Asperger syndrome and high-functioning autism in school-age children: the children’s sleep and behaviour, and aspects of their parents’ well-being

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To my family:

Mari, Lauri and Mare

For love and sacrifice
ABSTRACT

Asperger syndrome (AS) and high-functioning autism (HFA) are pervasive developmental disorders (PDD) in children of normal range intelligence. Individuals with AS/HFA have impairments in social interaction, communication, and restricted behavioural repertoire, deficits that significantly interfere with their well-being and ability to adapt to ordinary everyday life. Moreover, AS and HFA are presumed to be frequently accompanied by co-existing psychiatric problems and disturbed sleep. Such comorbidities may impose further distress on the children and may increase caregiver burden.

Two main objectives of this thesis were to explore if children with AS and HFA have disturbed sleep, and if their parents have impaired health-related quality of life (HRQL).

Thirty-two 8–12-year-olds with AS/HFA, 28 boys and 4 girls, and 32 age- and gender-matched typically developing children participated. Sleep patterns of the children were assessed at baseline, and at a follow-up, 2-3 years later, by parental questionnaire and by one-week sleep diary and actigraphy.

Paper I compared sleep patterns of the children with AS/HFA and the controls at baseline. The AS/HFA group had more parent-reported sleep problems, earlier sleep timing (bed- and get up time) at weekends, prolonged sleep latencies during the whole week, and lower sleep efficiencies on school days. Separate analyses within the AS/HFA group showed longer sleep latencies, and greater night-to-night variability of sleep latency in children with, compared to those without parent-reported sleep problems.

Paper II detailed a wide range of sleep-wake behaviour and symptoms of paediatric insomnia at baseline. Children with AS/HFA had more difficulties initiating sleep, and more daytime sleepiness than controls, and 10/32 children in the AS/HFA group, but none of the controls, fulfilled current criteria for paediatric insomnia. Within the AS/HFA group, children with insomnia had higher scores of parent-reported autistic and emotional symptoms, and more teacher-reported emotional and hyperactivity symptoms than those children without insomnia.

Paper III examined development of sleep patterns from baseline to a follow-up in 23/32 of the children with AS/HFA and in 22/32 of the controls. Results indicated that persisting parent-reported sleep problems were much more common in the children with AS/HFA than in the controls; 10/23 versus 1/22, respectively. Also, prolonged actigraphic sleep latencies on school days, and earlier sleep timing (get up time) on weekends were persistent in a significant proportion of children with AS/HFA.

Paper IV investigated the self-reported HRQL of the parents of the children with AS/HFA and of the parents of the controls. The mothers of the children with AS/HFA had poorer physical health than control mothers, and than fathers of both groups. Maternal HRQL in the AS/HFA group was also related to co-existing behaviour problems in the child.

Conclusion: In childhood AS/HFA, difficulty initiating sleep is a common and distressing symptom, and mothers of children with AS/HFA frequently report impaired physical well-being.
LIST OF PUBLICATIONS

The thesis is based on the following original papers. They will be referred to in the text by the Roman numerals.


