of endocrine, metabolic and gastrointestinal disorders, e.g. coeliac disease. In addition, ear, nose and throat and eye problems are overrepresented in DS.\(^14\) Solid tumours and other types of cancer is, apart from childhood leukaemia, uncommon in DS.

Respiratory and cardiac problems as well as sleep disorders are good examples of conditions where advances in knowledge and treatment options relevant for children with DS have been seen during the last years.\(^15\)

Children with DS have an increased incidence of respiratory infections, including a 30% incidence of pneumonia and 10% will be hospitalised for respiratory syncytial virus bronchiolitis before the age of two years. The abnormal anatomy of the upper airways predisposes to upper respiratory infections, while hypotonia, tracheobronchomalacia, abnormalities in immunological function and increased pulmonary vascular reactivity predispose to lower respiratory tract infections.\(^16\)

Respiratory infections can also result from silent aspiration due to swallowing difficulties and gastroesophageal reflux (GERD). Aspiration and GERD should be treated, as should any comorbidity such as asthma. Since certain high-risk infants, such as those with complex congenital heart disease or those who are oxygen dependent, are at particular risk of severe RSV bronchiolitis and passive immunisation should be considered.\(^15\)

Pulmonary arterial hypertension is more common in DS than in the general population and is often caused by the presence of a cardiac left-to-right shunt and chronic upper airway obstruction.\(^16\)

Children with DS have an increased risk of obstructive sleep apnoea syndrome, affecting 30-50%.\(^16\) Because of the high prevalence of asymptomatic airways obstructive disease (OSAS) and the risks of developing irreversible pulmonary arterial hypertension, routine sleep studies in children with DS, even in those without symptomatic airway disease, is recommended. A sleep
study or polysomnogram continues to be the criterion standard test for evaluation of sleep-disorder breathing and OSAS. However, this is still difficult to implement.

Infantile spasm, also known as West syndrome, is a severe epileptic syndrome with early onset and increased risk of cognitive disability. This is the most common type of epilepsy in infants with DS, and it has also been reported to be more prevalent among children with DS compared to children in general. In adulthood, there is a risk of early development of Alzheimer disease.

Hypothyroidism is common in DS and the risk of developing thyroid dysfunction increases with age. Congenital hypothyroidism occurs in 1/100 children with DS, representing 30-fold increase compared to other newborns, and acquired hypothyroidism occurs in 20-30% of children and in 50% of adults with DS. The thyroid gland in DS is known to be vulnerable to autoimmune diseases such as Hashimoto thyroiditis and more rarely Graves’ disease. The general opinion is that screening for thyroid dysfunction should be performed every 1-2 years throughout life.

The majority of individuals with DS will experience impaired hearing some time in life. Hearing losses may be conductive (such as in case of otitis media with effusion occurring in up to 90% of children with DS before one year of age), sensorineural (6% in newborn screening) or mixed. Since hearing is very important for development, particular as far as language is concerned, a hearing screening programme is recommended.

Ocular abnormalities which may have impact on visual function are found in up to 60% of subjects with Down syndrome. Congenital cataract is seen in 1.4% in DS and warrants neonatal screening. Refractive errors are common and regular eye examinations should continue through life.

National Medical Guidelines
The complex medical situation for children with DS has resulted in medical guidelines to meet the extensive medical needs of this group of patients. The first Swedish national medical guidelines were presented in 1995 fifteen years prior to the US guidelines “Health supervision for children with Down syndrome”. New national medical guidelines from the Swedish Neuropediatric Society were published in 2013 and the 4th revised version in 2017.

Medical conditions in relation to cognitive outcome
Theoretically, medical conditions, associated with DS, could affect the neurodevelopment of the child. The impact of congenital heart disease (CHD) on intellectual, cognitive, and learning deficits in children with DS was studied by Alsaeed et al, who reported that infants/toddlers with cardiac surgery had lower scores for language compared to those without CHD. However, at
school age there were no differences in intelligence quotient (IQ) scores or language scores nor in the incidence of ADHD.\textsuperscript{25}

The possible role of birth defects requiring early surgery has been studied in children with DS. However, no evidence of an association between such defects and a poor outcome regarding cognitive function and behaviour could be found.\textsuperscript{26}

On the other hand, a follow-up study of children with DS and infantile spasm demonstrated significantly lower scores in domains measuring cognitive, motor, and language functions.\textsuperscript{27}

**Intellectual disability**

Intellectual disability (ID) implies deficits in abstract, theoretical thinking, i.e. deficits in problem solving, reasoning and learning entailing difficulties to cope with daily life situations. The prevalence of ID all severities has been reported to be about 2\% in the general population in the Nordic countries.\textsuperscript{28-30}

The Diagnostic and statistical manual of mental disorders (DSM)\textsuperscript{31-33} is the standard classification system of mental disorders used by mental health professionals in United States and many other countries. It is applied in clinical settings as well as in research on clinical and community populations, and it is also used for collecting public-health statistics.

Mental retardation is, in DSM-IV, characterized by significantly impaired intellectual (IQ<70) and adaptive functioning and onset of symptoms before age of 18 years.\textsuperscript{32} The terminology was changed to Intellectual disability/Intellectual Developmental Disorder (ID/IDD), when DSM-5 was published in 2013, and is defined as an IQ<70±5 in addition to deficits in adaptive functioning that without ongoing support will affect activities of daily life\textsuperscript{33}.

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**Figure 4.** Normal distribution of IQ and the levels of intellectual disability
Diagnostic examination starts with a thorough neuropaediatric assessment, which is followed by cognitive tests to evaluate the intellectual function in detail. The Wechsler preschool and primary scale of intelligence\textsuperscript{34} (WPPSI) and the Wechsler intelligence scale for children\textsuperscript{35} (WISC) are widely used in clinical practice by psychologists for the assessment of specific and general cognitive abilities. Both yields information of general cognition based on full-scale IQ as an index of overall intelligence including verbal and performance IQ.\textsuperscript{34,35}

While intelligence reflects the maximum performance, adaptive behaviour refers to typical performance in everyday – behaviours that are possible to influence to a certain degree by training. Adaptive function includes communication, daily living skills, social and motor skills necessary for everyday function. The instrument Vineland Adaptive Behavior Scales-II\textsuperscript{36} (VABS-II) is often used to measure these skills. Another instrument for evaluating adaptive behaviour is the Adaptive Behavior Assessment System-II\textsuperscript{37} (ABAS-II). VABS-II is used from infancy and onwards, ABAS-II only from 5 to 21 years of age.

Assessment of adaptive functioning is an important complement to cognitive testing to determine a person’s all-around functioning in everyday life. In the general population adaptive behaviour and IQ are highly correlated.\textsuperscript{38} Individuals with ASD, however, are not acquiring skills in these areas at a pace consistent with chronological development or intellectual growth. IQ has been found to be a strong predictor of adaptive behaviour, although the gap between IQ and adaptive ability has been observed to decrease in the more cognitively impaired individuals compared to otherwise “high functioning” individuals with ASD.\textsuperscript{39,40} Deficits in both intellectual functioning and adaptive behaviour are central to intellectual disability.

Table 1. Definition of mental retardation according to DSM-IV. Throughout this thesis the terminology used is intellectual disability.

<table>
<thead>
<tr>
<th>Intellectual disability</th>
<th>A</th>
<th>Significant subaverage intellectual functioning: an IQ of approximately 70 or below on an individually administered IQ test</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Concurrent deficits or impairments in present adaptive functioning in at least two of the following areas: communication, self-care, home living, social/interpersonal skills, use of community resources, self-direction, functional academic skills, work, leisure, health, and safety.</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>The onset is before age 18 years.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Code based on degree of severity reflecting level of intellectual impairment</th>
<th>Mild ID</th>
<th>IQ level 50-55 to approximately 70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate ID</td>
<td>IQ level 35-40 to 50-55</td>
<td></td>
</tr>
<tr>
<td>Severe ID</td>
<td>IQ level 20-25 to 35-40</td>
<td></td>
</tr>
<tr>
<td>Profound ID</td>
<td>IQ level below 20 or 25</td>
<td></td>
</tr>
</tbody>
</table>
Intellectual disability in Down syndrome

Intellectual disability\(^3\) (i.e. mental retardation according to DSM-IV) is a cardinal feature of DS\(^4\) and is invariably diagnosed in individuals with DS. However, there are single cases with intelligence within the lower normal variation when tested before start of school. The developmental impairment results in a mean IQ of about 60 and a range from 25-70 in preschool-children with DS. For children with DS of school age a decline of IQ across time has been reported.\(^4\)\(^1\)-\(^4\)\(^5\)

The ID in DS is mainly a consequence of functional and developmental brain disturbances. In addition to ID many children with DS display other neurodevelopmental disorders, particularly ASD\(^4\)\(^6\),\(^4\)\(^7\) and ADHD.\(^4\)\(^8\),\(^4\)\(^9\). Moreover, children with DS have delays across different developmental domains including language, gross motor, fine motor, cognitive, personal-social and self-help skills.\(^5\)\(^0\)

Intellectual development in children with DS proceeds at a slower rate than that in typically developing children, leading to a progressively widening disparity in age-related performance.\(^4\)\(^1\),\(^4\)\(^5\)

Better understanding of the trajectory of cognitive development in children with DS may lead to the design of more effective interventions.\(^4\)\(^1\)

Autism spectrum disorder

Autism spectrum disorder is a group of neurodevelopmental/neuropsychiatric disorders characterized by impaired social communication and restricted behaviours and interests. The clinical presentations are very heterogeneous, depending on the severity of the ASD per se, on associated neurodevelopmental/neuropsychiatric disorders and on underlying medical disorders.\(^5\)\(^1\),\(^5\)\(^2\). In addition to the core symptoms, most individuals with ASD also display other impairments, such as intellectual/learning problems and attention and activity regulation deficits. Clinical presentations vary from severe multi-impairments with ID to high-functioning individuals with IQ within the “normal distribution”.\(^5\)\(^2\) There is a significant overlap with other neurodevelopmental disorders, such as ID, speech and language impairment, ADHD and epilepsy illustrating that co-existence of disorders is the rule rather than the exception.

The prevalence of ASD in children is currently reported to be around 1% in the general population.\(^5\)\(^3\) In individuals with ID the prevalence of ASD has been reported to be as high as 40%.\(^4\)\(^4\) Rates of ASD are generally reported to be higher in males than in females; about 4:1 in population cohorts. The highest sex-ratios have been reported in so called high-functioning ASD, i.e. those without ID. In children with ASD and ID the ratio is about 2:1.\(^5\)\(^4\)-\(^5\)\(^9\)

The term infantile autism\(^6\)\(^0\) was introduced in the DSM-III\(^3\)\(^1\), substituted by autistic disorder in the following DSM-III-R and DSM-IV\(^3\)\(^2\), and recently, in
the DSM-5, changed to autism spectrum disorder. The autism criteria set in the DSM-IV are based on the triad of symptoms concerning qualitative impairment in A1) social interaction, A2) qualitative impairments in communication and A3) restricted repetitive and stereotyped patterns of behaviour, interests and activities. B) Delays or abnormal functioning in at least one of these areas should have had its onset prior to age three years. The diagnostic criteria can be seen in Table 2.

One single umbrella term, ASD, was introduced with the publication of DSM-5. The DSM-5 also requires specification of additional information including severity level of ASD, level of adaptive functioning, and occurrences of intellectual disability.

The other widely used manual for ASD classification is the International Classification of Diseases, ICD, published by the World Health Organization (WHO). Currently the ICD-10 is in use, with ASD subcategories resembling those of the DSM-IV.

**Autism spectrum disorder – Diagnostic assessments**

The neuropaediatric assessment is supplemented with structured interviews, developed to improve reliability and validity in the diagnostic process of autism. Examples of these are the Autism diagnostic interview-revised (ADI-R) or the Diagnostic interview for social and communication disorders (DISCO), both focusing on neurodevelopmental/neuropsychiatric symptoms. Autism diagnostic observation schedule (ADOS) is a frequently used observational instrument to complete the assessment. To assess the child’s adaptive function, a structured interview according to the VABS-II or ABAS-II is often used.

**Table 2.** Definition of autistic disorder according to DSM-IV in short. Throughout this thesis the terminology used is autism spectrum disorder.

<table>
<thead>
<tr>
<th><strong>Autism spectrum disorder</strong></th>
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<tr>
<td><strong>A</strong></td>
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<tr>
<td></td>
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<tr>
<td></td>
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<tr>
<td><strong>B</strong></td>
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<tr>
<td><strong>C</strong></td>
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</tbody>
</table>
Intellectual disability and autism spectrum disorder

Matson and Shoemaker (2009)\textsuperscript{46} pointed out that ID and ASD co-vary at high rates and that a greater severity of one of these two disorders appears to have effects on the other disorder. In the 1980s the percentage of ID in children with ASD was estimated to be 70-90\%.\textsuperscript{66} Today, considering the total ASD spectrum, including an increasing number of “high-functioning” children with ASD, the rate of ID in children with diagnosed ASD can be estimated to about 15-25\% at school age. However, at preschool age the corresponding rate would probably be about 50\%.\textsuperscript{67} There is a close relation between ID and ASD, and when one of these impairments is severe the other is likewise affected.\textsuperscript{46,52} It has also been demonstrated that the severity of ASD and challenging behaviours escalates when IQ decreases.\textsuperscript{46}

Autism spectrum disorder in Down syndrome

It has often been claimed that individuals with DS display an affectionate and social personality. Even so, when screening to identify ASD it has been reported that ASD is more common in individuals with DS, with varying rates up to over 30\%.\textsuperscript{12,68-72} Two population-based studies have been performed using screening-instruments and interviews reporting a prevalence 10-20\%.\textsuperscript{42,73} It has been suggested that the increased frequency of ASD in DS should motivate larger epidemiological studies.\textsuperscript{73-75}

Rasmussen et al\textsuperscript{72} studied several medical factors in a clinically based sample including 25 individuals, age range 4 to 33 years, with DS and ASD. The subjects had been referred for assessment due to suspected ASD and all met the criteria according to DSM-III-R\textsuperscript{31} or DSM-IV\textsuperscript{32}. It was pointed out that ASD should always be considered as a comorbid disorder in patients with DS and that the diagnosis of ASD was delayed when compared to children without DS.

Moss et al\textsuperscript{74} studied individuals with DS and found that 19\% met criteria for ASD. They concluded that individuals with DS and ASD had broad similarities to those with idiopathic ASD regarding autistic and behavioural characteristics; however, subjects with DS tended to be less withdrawn.

In a report by Warner et al\textsuperscript{75} the profiles of autism symptoms in children with DS were analysed and compared to those of children with ASD but without DS. Profiles of autistic symptoms in the two groups were similar, however children with DS and ASD tended to have milder social difficulties but similar profiles of communication and repetitive behaviour.
Attention-Deficit/Hyperactivity Disorder

Attention-deficit/hyperactivity disorder, characterized by either inattention or hyperactivity-impulsivity or both, has been reported to occur in 5-7% of children in general\textsuperscript{76} and in up to 44\% in children with DS\textsuperscript{48}. The DSM-IV states that there should have been a certain number of symptoms from each category that have persisted for at least six months and to a degree that is maladaptive as well as inconsistent with developmental level. Moreover, some symptoms should have appeared before the age of seven years (this age level has been changed in DSM-5 to 12 years) and present in two or more settings (such as school, home or recreational activities). The main cognitive deficit in ADHD is impaired executive functions. Attention-deficit/hyperactivity disorder is categorised into three types; ADHD combined type, ADHD predominantly inattentive type or ADHD predominantly hyperactive-impulsive type. A correlation between intellectual level and executive function has been demonstrated; when intellectual level declines, executive problems increase\textsuperscript{77}.