<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>AS</td>
<td>Asperger Syndrome</td>
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<tr>
<td>ADHD</td>
<td>Attention Deficit Hyperactivity Disorder</td>
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<td>ANOVA</td>
<td>Analysis of Variance</td>
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<td>ASSQ</td>
<td>Autism Spectrum Screening Questionnaire</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<td>DS</td>
<td>Down Syndrome</td>
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<td>DSM-III</td>
<td>Diagnostic and Statistical Manual of Mental Disorders III</td>
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<td>DSM-III-R</td>
<td>DSM-III Revised</td>
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<td>DSM-IV</td>
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<td>EEG</td>
<td>Electroencephalography</td>
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<td>HFA</td>
<td>High-Functioning Autism</td>
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<td>HRQL</td>
<td>Health-Related Quality of Life</td>
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<td>ICD-10</td>
<td>International Classification of Diseases 10th edition</td>
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<td>ICSD-R</td>
<td>International Classification of Sleep Disorders Revised</td>
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<td>IQ</td>
<td>Intelligence Quotient</td>
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<td>MCS-12</td>
<td>Mental Component Summary</td>
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<td>MR</td>
<td>Mental Retardation</td>
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<td>NLD</td>
<td>Nonverbal Learning Disability</td>
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<td>NREM</td>
<td>Non-Rapid Eye Movement</td>
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<td>OCD</td>
<td>Obsessive-Compulsive Disorder</td>
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<td>PCS-12</td>
<td>Physical Component Summary</td>
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<td>PDD</td>
<td>Pervasive Developmental Disorder</td>
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<td>PDD-NOS</td>
<td>Pervasive Developmental Disorder Not Otherwise Specified</td>
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<td>PSG</td>
<td>Polysomnography</td>
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<td>REM</td>
<td>Rapid Eye Movement</td>
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<td>SCN</td>
<td>Suprachiasmatic Nucleus</td>
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<td>SD</td>
<td>Standard Deviation</td>
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<td>SDQ</td>
<td>Strengths and Difficulties Questionnaire</td>
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<td>SF-12</td>
<td>The 12 Item Short-Form Health Survey</td>
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<td>SPSS</td>
<td>Statistical Package for Social Sciences</td>
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<td>SWS</td>
<td>Slow Wave Sleep</td>
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<td>TS</td>
<td>Tourette Syndrome</td>
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<td>WISC-R</td>
<td>Wechsler Intelligence Scale for Children</td>
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<td>WPSSI</td>
<td>Wechsler Preschool and Primary Scale of Intelligence</td>
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1 PROLOGUE

Working as a young paediatrician at the Children’s Hospital of Tartu University, I met several children with autistic disorder whose sleep was very disturbed. All of these children had also intellectual disability and severe impairment in daytime functioning. The uniqueness of the combination between autistic disorder and disturbed sleep called forth my great curiosity and interest. This interest continued further at the Psychiatric Clinic of Tartu University, where we together with Associate Professor Jüri Liivamägi planned to start a double-blind melatonin treatment study in children with autism. This project was planned in a collaboration with Professor Jaak Panksepp from Bowling Green State University, USA.

My interest for sleep pattern in autism continued in Stockholm. I met Berit Lagerheim, a child and adolescent psychiatrist who had close contacts with Jüri Liivamägi and colleagues at Tartu University. Berit provided me with the opportunity for auscultation at the Neuropsychiatric Unit, Astrid Lindgren Children’s Hospital, in Dr. Harald Sturm’s team. During this 12-month study period, I obtained invaluable knowledge about the screening and nature of neuropsychiatric disorders in children and adolescents, among these also autistic spectrum disorders. Moreover, I met many children and adolescents with autism who did not show intellectual disability, with diagnoses such as high-functioning autism (HFA) and Asperger syndrome (AS). These experiences supported and extended my conviction that parent-reported sleep problems were very common and distressing in autism at all levels of intellectual functioning. Such recognition also gave support to the wish to explore sleep patterns in these children, and led finally to my doctoral studies and this thesis.

During the study period at the Astrid Lindgren Children’s Hospital, I contacted Professor Per-Anders Rydelius at the Karolinska Institutet, Department of Woman and Child Health, Child and Adolescent Psychiatric Unit. Per-Anders Rydelius provided me with the opportunity to start with my doctorate studies. Moreover, communication with the researchers at the Sleep Research Centrum of Uppsala University enabled me to start the project in collaboration between Karolinska Institutet and Uppsala University.
2 INTRODUCTION