Table 3. Definition of Attention-deficit/hyperactivity disorder according to DSM-IV in short.

<table>
<thead>
<tr>
<th>A</th>
<th>Either 1 or 2, or both</th>
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<tbody>
<tr>
<td></td>
<td>1. <strong>Inattention</strong>: six (or more) defined symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level</td>
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<tr>
<td></td>
<td>2. <strong>Hyperactivity-Impulsivity</strong>: six (or more) defined symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level.</td>
</tr>
<tr>
<td>B</td>
<td>Some symptoms that caused impairment present before 7 years of age</td>
</tr>
<tr>
<td>C</td>
<td>Some impairment is present in two or more settings</td>
</tr>
<tr>
<td>D</td>
<td>Clear evidence of clinically significant impairment</td>
</tr>
<tr>
<td>E</td>
<td>The symptoms do not occur exclusively during the course of, and are not better accounted for by, another mental disorder</td>
</tr>
</tbody>
</table>

Attention-deficit/hyperactivity disorder in Down syndrome

There are reports on prevalence of ADHD in DS with results varying between 14 and 43\%.\textsuperscript{48} In the assessment process of ADHD in children with DS it is important to consider that visual and hearing impairment, obstructive sleep apnoea syndrome and thyroid disease are associated with DS and may mimic symptoms of ADHD.
Other neurodevelopmental/neuropsychiatric disorders in Down syndrome

In addition to ID, ASD and ADHD there are also other neurodevelopmental/neuropsychiatric disorders that may occur in children with DS. Conduct disorder appears in more than 10%; however, the prevalence is lower than that in other groups with ID.\(^78^,79\) The prevalence of depression in DS has been reported to be around 11% and the most common symptom to be loss of interest.\(^79\) It has been suggested that 10-22% of the individuals with DS have met diagnostic criteria for anxiety disorder\(^79\); i.e. a rate higher than that in the general population. The prevalence of obsessive-compulsive disorder (OCD) in DS has been found to be comparable to that of the general population, around 3.5%.\(^79\) No increased risk of bipolar disorder has been reported in DS. Acute regression has been reported to occur in children and adolescents with DS. The regression occurs regardless of cognitive level and includes loss of independence in activities of daily living, language deterioration and loss of cognitive skills. In the study by Mirches et al\(^80\), all patients had experienced severe emotional stress prior to regression.\(^80\) Catatonia in DS has also been reported.\(^79,81\) A decline, termed Down syndrome disintegrative disorder, with cognitive deterioration featuring autistic characteristics and catatonia, has recently been recognized in young adults with DS. In this group, symptoms were reported to improve after immunotherapy.\(^82\)

Behavioural phenotype

The concept of behavioural phenotype was introduced by Nyhan\(^83\), in 1972 when describing the Lesch-Nyhan syndrome as an identifiable biological disorder with behavioural features. Flint and Yule\(^84\) proposed a definition of behavioural phenotype in 1994: “The behavioural phenotype is a characteristic pattern of motor, cognitive, linguistic and social abnormalities which is consistently associated with a biological disorder.” It has been suggested that delineation of a behavioural phenotype could be the first step towards the molecular characterization of behaviour.\(^85\) Autism spectrum disorder is increasingly reported in syndromes with genetic origin\(^52,86-92\) and autism symptoms in specific syndromes have been analysed in order to reveal a distinct profile, i.e. an autism phenotype.
Intervention

Interventions in intellectual disability in childhood

In Sweden, children with DS are assessed with a cognitive test at the age of 5 to 6 years, before they start school. When there is a clear ID the child is entitled to attend the special school for children with ID. When test results and the child’s adaptive functioning indicate a mild ID or borderline intellectual functioning the parents may choose to let their child start off in a mainstream school.

Communication and speech impairments are important parts in the cognitive impairment in DS and a main target for intervention. Augmentative and alternative communication (AAC) refers to the use of non-vocal communication systems. The AAC systems are recommended for individuals who either have unintelligible or limited speech abilities, or who lack speech altogether. Individuals with disorders that affect the functional use of speech, and therefore may be more likely to use AAC, include those with a variety of developmental disabilities such as ID and ASD. The most obvious role is to provide a way to communicate. The AAC can also be used to augment existing speech and to replace or mitigate problem behaviours, such as screaming or hitting, with an alternative mean of communication. A frequently used method for training of communication for children without verbal language is the Picture exchange communication system (PECS).

Figure 5. Augmentative alternative communication with PECS
To adequately measure whether an intervention aimed at enhancing cognitive/communicative functions in children with DS is effective, (irrespective of whether the intervention is pharmacological or educational) the typical age-related changes in cognitive functioning – across multiple domains – need to be considered. In this way, the effects of treatment versus the effects of age-related developmental changes can be differentiated. The use of specific standardized neuropsychological tests that have a sufficiently low baseline to eradicate floor effects would allow for more precise evaluations of the effects of interventions.

Autism intervention in childhood

It is important to identify developmental disorders, including autism, early in order to inform parents and staff in the preschool setting about basic cognitive problems of the child. Diagnosis and information are often major components of good treatment. Earlier diagnosis creates opportunities for children with autism spectrum disorder to benefit more fully from intervention. Intervention should be performed to improve the situation of the child and family rather than to cure the underlying disorder.52,96-99

The specific social, communicative and behavioural impairments that characterize ASD require special approaches when it comes to intervention.52,100-103 It has been recognised since the 1970s that structured educational programmes is one of the most important aspects of successful treatment of children with ASD.104 Treatment and education of autistic and communication related handicapped children (TEACCH) is an example of a highly structured and visually based program developed by Schopler and colleagues105 at the University of North Carolina. The program includes a series of cognitive, developmental, educational and behavioural strategies to create highly individualized curricula and visual work systems and has been especially valuable for children with lower intellectual function.

Figure 6. Girl with Down syndrome working with the communication aid together with her father
The techniques based on Applied behavioural analysis (ABA) was developed by Lovaas in the 1960s to systematically change non-functional behaviours\textsuperscript{105} and it is now often referred to as Early intensive behavioral intervention\textsuperscript{106} (EIBI), to emphasize intensity. There has been a clear trend towards merging ABA and behavioural interventions that utilize more “naturalistic” approaches, such as the Early start Denver model\textsuperscript{100}, implemented in the child’s natural settings to teach developmentally appropriate and prerequisite skills\textsuperscript{107-109}. Applied behavioural analysis has been modified for the Swedish habilitation organization.\textsuperscript{110,111} The main principle for ABA is to reduce negative and enhance positive behaviours as well as to achieve new skills. An important goal is to focus not only on the child itself but also on the child in interaction with the environment. Problematic behaviours are often understood as a lack of ability to communicate. A way of reducing the negative behaviour (e.g. head-banging, screaming) is to find adequate methods for communication.

A higher cognitive level and acquisition of speech before five to six years of age have been found to be associated with better outcomes in children with ASD, for example regarding adaptive skills.\textsuperscript{67,112-114} The importance of IQ for outcome has also been demonstrated in follow-up studies of preschool children.\textsuperscript{114-116} The degree of autism may not be crucial for outcome, but coexisting conditions (i.e. ID, ADHD, epilepsy) influence outcome.\textsuperscript{117-120}

Information to parents about diagnosis, prognosis and how to help to develop skills or to compensate for communicative, cognitive and behavioural deficits, are included in almost all intervention programmes aimed for children with ASD. Parents may also need education on how to cope with challenging behaviour.

**Autism intervention in adolescents with intellectual disability and ASD**

Social skills are important for individuals with ASD across the lifespan. Walton and Ingersoll\textsuperscript{121} reviewed specific interventions with the aim to improve social skills in adolescents with ASD combined with severe or profound ID. They reported that studies in the field were associated with significant challenges regarding research design and methodology.\textsuperscript{121} Individuals with ASD and ID tended to display fewer positive verbal and nonverbal social skills and more challenging nonverbal social behaviours than those with a similar level of ID without ASD.\textsuperscript{121} Individuals with ASD and ID also displayed higher rates of problem behaviours than those with ID alone. The differences in challenging behaviours between individuals with ASD and ID and those with ID only demonstrate that those with ASD and ID have unique needs. Consequently, they may not be well served by existing intervention programmes designed for individuals with ID only.\textsuperscript{121}
Walton et al.\textsuperscript{121} proposed a developmental framework of adapting early childhood interventions for use with youth and adults with ASD and severe/profound ID. One example would be the naturalistic behavioural interventions, successfully used to promote social skills in young children with ASD and ID.\textsuperscript{121}
Aim

The aim of the thesis was to investigate the neurodevelopmental/neuropsychiatric aspects of DS in a population-based cohort of children and adolescents, 5-17 years of age at time of inclusion.

The specific aims were

…to investigate the prevalence of ASD and ADHD in subjects with DS

…to investigate levels and profiles of ID in relation to age, gender and co-occurring ASD and/or ADHD

…to describe the autism phenotype in children with DS and ASD

…to evaluate the effects of a psycho-educational intervention in subjects with DS and ASD
Subjects and Methods

The study was performed in the county of Uppsala with around 350 000 inhabitants. All children with DS living in the county have their medical service at a specialized outpatient clinic at Uppsala University Children’s Hospital, in close collaboration with the rehabilitation teams of Uppsala County. All patients with DS are followed according to the national medical guidelines for DS in Sweden. These guidelines are in good agreement with those from the United States.

Medical records of the children who did not take part in the studies were reviewed by the responsible neuropaediatrician. The team, consisting of one neuropaediatrician, two neuropsychologists, one special-teacher and two paediatric nurses, conducted all assessments. Paediatric records of the subjects were reviewed regarding perinatal and neonatal data, growth, medical disorders, visual and hearing status, as well as previously recognized and diagnosed neurodevelopmental/neuropsychiatric disorders. All children had been subjected to a medical work-up according to the national care programme for DS during the year preceding the study. An overview of all subjects participating in the studies is presented in Table 4.

Table 4. Study group and methods used in study I-IV

<table>
<thead>
<tr>
<th></th>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
<th>Study IV</th>
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<tbody>
<tr>
<td>Object of study</td>
<td>Prevalences of ASD/ADHD</td>
<td>Level of ID</td>
<td>Autism phenotype</td>
<td>Autism intervention</td>
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<tr>
<td>Target group n=60</td>
<td></td>
<td>n=60</td>
<td>n=17</td>
<td>n=17</td>
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<tr>
<td>Study group n=41</td>
<td></td>
<td>n=60</td>
<td>n=17</td>
<td>n=14</td>
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<tr>
<td>Methods for assessment</td>
<td>ADI-R</td>
<td>WPPSI-III</td>
<td>ADOS</td>
<td>Goal achievement</td>
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<tr>
<td></td>
<td>ADOS</td>
<td>WISC-IV</td>
<td>VABS-II</td>
<td>Parental report</td>
</tr>
<tr>
<td></td>
<td>WPPSI-III</td>
<td>ABAS-II</td>
<td>Leiter-R*</td>
<td>FSI</td>
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<tr>
<td></td>
<td>WISC-IV</td>
<td>VABS-II</td>
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<td></td>
<td>ABAS-II</td>
<td>SNAP-IV</td>
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<td></td>
<td>VABS-II</td>
<td>SCQ</td>
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*) Leiter-R had been used for one child
The study cohort

A population-based cohort of 60 children and adolescents with Down syndrome, aged 5-17 years and living in Uppsala County, constituted the study group. Forty-one individuals (29 M, 12 F; mean age 11 years) for whom parents gave consent for participation were clinically assessed regarding ASD and ADHD and the level of ID (Paper I). At the time of the cognitive assessment, three subjects had turned 18 years. In 21 subjects (14 M, 7 F), a cognitive test had been performed less than three years earlier and this group was not re-tested. Twenty children (15 M, 5 F) were tested within the study by the neuropsychologist in the team. The remaining 19 children (12 M, 7 F) did not take part in the ASD-ADHD assessment. Instead, the cognitive tests performed before school-start (at the age of 6 years) were reviewed (Paper II).

The children were evenly distributed across the age-span; 29 were 5-12 years old and 31 were teenagers, 13-18 years old. The M/F ratio in the total group was 2.2:1.

All children with ASD were analysed regarding data on degree of autism-symptoms and the results were compared to those of the children with DS but without ASD and to those of a normative group of children with ASD from the ADOS test manual (Paper III). Finally, of the 17 children who obtained a diagnosis of ASD at the assessment, 14 children took part in an intervention targeting social/communication and daily activity skills (Paper IV).

![Figure 7. Flowchart demonstrating the inclusion procedure and groups of investigation for the study I–IV](image-url)
Paper I – Prevalence study

Of the 60 subjects with DS, aged 5-17 years, 41 participated in the ASD and ADHD prevalence study. Six children did not complete the investigation and 13 families declined participation. The prevalence’s of ASD and ADHD were investigated, and the results were related to the level of ID and to medical factors. The assessments included questionnaires to parents and teachers, a structured interview with the parents as well as an observation and examination of the child. Several questionnaires and diagnostic tools were used.

Strengths and Difficulties Questionnaire (SDQ) was completed by both parents and teachers. The psychometric properties of the SDQ parent form have been evaluated and good internal consistency has been found. SDQ has been used for children with ID123 and adults with DS.124

SNAP-IV Rating Scale125 is a screening tool for ADHD and includes the items according to DSM-IV32 and DSM-5.33 SNAP-IV was completed by parents as well as teachers.

Social Communication Questionnaire (SCQ) is a parent-report questionnaire that identifies symptoms associated with ASD.126

Autism Diagnostic Interview-Revised (ADI-R), is a semi-structured, investigator-based interview, aimed for caregivers of children for whom autism or pervasive developmental disorders are possible diagnoses.127 The instrument has been reported to have a good reliability.62

A structured observation of the child with a video-camera was performed. The child’s performance was scored according to the Autism Diagnostic Observation Schedule (ADOS), which is a semi-structured observation for individuals suspected of having autism.64

All results of SDQ and SNAP-IV were analysed by a neuropaediatrician and a paediatric nurse. Diagnosis of ADHD was based on results from SDQ, SNAP-IV and the clinical assessment. The child’s cognitive level was taken into account when diagnostic criteria were evaluated in accordance with DSM-IV and DSM-5. ADI-R and ADOS assessments were performed by a child-neuropsychologist and a special-teacher, both well-experienced in the field. The child was also assessed by the neuropaediatrician and paediatric nurse to include other neurodevelopmental and medical aspects. DSM-IV and DSM-5 criteria for ASD were assessed with regard to the child’s cognitive level. The child had to meet both ADI-R and ADOS criteria, DSM IV/DSM-5 criteria and the team’s conjoint clinical assessment in order to be diagnosed with ASD.

Paper II – Intellectual disability study

The assessment included all 60 children of the population-based cohort. Intellectual disability was defined according to DSM-IV, which was used at study start. Scientific reports often use the classification by the American Academy
of Mental Retardation\textsuperscript{128}, i.e. mild ID IQ 50-70 and severe ID IQ<50 (see Table 5). These two categories were used in the main evaluations.