Asperger syndrome (AS) and high-functioning autism (HFA) are pervasive developmental disorders (PDD) in individuals of normal intelligence. Both disorders are characterized by a pattern of social deficits, rigid ritualistic behaviours, interests, or activities, and, primarily in HFA, communication problems. AS differs from HFA by the lack of clinically significant cognitive or language delay [1]. Research indicates a marked increase of the prevalence of childhood PDD over the course of the past 20–30 years. Current prevalence estimates suggest that up to 6 per 1.000 children have a PDD [2, 3], and also that approximately half of these individuals have normal intelligence [4]. Moreover, a Welsh study reported a minimum prevalence of 2 out of every 1.000 for PDD in mainstream school children [5]. Further, childhood AS and HFA are presumed to be often associated with co-existing behavioural or psychiatric disorders, including sleep disturbance. Such comorbidities may compromise the well-being and daytime function of these children and possibly worsen long-term outcome [6]. Usually, children with AS or HFA live in the family along with their parents. Some data indicate that parenting a child with AS/HFA may be associated with high levels of stress and burden [4, 7] which could also take a toll on the health-related quality of life (HRQL) in parents of these children. However, research about the topics of sleep pattern and parental HRQL in childhood AS and HFA is still scarce.

2.1 CLASSIFICATION OF PERSISTIVE DEVELOPMENTAL DISORDERS

2.1.1 Historical aspects

In 1943/1944, Leo Kanner, a psychiatrist at the John Hopkins Hospital in the United States, and Hans Asperger, an Austrian paediatrician, unaware of each other’s work, presented clinical cases which described children with similar characteristics regarding impairments in two-way social interaction, affect and communication, and patterns of interest [8, 9]. Cases in Asperger’s account (aged 6–11 yrs) differed from cases in Kanner’s description (aged 2–11 yrs) as follows: speech delay was less common; motor deficits were more common; onset of manifestation was delayed, and exclusively boys were affected. Due to resemblance to core symptoms of schizophrenia, Kanner termed the condition “Autistic Disturbance of Affective Contact,” and Asperger called the condition “Autistic Psychopathy.” However, both authors emphasized considerable differences between schizophrenia and their new descriptions. Moreover, Kanner as well as Asperger implied that there could be a hereditary component in the aetiology of the autistic conditions. In particular Asperger noted that the fathers of the boys in his clinical material had similar difficulties as their off-springs.

Some earlier papers could also have included cases with behavioural features resembling those of the children presented by Asperger [10]. In 1926 Ewa Ssuchareva [10], the Russian neurologist, gave a detailed description of schizoid personality disorder in six boys (aged 12–14 yrs) of average or high range intelligence. Ssuchareva’s description of these boys (odd type of thinking, an inner directed attitude,
avoidance of other people, in- or oversensitivity, a tendency towards automatisms, obsessive-compulsive behaviour, peer problems, and motor impairments) was very similar to the clinical account by Asperger some two decades later.

Further, Kanner’s Autistic Disturbance (Early Infantile Autism) and Asperger’s Autistic Psychopathy were presented as two separate clinical entities in Dutch and German literature in 1960s and 1970s. The Dutch authors, Van Krevelen and Kuipers [11] analysed in detail Autistic Psychopathy, and made a categorical distinction between Autistic Psychopathy and Early Infantile Autism. In further reports [12, 13], Van Krevelen continued to distinguish between these two categories on the basis of symptoms related to onset, speech development, sex distribution, presence of cognitive deficit, prognosis, use of speech, presence of eye contact, and anxiety to leave home (homesickness). Similarly, German researchers distinguished between Kanner Syndrome (Frühkindlicher Autismus) and AS (Autistische Psychopathie) already in 1970s. Nissen [14] suggested that these two syndromes belonged to the same continuum of disorders, including also Psychogenic Autism (Psychogener Autismus), Somatogenic Autism (Somatogener Autismus), and Pseudoautism (Pseudoautismus), and were caused by hereditary “autism factor” (Autismusfaktor). According to Nissen, emotional defect (Emotionaler defekt) in Kanner Syndrome and AS was the consequence of the difficulties with sensory (auditory and/or visual) decoding. The same author proposed five distinguishing domains between these two syndromes: type of social disturbance (Art der Kontaktstörung), gender (Geschlechtsverteilung), motor and speech development (Sprachliche und motorische Entwicklung), intelligence (Intelligenz), and family history (Aszendenz).