The major part of the children (n=41) had their cognitive testing performed with \textit{Wechsler Preschool and Primary Scale of Intelligence}\textsuperscript{34} (WPPSI-III). WPPSI-III is recommended for children with a mental age >2.5 years and provides a full scale IQ, verbal IQ and performance IQ. It has been established that WPPSI-III can be used for older children with intellectual disability.\textsuperscript{129,130} Seven children were tested with Wechsler Intelligence Scales for Children-IV (WISC-IV),\textsuperscript{35} one with Leiter-R test\textsuperscript{131} and 11 children were clinically assessed by a special-teacher without formal testing due to profound ID.

\textit{Adaptive Behavior Assessment System-II} (ABAS-II)\textsuperscript{37} and \textit{Vineland Adaptive Behavior Scales-II} (VABS-II)\textsuperscript{36} were used for assessment of adaptive functions. The psychologists at the local rehabilitation centres in the county commonly use ABAS-II. The ABAS-II is a validated questionnaire and provides norm-referenced standard scores for three domains: conceptual domain, social domain and practical domain and a merged score – general adaptive composite (GAC).

Within this study ABAS-II was supplemented with VABS-II as many subjects were at such a low level of functioning that it was assumed they would be at floor level in the ABAS-II test. The Vineland Adaptive Behavior Scales (VABS-II) yields a composite score and four domain scores: communication, daily living skills, socialization and motor skills (younger children).

A tested IQ-value could be obtained in 33 children and in another 16, it was only possible to decide the broader level of ID (mild, moderate, severe or profound). The remaining 11 subjects had such a low level of function that it was not possible to perform a cognitive test, but these children had been considered to have profound ID by clinical examination. Thus, a level of ID was obtained for all 60 children in the cohort. In the main analysis, ID was classified into mild (IQ 50-70) or severe (IQ <50).\textsuperscript{128} In the analyses comparing two assessments at different ages in the same child, the DSM-IV classification was used; mild (IQ 50-70), moderate (IQ 35-50), severe (IQ 20-35) and profound (IQ <20).\textsuperscript{32}

\textbf{Table 5.} The differences in terminology regarding intellectual disability in DSM-IV and AAMR

<table>
<thead>
<tr>
<th>DSM-IV</th>
<th>AAMR</th>
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<tr>
<td>Mild</td>
<td>55 to 69</td>
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<tr>
<td>Moderate</td>
<td>40 to 54</td>
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<tr>
<td>Severe</td>
<td>25 to 39</td>
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<tr>
<td>Profound</td>
<td>&lt;24</td>
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<tr>
<td>Mild</td>
<td>51 to 75</td>
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<tr>
<td>Severe</td>
<td>&lt;50</td>
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32
Paper III – Autism phenotype study

The autism assessment included observation according to ADOS\textsuperscript{64}. There are four major domains in ADOS Module-1; verbal and nonverbal communication (A), reciprocal social interaction (B), play (C) and stereotyped behaviour and restricted interests (D). The diagnostic algorithm for autism includes the domains of A, B and D which are the domains used in the study.

Forty-one subjects had been assessed within the ASD and ADHD prevalence study which revealed that 17 (41\%) had ASD and 14 of those had severe/profound ID.\textsuperscript{132} Six (25\%) children among those without ASD had severe/profound ID.

Profiles of autistic symptoms in the children assessed with ADOS Module-1 (15 children with ASD, 12 children without ASD) were compared (comparison A, fig 8). Furthermore, the profiles of autistic symptoms in the children with severe/profound ID, with or without ASD, were compared (comparison B, fig 8). Additionally, children with DS and ASD assessed with Module-1 were compared with the reference group of children with idiopathic autism available in the ADOS manual Module-1 (comparison C, fig 8).

Paper IV – Intervention study

Parents of the 17 subjects, diagnosed with ASD after assessment within the ASD and ADHD prevalence study were asked if they wanted to participate with their child in the intervention study. A targeted intervention was performed in which 14 of the subjects with DS and ASD from study I, (age range
6-18 years, median 13.0 years) participated. Three subjects could not participate; one due to severe behavioural problems for which an individualized intervention had already been initiated, one family moved from the county and the parents of the third patient did not respond to the invitation. The sex ratio of the participating 14 children was M:F=10:4. Eleven of the 14 participants had severe/profound, two had moderate and one had mild ID. Seven subjects had no verbal speech and the remaining seven had major communication difficulties using picture communication aids as alternative means of expressing themselves. All participants had very few activities outside school.

Parents of the 14 children were offered to participate with their child in a comprehensive psychoeducational intervention programme, based on ABA principles but modified and adapted for the group of children and teenagers with DS, ASD and mostly severe/profound ID. Communication and leisure activities were the main focus of the intervention. The intervention aimed to improve social skills and communication abilities of the children and, as a very important part, the intervention also provided an education programme to parents and teachers.

The programme included information to parents and preschool/school staff about the cognitive and behavioural deficits that underlie and characterize ASD and about specific interventions for the disorder.

Table 6. The information and preparation phase comprised six steps.

<table>
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<tr>
<th>Intervention programme</th>
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<td>5</td>
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<td>6</td>
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</table>

In the preparation and training phase, the parents and staff chose 1-2 communication tasks and 1-2 physical tasks for their child to train. These tasks had not been managed by the child before start of the intervention. The goals were set with guidance from the professionals. Thereafter, the child’s training
started at home and in school in order to achieve the goals. After a training period of three months, there was an evaluation of the goals.

A follow-up, 18 months after the completion of the intervention programme, was carried out. The follow-up included questionnaires and interviews with the parents focusing on the child’s well-being and level of function at home and in school as well as well-being of parents and siblings. All 14 children took part in the whole programme and they served as their own controls.
Statistics

In paper I the statistical analyses used were Fisher’s exact test and Jonckheere-Terpstra trend test. The p-values of Fisher’s exact test are exploratory and i.e. calculated without adjustments for multiple testing. The Jonckheere–Terpstra trend test was used to analyse the association between intellectual disability and diagnosis.

In paper II the intellectual level of two age groups were compared using odds ratios with 95% confidence intervals. The mean IQ in the verbal domain was compared with the mean performance on the nonverbal domains using a paired samples t-test for a subgroup.

In paper III, mean scores on the ADOS algorithm items for children with ASD were compared with those for children without ASD, using two sample t-tests. The means for the two groups on each item were also illustrated using 95% confidence intervals. The t-tests were supplemented with chi-square tests due to skewed distributions. For each ADOS algorithm item, mean scores for children with DS and ASD were compared with the mean scores for the idio-pathic autism group, presented in the ADOS manual, using one sample t-tests, also supplemented with chi-square tests.

In paper IV goals for children with DS and ASD were set and the mean number of goals was computed for home and for school, respectively. A paired sample t-test was used to compare the mean scores before and after the intervention for the “Family Strain Index”. Mean scores and 95% confidence intervals measuring parent’s perception of the intervention 18 months after completion were computed. An alpha level of .05 was used for all statistical tests in all four papers.

Ethics

The Regional Ethical Review Board of Uppsala approved the studies (Dnr 2011-365 (Study I-III) and 2014-461 (Study IV)).
Results

Paper I – Prevalence study

Autism Spectrum Disorder
Forty-one subjects (29 boys, 12 girls) with an age range of 5-17 years, mean age 11 years, comprised the study group. Based on performed test data and cognitive data in the medical records, all children had ID. There was no evidence of any difference in medical conditions (preterm birth, neonatal hyperbilirubinemia, neonatal respiratory distress, congenital heart disease, West syndrome, treatment with thyroxin or growth hormone) between the groups with and without ASD.

According to ADI-R, ADOS, DSM-IV/DSM-5 criteria and the conjoint clinical assessment of the research-team, 17 (41%) children (13 M, 4 F) met criteria for ASD. In total, 22 (54%) children (16 M, 6 F) had ASD and/or ADHD in addition to ID, while the remaining children (13 M, 6 F) had neither ASD nor ADHD. When analysing the SCQ, almost all children (16/17) with ASD had a score above 13, supporting ASD.

In the group with ASD (n=17), nine subjects (6 M, 3 F) (53%) also met the criteria for ADHD.

Attention-deficit/hyperactivity disorder
Fourteen (34%) subjects (9 M, 5 F) met DSM-IV/DSM-5 criteria for ADHD. The inattentive presentation was seen in seven of the 14 children and seven children met criteria for the combined presentation.

Sixty-four percent (9/14) of the children with ADHD also had ASD. Another eight children met 4-5 DSM criteria, i.e., corresponding to subthreshold ADHD. There was no evidence of any difference in the medical conditions listed above between the groups with and without ADHD.

Comorbidity – ASD and ADHD
Nine children (22%) were diagnosed with both ASD and ADHD. All of these had ADHD with the combined presentation and they all had profound ID.
There was no evidence of a difference in medical conditions between the groups with and without ASD and/or ADHD.

**Paper II – Intellectual disability study**

**Intellectual function**

The cognitive/intellectual functions in this population-based cohort (n=60) was studied and an ID-level was obtained for all 60 children in the cohort. In the total group, 15 subjects (25%) had mild ID, 19 (32%) had moderate ID, 16 (27%) had severe ID and 10 (17%) had profound ID.

Of the 37 younger children (5-12 years), 13 (35%) had mild ID, 14 (38%) had moderate, four (11%) had severe and six (16%) had profound ID. Of the 23 teenagers (13-18 years), two (9%) had mild, eight (35%) had moderate, 11 (48%) had severe and two (9%) had profound ID. Fifty-seven percent of the teenagers (13/23) had severe or profound ID, whereas the corresponding figure in the younger age group was 27% (10/37).

Ninety-one percent of the teenagers had severe ID according to the AAMR classification (IQ <50). This should be compared to 65% of the younger children. Further, the most marked difference between mild and severe ID in relation to age was found below and above the age of eight years (OR: 16.0, 95% CI: 3.2-81.0, p<0.001). Hence, the risk of having severe ID was markedly increased above eight years of age.

More boys than girls had severe ID, although the difference was not significant (OR: 2.83, 95% CI: 0.82-9.76, p=0.111).

The severity of ID increased in seven of the eight children assessed twice. Two of the children, tested prior to the study, had borderline intellectual functioning with IQs between 70 and 84 at the first assessment before starting school.

It was only possible to assess the intellectual profiles, regarding verbal and nonverbal domains, in 20 of the 60 subjects. In 11 of these the IQ-scores in the verbal domain were higher than those in the nonverbal domain, whereas in six subjects the opposite was seen. The difference between the domains was less than 13 IQ-points in all subjects. For the remaining 40 subjects no information regarding profile could be obtained. It was not possible to evaluate the processing speed due to a largely low level of cognitive function in this cohort of children.

**Adaptive function**

A General Adaptive Composite score (GAC) from ABAS-II was obtained in 35 of the 60 children. Twenty-four, all with severe/profound ID, had a GAC
score corresponding to floor level. VABS-II was sent to parents of the 41 children who took part in the ASD/ADHD/ID assessment. A complete VABS-II was obtained from parents of 13 children.

A total of nine children had both ABAS-II and VABS-II results. In the five children with ABAS-II at floor level, VABS-II data gave a more detailed picture. Thus, Vineland adaptive data particularly supported the classification of ID level in the differentiation between severe and profound ID.

**Level of ID in relation to ASD and ADHD**

Of the 41 subjects tested; 17 had ASD, 14 had ADHD and nine had both ASD and ADHD. The subjects with ASD had generally a more severe ID. Thus, one child had mild ID, three moderate, seven severe and six children had profound ID. The children with ADHD had varying levels of ID; four mild, four moderate, four severe and two had profound ID. All children with combined ASD and ADHD had severe or profound ID. There was no evident difference in the verbal vs nonverbal results between the groups, neither for those with ASD nor for those with ADHD.

**Gender distribution**

In the cohort of 60 children with DS, age 5-17 years, the M:F ratio was 2.2:1 (Paper I and II). This is a higher proportion of boys than normally reported for children with DS for which the ratio often is found to be 1.3:1. The gender distribution of the children with DS who were born in the county of Uppsala (M:F ratio 1.6:1) was in line with national data. The major part of the children who had moved into the county represented males (M:F ratio 3.0:1).

**Paper III – Autism phenotype study**

**Autism phenotype**

An essential finding in the present study was that, according to ADOS Module-1, the group of children with DS and ASD differed significantly within all autism domains, from those with DS without ASD. This was also evident when the level of ID had been taken into consideration, i.e. when children with DS and severe ID with and without ASD were compared. Thus, there was a group of children with DS and severe ID who did not have ASD.

The group with DS and ASD had a relatively similar ADOS Module-1 profile as the “matched autistic group” (idiopathic autism group). However, there were some significant differences, i.e. less severe symptoms in the DS and ASD group in the communication domain, mainly with regard to the item
“Stereotyped/idiosyncratic use of words or phrases”. No specific autism phenotype or profile was evident in the group of children with DS and ASD.

Thus, a considerable proportion of children with DS exhibited ASD in addition to severe/profound ID and their autism profile was found to be rather similar to that of children with idiopathic autism with a level of ID corresponding to “lower-functioning autism”. No specific autism phenotype or profile could be demonstrated in this group of children with DS and ASD.

Paper IV – Intervention study

Evaluation of goals achieved, after intervention

Nine children had evaluations both from home and school, whereas for four children, results could only be obtained from home. The parents of one child did not complete the intervention period and this child could not be evaluated. The number of goals set varied from 2 to 5 ($M = 3.77, SD = 1.09$). On average, 92.31% ($SD = 18.78\%$) of the goals were (to some extent or completely) achieved at home and 95.56% ($SD = 13.33\%$) of the goals were (to some extent or completely) achieved at school. On average, over 90% of the goals were to some extent or completely achieved, both at home and at school.

Family strain index questionnaire

Parents of 11 of the 14 children (79%) completed the “Family strain index questionnaire” both before the intervention and at follow-up 18 months after the intervention had been completed. Parents of three children declined this part of the follow-up for various reasons that were unrelated to their child’s disability. The mean scores were almost identical at the follow-up ($M = 10.91, SD = 4.78$) to those before intervention ($M = 11.27, SD = 5.02$); $t_{10} = .48, p = .640$, Cohens’ $d = .07$.

Parents’ perception of the intervention

Parents of 10 of the 14 children (71%) completed the six items using the 120 mm horizontal line indicating level of satisfaction. Parents of four children declined this part of the follow-up for various reasons, including severe medical disorders in two children. The 95% confidence intervals for the mean ratings on the six items are presented in the visual scale in Figure 9.
During the interview, the parents made several comments, e.g.

"We suspected autism long ago; we are relieved to have it confirmed. Now we can get appropriate help and support”.

“Our son is treated in another way now, we understand his behaviour better.”

“We prepare more before activities. We have a changed mind-set, we don’t have to do things that don’t work, e.g. travel while on vacation.”

“My worries and stress concerning my child’s behaviour and my own shortcomings were reduced by the intervention.”
Children with DS and co-existing neurodevelopmental/neuropsychiatric disorders in addition to ID and medical disorders constitute a severely disabled group. This thesis intends to explore neurodevelopmental/neuropsychiatric aspects of DS and to highlight the importance of considering the occurrence of ASD as well as ADHD, in addition to ID in these children.