However, it was not until 1981 that Asperger’s work became widely known to the English speaking world when Lorna Wing gave a clinical account to AS [15]. Wing presented her own clinical cases which were strikingly similar to the cases presented by Hans Asperger. Importantly, Lorna Wing proposed, that instead of “Autistic Psychopathy,” the condition should be called Asperger Syndrome. It deserves also to be noted that, different to the cases presented by Asperger, some of the cases in the report by Wing had intellectual disability, and that some had a history of speech delay in the first years of life. Similarly to Nissen [14], Wing considered both AS and Early Infantile Autism as belonging to the same group of conditions with impairments in reciprocal social interaction, communication and imagination. Other authors have also supported the existence of a continuum of disorders in PDDs [16, 17].

### 2.1.2 Diagnostic criteria

PDDs were introduced as a separate category into the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) [18] in 1980 in order to describe a developmental disturbance over a range of different domains, and to distinguish clearly from mental retardation (MR) and other specific developmental disorders. PDDs were presented in the DSM-III in two separate subtypes: Infantile Autism and Childhood Onset PDDs. The revised version, DSM-III-R [19] in 1987, modified criteria for PDDs, and renamed also these two subtypes into Autistic Disorder, and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS). As stated in the DSM-III-R, PDDs were
characterized by qualitative impairments in reciprocal social interaction, verbal and non-verbal communication skills, and in imaginative activity, and by markedly restricted repertoire of activities and interests.

AS received “official” diagnostic status under category PDDs in 1992 in the International Classification of Diseases (ICD-10), Classification of Mental and Behavioural Disorders [20] and as Asperger’s Disorder in 1994 in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [21]. AS is distinguished from the Childhood Autism as follows [22]: 1) “There is no clinically significant general delay in spoken or receptive language or cognitive development in AS. Diagnosis requires that single words should have developed by 2 years of age or earlier, and that communicating phrases be used by 3 years of age or earlier;” and 2) no requirement of “qualitative abnormalities in communication.” (Tables 1, 2).

Table 1. ICD-10 research criteria for Childhood Autism

A. Abnormal or impaired development is evident before the age of 3 years in at least one of the following areas:
   (1) receptive or expressive language as used in social communication;
   (2) the development of selective social attachments or of reciprocal social interaction;
   (3) functional or symbolic play.

B. A total of at least six symptoms from (1), (2), and (3) must be present, with at least two from (1) and at least one from each of (2) and (3):
   (1) Qualitative abnormalities in reciprocal social interaction are manifest in at least two of the following areas:
      (a) failure adequately to use eye-to-eye gaze, facial expression, body posture, and gesture to regulate social interaction;
      (b) failure to develop (in a manner appropriate to mental age, and despite ample opportunities) peer relationships that involve a mutual sharing of interests, activities, and emotions;
      (c) lack of socio-emotional reciprocity as shown by an impaired or deviant response to other people’s emotions, or lack of modulation of behaviour according to social context, or a weak integration of social, emotional, and communicative behaviours;
      (d) lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g. a lack of showing, bringing, or pointing out to other people objects of interest to the individual).

   (2) Qualitative abnormalities in communication are manifest in at least one of the following areas:
      (a) a delay in, or total lack of, development of spoken language that is not accompanied by an attempt to compensate through the use of gesture or mime as an alternative mode of communication (often preceded by a lack of communicative babbling);
      (b) relative failure to initiate or sustain conversational interchange (at whatever level of language skills is present), in which there is reciprocal responsiveness to the communications of the other person;
(c) stereotyped and repetitive use of language or idiosyncratic use of words or phrases;
(d) lack of varied spontaneous make-believe or (when young) social imitative play.

(3) Restricted, repetitive, and stereotyped patterns of behaviour, interests, and activities are manifest in at least one of the following areas:
   (a) an encompassing preoccupation with one or more stereotyped and restricted patterns of interest that are abnormal in content or focus; or one or more interests that are abnormal in their intensity and circumscribed nature though not in their content or focus;
   (b) apparently compulsive adherence to specific, non-functional routines or rituals;
   (c) stereotyped and repetitive motor mannerisms that involve either hand or finger flapping or twisting, or complex whole body movements;
   (d) preoccupations with part-objects or non-functional elements of play materials (such as their odour, the feel of their surface, or the noise or vibration that they generate).