It has been increasingly recognized that neurodevelopmental/neuropsychiatric disorders coexist and overlap to a large extent. This broad group of disorders includes intellectual disability/intellectual developmental disorder (ID/IDD), autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD) with and without oppositional defiant disorder and conduct disorder, speech and language disorders, obsessive compulsive disorder, tics and Tourette syndrome, developmental coordination disorder (DCD) as well as eating and sleeping disorders. Today these disorders are often referred to as ESSENCE (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations), which is an umbrella term for the conditions. Specific underlying cognitive deficits (e.g. concerning theoretical/abstract thinking, executive functions, “theory of mind” and central coherence) have been identified. The symptoms that define the disorders are detailed in the diagnostic and statistical manual of mental disorders, now the 5th edition. There are also individuals with clear symptoms but not meeting full criteria for a disorder/diagnosis who may for example present with autistic symptoms. Underlying medical disorders, pre-, peri- or postnatally derived always need to be considered in children with ESSENCE. The prevalence of neurodevelopmental/neuropsychiatric disorders is often considerably increased in defined etiological diagnoses such as specific syndromes.

Prevalence study

The study aimed at identifying children with DS and ASD and/or ADHD, based on the total population of children and adolescents with DS, 5-17 years old, in the county of Uppsala.

A high proportion of ASD was found. For the group of children, assessed within the study, the rate was 41%. Even though there is one previous population-based prevalence study of ASD in DS, this is to our knowledge the first time such a study has been performed in which all participating children...
had a comprehensive clinical assessment including ADI-R, ADOS and an
evaluation by an experienced clinical staff.

The proportion of children with ADHD was 34%. The results are in agree-
ment with those of a clinically based study from Israel, reporting a prevalence
of 44%.

Some of the children in our study group had the predominantly in-
attentive presentation. Evaluation of inattentive symptoms is difficult in a
child with severe ID and in many of these children, the inattentiveness was
not considered as an additional problem by the parents.

The prevalences of ASD and ADHD were high. The rates are in line with
the findings by Strömme and Diseth, reporting that 42% of children with
ID, with a defined aetiology, had co-occurring psychiatric diagnoses, most
common ADHD and ASD. Even if there were no child with ASD or ADHD
in the non-participating group, the prevalences, 28% and 23%, respectively,
would still be markedly high.

In a Finnish study from 2006 of school-aged children with DS, it was
discussed that ADHD was common but neither diagnosed nor medically
treated. The authors commented that surprisingly little has been published on
attention problems in subjects with DS, and that there are no evidence-based
recommendations for treatment of such problems in this group. In accordance
to this study and to our knowledge, there is no published study on pharma-
co-logical treatment for ADHD in children with DS.

A lower recognition in clinical practice of ASD, ADHD and mental health
conditions in children with genetic syndromes – compared with research stud-
ies – have been reported. The reason behind these lower rates of ASD and
ADHD, i.e. not identifying these disorders in children with intellectual disa-
Bility and a genetic syndrome may be referred to the concept of "diagnostic
overshadowing".

To our knowledge, there is no population-based study of children and ado-
lescents with DS in which comprehensive assessments of ASD, ADHD and
ID have been performed. Neither is there any study in children and adolescents
with DS that includes a systematic testing of intellectual levels with verbal
and nonverbal domains, related to co-occurring developmental disorders.
There are several studies on the autism phenotype in different genetic syn-
dromes but only few of these involve individuals with DS. Likewise, although
many studies report on autism intervention only a few involve children and
Teenagers with DS, ASD and severe/profound ID.

**Intellectual disability study**

The ID in children with DS was more profound than reported earlier. Mean
IQ was lower in the older group (13-18 years) than in the younger (5-12 years).
A majority, (57%) of the teenagers had severe or profound ID. The corre-
sporing figure in the younger age group was 27%. The WPPSI-III was used
also in the older age group since no other cognitive test would be appropriate for teenagers with this low level of intellectual function and it has been claimed that WPPSI-III can be used for older children with intellectual disability.\textsuperscript{130}

A more severe ID was found in subjects with ASD or combined ASD and ADHD. Furthermore, the ID was more severe in this cohort of subjects with DS, than that reported in earlier studies.\textsuperscript{41} This could be due to the population-based design, which made it possible to acquire cognitive/IQ results from the total group of 60 individuals, also including children with the most profound ID. Our results demonstrated that the severity of ID increased in children who had two tests performed, the first at an age of 5–7 years and the second at 11–16 years. It is not evident whether this is a sign of early intellectual decline or if this subset differs in other aspects.

Our results demonstrate a lower level of IQ in the teenagers compared to the younger children. A lower level of IQ was particularly prominent in children older than eight years. It is not evident whether this is due to an early intellectual decline or if the age-groups differ in other aspects. The results do not confirm higher scores in nonverbal compared to verbal tests as reported earlier.\textsuperscript{137} In fact, all children, possible to test, had even profiles in the verbal and nonverbal domains.

Autism phenotype study

In the clinically assessed study group of 41 children with DS it was evident that one group met criteria for ASD and one group did not. This was further confirmed in this study when ADOS profiles were analysed in detail, both in the total group of children with DS and ASD and in those with DS, ASD and severe ID. Both groups diagnosed with ASD had higher scores in 12 and 10 of the 15 ADOS algorithm items, respectively.

The study also demonstrated that the group with DS and ASD basically had a similar profile as that of the idiopathic autism group. However, there were some differences, i.e. there were less severe symptoms in the DS and ASD group with regard to communication problems, e.g. stereotyped/idiosyncratic use of words or phrases. This could possibly be related to the severely impaired verbal abilities seen in the DS group.

No specific autism phenotype or profile was evident in the group of children with DS and ASD. Different genetic syndromes have been investigated regarding autism phenotype according to ADOS, e.g. 22q11 deletion syndrome,\textsuperscript{138} fragile X syndrome,\textsuperscript{139} Cornelia de Lange syndrome,\textsuperscript{140} and Phelan-McDermid syndrome\textsuperscript{91} and compared to children with idiopathic autism. Varying differences, from subtle to more pronounced, between idiopathic autism and the different syndrome groups have been identified. The presentation of
ASD in children with DS seems to be similar to what has been shown in other syndromes.

An important finding in our study group was that only four of the 17 children with DS and ASD had obtained a diagnosis of ASD before the study was carried out. This is probably due to that children with ID, regardless of associated neurodevelopmental disorders and regardless of aetiology are entitled to attend special schools for children with intellectual disability and entitled to receive measures from rehabilitation services.

Autism in children with DS cannot entirely be referred to the level of ID, thus awareness and recognition of autism in these children are important. However, as shown earlier, the more severe ID the more increased risk to develop ASD. An important finding is that there is a group of children with DS and severe/profound ID that does not have autism. Since the autism phenotype in children with DS and ASD was similar to that in idiopathic autism, common clinical methods to assess ASD should be appropriate to use in children with DS.

**Intervention study**

The most important finding in the intervention study, based on modified ABA principles, was that the children were able to achieve new goals and skills they had not previously managed. The goal setting was individualized to the severity of ID of each child, which made it possible to address specific problems of communication and daily activities. Most children achieved the goals that had been set, either fully or to some extent, and the results demonstrated some improvements in all children.

The role of intellectual level on the outcome of behaviour modification programmes in children with ASD is important to consider and children with higher cognitive levels have been found to have better acquisition of skills and better adaptive functioning outcome. To understand problem behaviour a variety of factors need to be considered; medical or psychiatric conditions, adaptive functions and environmental factors that may influence the behaviour. Since the strongest predictor of a favourable outcome is related to the level of IQ, there is a need to consider the child’s IQ-level, not only the ASD diagnosis per se when planning the intervention. Therefore, developmental assessments with appropriate test instruments need to be part of any ASD assessment.

The “Family Strain Index” interview demonstrated that the parents rated the stress and burden of illness correspondingly high before intervention and at the follow-up. Our results are in agreement with those of the study by Silva et al. where no difference in parental stress before and after an intervention could be demonstrated in children with ADHD combined with either externalizing disorders or ASD.
The parental interviews revealed that almost all parents expressed a sense of relief when they received confirmation that their child also had ASD. Many of the parents had experienced that their child had been misunderstood for many years. It had been evident for the parents that their child had additional difficulties compared to other children with DS. Many parents had experienced a feeling of loneliness and insufficiency in the attempts to meet the needs of the child. The evaluation also demonstrated that the use of strategies, intended to facilitate activities and communication, remained to a large extent 18 months after completion of the intervention.