C. The clinical picture is not attributable to the other varieties of pervasive developmental disorder; specific developmental disorder of receptive language (F80.2) with secondary socio-emotional problems; reactive attachment disorder (F94.1) or disinhibited attachment disorder (F94.2); mental retardation (F70–F72) with some associated emotional or behavioural disorder; schizophrenia (F20.–) of unusually early onset; and Rett’s syndrome (F84.2).

Table 2. ICD-10 research criteria for AS:

A. There is no clinically significant general delay in spoken or receptive language or cognitive development. Diagnosis requires that single words should have developed by 2 years of age or earlier and that communicative phrases be used by 3 years of age or earlier. Self-help skills, adaptive behaviour, and curiosity about the environment during the first 3 years should be at a level consistent with normal intellectual development. However, motor milestones may be somewhat delayed and motor clumsiness is usual (although not a necessary diagnostic feature). Isolated special skills, often related to abnormal preoccupations, are common, but are not required for diagnosis.

B. There are qualitative abnormalities in reciprocal social interaction (criteria as for autism).

C. The individual exhibits an unusually intense, circumscribed interest or restricted, repetitive, and stereotyped patterns of behaviour, interests, and activities (criteria as for autism; however it would be less usual for these to include either motor mannerisms or preoccupations with part-objects or non-functional elements of play materials).
D. The disorder is not attributable to the other varieties of pervasive developmental disorder; simple schizophrenia (F20.6); schizotypal disorder (F21); obsessive-compulsive disorder (F42.–); anankastic personality disorder (F60.5); reactive and disinhibited attachment disorders of childhood (F94.1 and F94.2, respectively).

In the literature, PDD are on the basis of the individual level of intellectual functioning often subclassified into high-functioning and low-functioning subcategories [23, 24]. The high-functioning PDD (Intelligence Quotient, IQ > 70) include AS, high-functioning autism (HFA) and PDD-NOS. The label HFA, introduced by DeMyer et al [25], was considered to describe subjects with Autistic Disorder and of normal intelligence. A third separate sub-category among the high-functioning PDDs is PDD-NOS (including Atypical Autism) [23, 26]. The PDD-NOS concept is used for conditions that are characterized by pervasive impairments in reciprocal social interaction, verbal and nonverbal communication, or rigid and stereotyped behaviour patterns which fail to meet the full set of criteria for autistic disorder [27].

2.1.3 Prevalence of Pervasive Developmental Disorders

The prevalence of PDD in children has increased from 0.4 in 1,000 during the 1970s to current estimates of up to 6 per 1,000 [3, 28, 29]. This increase is presumably a consequence of improved ascertainment and considerable broadening of the diagnostic concept [30]. While PDDs were previously only diagnosed in children with MR, recent studies suggest that approximately 50–74 per cent [4, 28] of individuals diagnosed with PDDs have normal intelligence. A Welsh study suggest that the minimum prevalence of high-functioning PDDs in mainstream school children is around 2 per 1,000 [5]. Prevalence estimates of AS range from 0.3–48.4 per 10,000, the huge variation may reflect methodologic differences across studies [31, 32]. Prior to the inclusion of specific criteria for AS in ICD-10 and DSM-IV, at least five sets of clinically diagnostic features for AS were proposed in the literature [33, 34]. Two Swedish studies based on Gillberg and Gillberg’s criteria for AS, have presented the prevalence rates between 0.9 and 3.6 per 1,000 children in school-age [35, 36].

2.1.4 Differences and similarities between AS and HFA

Issues concerning differences and similarities between AS and HFA have received considerable attention and debate throughout the years. As mentioned earlier, a Dutch author Van Krevelen [11] indicated that there were essential differences between Asperger’s and Kanner’s description of cases with autism with respect to the onset of symptoms, speech development, sex distribution, presence of cognitive deficit, prognosis, use of speech, presence of eye contact, and homesickness. Also Nissen [14] distinguished between Kanner Syndrome and AS according to the type of social disturbance, gender, motor and speech development, intelligence, and family history. Nevertheless, Nissen suggested that these two categories belong to the same continuum of disorders, caused by hereditary “autism factor.”
Some authors have not found valid distinctions between AS and HFA [37-39], and even a dimensional view of the autistic spectrum has been proposed [15, 40, 41]. Szatmari et al [42] used criteria for AS, adapted from Wing [15], and could not find any substantive, qualitative difference between the AS and HFA groups. Some clinical differences in terms of social responsiveness, communication and restricted range of activities were regarded as reflecting severity of the disorder. Thus, Szatmari et al suggested that AS is a mild form of HFA. Further DSM-IV-based research, by Miller & Ozonoff [38], could not find any difference between AS and HFA in intellectual, motor, visuospatial, and executive function domains, and argued that AS may simply be “high-IQ autism.” It has been stated [43] that current DSM-IV criteria for AS do not identify the types of individuals originally described by Hans Asperger, or that DSM-IV criteria for AS are overly restrictive [44] or virtually unworkable [45]. Some research does not endorse the importance of the history of speech delay as a differentiating characteristic between AS and autistic disorder [46], and considers the degree of social and cognitive impairment as the primary differentiating feature between subgroups of high-functioning PDD [26].

Conversely, several other authors [47-49] postulate that it is relevant to differentiate between AS and HFA as separate clinical subtypes of PDDs. Klin and colleagues [47] explored the validity of AS as distinct from other conditions, particularly from HFA, on the basis of the ICD-10 research criteria, and found that the neuropsychological profile differed between AS and HFA in 11 domains. Moreover, Klin et al also found that a high level of concordance between AS and non-verbal learning disability (NLD) was estimated. NLD is defined on the basis of a cluster of deficits affecting the non-verbal aspects of the child’s functioning including deficits in tactile perception, psychomotor coordination, visual-spatial organization, non-verbal problem-solving, and appreciation of incongruities and humour [47]. Individuals with NLD are also reported to reveal difficulty in adapting to novel and complex situations, poor pragmatics and prosody in speech, and significant deficits in social perception, social judgment, and social interaction skills.

Also findings by Tonge et al [48] and Starr et al [49] supported the validity of distinction between HFA and AS. Tonge et al [48] compared behavioural and emotional disturbance between HFA and AS (DSM-IV), and found higher levels of psychopathology (more disruptive, antisocial and anxious behaviour) in AS. Further, Starr and colleagues [49] compared the 2-year outcome between the AS and HFA subgroups, and found that despite similar developmental trajectories in both groups, the AS group showed fewer and/or less severe symptoms related to domains of social interaction, communication, and repetitive activities. Thus, the authors viewed autism and AS as representing two independent phenotypes of PDDs.

Kugler (1998) [33] stated that despite evidence of a good reliability of the diagnoses AS and HFA (DSM-IV and ICD-10), there is still a need for further evidence which demonstrates the validity of these subtypes within PDD spectrum. Rinehart et al [50] inferred further (2002), that “In light of the growing body of epidemiological information, genetic, and neurobehavioural evidence that distinguishes autism from Asperger’s disorder, it is premature to rule out the possibility that these disorders may be clinically, and possibly neurobiologically separate.”

It has also been noted that parents of children given a diagnosis of AS experience significantly longer delays and greater frustration in obtaining a diagnosis (around 11 years of age) than those with a child with autism (at 5.5 years of age) [51]. Parents of
children with autism also became aware earlier of problems in their child’s
development, by 18 months of age, while in the AS groups concerns emerged later, at
around 30 months.

2.2 PSYCHIATRIC COMORBIDITY IN AS/HFA

AS and HFA are often associated with comorbid/co-existent behavioural or psychiatric
disorders such as Attention Deficit Hyperactivity Disorder (ADHD), depression and
other mood disorder, tic disorder, Tourette syndrome (TS), Obsessive-Compulsive
Disorder (OCD), anxiety disorder, anorexia nervosa, eating disorder, sleep disorder [6,
52-56]. Disturbed sleep in AS/HFA has been proposed to be a salient feature of the
PDD phenotype [57], or related to neuropsychiatric deficits inherent of AS [58], or co-
existent anxiety and heightened arousal [59].