When planning an intervention for a child with ASD, it is important to assess and consider the general cognitive functioning. Most current ASD interventions include elements of ABA, which can be applied both with an intensive and a non-intensive approach. However, they must be individualised and also include all the “non-ASD” aspects (i.e. other ESSENCE symptoms).

The strongest predictor of favourable outcome is undoubtedly the level of IQ, which underscores the need not to consider an ASD diagnosis in itself “enough”. The IQ-level, not the ASD diagnosis per se, is the most important variable in predicting outcome.

The results demonstrate that a psychoeducational programme can be adapted for schoolchildren with DS, ASD and severe or profound ID. The goal setting was individualized to the severity of ID of each child, which made it possible to address specific problems of communication and daily activities. To our knowledge, no similar intervention in schoolchildren with DS, ASD and severe/profound ID has been reported.

**Sex ratio**

The cohort of 60 children had a higher proportion of boys (the M:F ratio in the study cohort was 2.2:1) than generally seen in DS (1.3:1). However, analysis of the M:F ratio for the total DS population year by year between 2005 and 2014 demonstrated similar ratios as that in the cohort.

Gender distribution in the prevalence study cohort was also analysed. The 41 children taking part in the prevalence study had a M:F ratio of 2.4:1, while the 19 children, not participating in the study had a M:F ratio of 1.7:1.

The M:F ratio for children born in Uppsala County between 1997 and 2005 was 1.6:1, i.e. similar to that in the total population of newborn infants with DS in Sweden. The population of Uppsala is increasing, partly due to migration, and consequently families with children with DS have also moved into the county. The gender distribution of the children moving into Uppsala County was skewed with a M:F ratio of 3.0:1, explaining the high M:F ratio in the cohort.
Strengths and limitations

Strengths of the thesis is the population-based design and that the centralized follow-up programme, that is applied in Uppsala County, made it possible to include all children (5–17 years) with DS. Furthermore, the organisation with a specialized outpatient clinic where all children with DS in the county are cared for provides a holistic approach regarding medical, neuropsychological and educational areas.

A strength of the prevalence study is that all participating subjects were comprehensively, clinically assessed by a team using well-validated instruments, with interviews and observations of the child, including a clinical neuropediatric evaluation. A strength of the ID severity study was that it was based on the total population of 60 children. A limitation that should be mentioned relate to that only two thirds (41 of the 60 children) of the children took part in the study regarding the ASD and ADHD assessments in the prevalence study. An analysis of the 19 children (M:F ratio 1.7) who did not participate in the study revealed that 13 families denied participation and 6 families were not able to cope with the assessments. Based on the records from the outpatient clinic; five of these children (n=19, M:F ratio 1.5:1) had suspected ASD (26%) and two boys (11%) had an ADHD diagnosis, one of whom also had suspect ASD.

The ID severity study was limited by the fact that some of the children who did not take part in the ASD and ADHD assessment had their assessment of intellectual level several years earlier, before school start. Moreover, only eight of 60 children (13%) had been assessed twice enabling evaluation over time. Another limitation is that the available IQ tests are not adjusted for teenagers with low levels of ID.

A limitation in the intervention study was the lack of controlled randomised design. However, since the study group was small, and the study period extended over 2 years, randomization was not considered possible.
Conclusions and clinical implications

The thesis investigates associated neurodevelopmental/neuropsychiatric aspects in a population-based cohort of children with DS.

Forty-one children with DS were assessed, 41% had ASD and 34% had ADHD in addition to ID. Nine of the 41 (22%) had both ASD and ADHD. The coexistence of ID, ASD and ADHD in these children results in a particularly difficult situation.

We suggest a screening procedure at 3–5 years of age for ASD and for ADHD at early school years. These recommendations should be included in guidelines for DS.

The cohort of children with DS had a more severe level of ID than previously reported – 75% had moderate to profound ID. We found a more severe level of ID in the teenage group compared to that of the younger children. There was no obvious gender difference concerning level of ID. Children with ASD had a more severe level of ID; no difference was seen concerning ADHD.

We suggest that children with DS should be re-evaluated regarding level of ID before entering secondary school. These recommendations should also be included in guidelines for DS.

Children with DS and diagnosed ASD, at different levels of ID, had significantly more symptoms, within all autism domains, compared to those with DS without ASD. Thus, there was a group of children with DS and ID who did not have ASD. This was also evident when the comparison between those with and without ASD also included the subjects with severe ID.

Overall, the autism phenotype in children with DS and ASD was similar to what is seen in idiopathic autism. The commonly used interviews and observations, combined with comprehensive clinical neuropaediatric and neuropsychological assessments, used to diagnose ASD in the study, seemed to be appropriate in this patient group.

The results of the ASD intervention demonstrated that a psychoeducational programme could be adapted for schoolchildren with DS, ASD and with severe or profound ID. The individualized goal setting made it possible to address specific problems of communication and daily activities. In addition, the parents’ views on the intervention were encouraging.
Epilogue

During my years of clinical work, I have learnt that our medical care is appropriate and for most children with DS the physical health is relatively good. In this research work, we have found that the health, in many children with DS, is much more affected by neurodevelopmental/neuropsychiatric disorders than by medical disorders.

In the same way as we have created a medical health care programme, I hope that we will now focus on identifying ASD and ADHD in children with DS and develop effective interventions for treatment, education and training.
Denna avhandling undersöker associerade utvecklingsneurologiska och neuropsykiatriska aspekter hos en populationsbaserad grupp av barn med Downs syndrom (DS).

Vi har undersökt förekomst av autismspektrumtillstånd (ASD) och ADHD, i relation till grad av intellektuell funktionsnedsättning (ID) och medicinska tillstånd. När studien startade fanns i Uppsala län 60 barn med DS i åldersspannet 5–17 år och 41 av dessa deltog i studien. Vi fann att 17 barn hade ASD (41%) och 14 hade ADHD (34%). Vi föreslår att alla barn med DS ska genomgå screening för ASD i 3–5 års ålder och för ADHD i tidig skolålder.

Alla 60 barn har bedömts avseende grad av ID. De 41 barn som deltog i studien genomgick utvecklingsbedömning inom studien eller nära i tid (<3 år före studien). De övriga 19 barnen hade testats inför skolstart och dessa bedömningar granskades. I den totala gruppen av 60 barn fann vi en svårare grad av ID än vad som tidigare rapporterats; eftersom 75% av barnen hade medelstark–grav ID (IQ <50). Vi fann att tonåringar (13–18 år) hade en svårare grad av ID än yngre barn (5–12 år). Barn med ASD hade dessutom svårare grad av ID, detta var dock inte fallet för barnen med ADHD. Vi föreslår att alla barn med DS bör genomgå en ny utvecklingsbedömning inför högstadiet.


De 17 barn som fick diagnos ASD erbjöds att delta i ett interventionsprogram, och 14 av dessa familjer tackade ja. Interventionen innehöll föreläsningar och workshops för både föräldrar och skolpersonal, och därutöver bildades en särskild föräldragrupp för att möjliggöra erfarenhetsutbyte. Individuella mål för barnen fastställdes, varefter en träningsperiod på 3 månader genomfördes i hem och skola. Därefter följde en utvärdering som visade att
barnen kunde nå nya mål och hitta nya förmågor, samtidigt som föräldrarna upplevde en positiv effekt av interventionen.

Sammanfattningsvis är ASD och ADHD vanligt hos barn med DS. Svårighetsgraden av ID kan öka i tonåren. Profilen av autism-symtom är relativt lika den hos barn med idiopatisk autism. Även äldre barn och tonåringar med svår–grav ID kan ha nytta av individuellt anpassad autismintervention.
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References


A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)