The term “comorbidity” refers to the occurrence of two or more disorders
together. Individuals with AS/HFA are suggested as being particularly vulnerable to
anxiety [48, 60], and such vulnerability may be an intrinsic feature of AS/HFA [61].
Kanner had previously proposed that many of the core features of autism, particularly
the insistence on sameness and the repertoire of fixed behaviours, routines and
obsessions, were anxiety driven [9]. In school-age children with AS, depression and
anxiety are suggested to be related to peer shunning and victimization [62]. Ghaziuddin
et al found [52] symptoms of a comorbid psychiatric disorder, particularly ADHD and
depression in 23 of 35 individuals with AS (65%). Further, while highlighting the wide
scope of mental health aspects of autism and AS [6], Ghaziuddin emphasized the
importance of identification and treatment of co-occurring conditions in order to
ameliorate the long-term outcome of these individuals. The same author also indicated
that the occurrence of comorbid psychiatric disorders is higher in individuals with
autism and AS than in the general population.

Studies have also compared rates of comorbidity between AS and HFA sub-
groups. Kim et al [53] assessed three groups of children, 19 children with AS, 40
children with HFA (aged 9–14 yrs), and a sample of community children, and found a
higher frequency of depression and anxiety in the AS and HFA groups compared to the
community sample. There was no difference between the AS and HFA subgroups. The
authors indicated also a significant impact of comorbidity on children’s overall
adaptation. Another report [48] compared behaviour between 75 subjects with HFA
and 52 subjects with AS (aged 4–18 yrs), and detected higher levels of disruptive
behaviour, antisocial behaviour, anxiety, and problems with social relating in AS. It
was speculated whether people with AS have a greater risk for psychiatric disorders,
due to the higher levels of difficulties with social interactions. Also research on
adults with AS has pointed at the high frequency of comorbidity [55, 58].

Finally, it is worth noting that it is difficult to establish a rate of prevalence of
depression in autism and AS, since as noted by Stewart and colleagues: “There are
diagnostic difficulties when considering depression in autism and AS, as the
characteristics of these disorders, such as social withdrawal and appetite and sleep
disturbance, are also core symptoms of depression. Impaired verbal and non-verbal
communication can mask the symptoms of depression. Symptoms associated with
autism and AS such as obsessionality and self-injury may be increased during an episode of depression” [56].

2.3 SLEEP

2.3.1 The nature of sleep

According to sleep researchers, human existence can broadly be divided into the three basic physiological states: wakefulness, non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep [63]. Each has its distinctive physiological characteristics. Sleep as a whole is a reversible, relatively inactive state. The fundamental purposes of sleep are related to physical and psychological restoration, energy conservation, consolidation of memories, discharge of emotions, brain growth, and other basic biological functions including the maintenance of immune systems. Different stages of sleep are distinguished from each other according to specific patterns, recorded by polysomnography (PSG). Sleep onset begins with NREM sleep divided into four distinct stages. Stage 1 is the briefest stage characterized by disappearance of alpha waves, introduction of theta waves, slower frequency brain waves from 3-7 cycles per second. Within a few minutes Stage 2 develops, characterized by sleep spindles (thalamically generated) and K-complexes [64]. Stages 3 and 4, also referred to as slow wave sleep (SWS) or delta sleep, are characterized by the slowest electroencephalography (EEG) activity, and by the highest arousal threshold. It is difficult to awaken a child from this deep sleep, and once awakened, the child is often disoriented and confused. Confused partial arousals, including sleepwalking and sleep terrors, arise from deep sleep [64].

Latency from sleep onset to REM sleep is, by average, approximately 180 minutes at age 10, and 90–110 minutes at age 13 years [64]. During REM sleep, brain wave activity resembles the frequency and amplitude of Stage 1 brain waves, which are similar to wakefulness. Dreaming accompanies these brain wave alterations. REM sleep is characterized by a high rate of brain metabolism, and absence of muscle tone. REM sleep accounts for 50 per cent or more of sleep in the term neonate, reducing to 20–25 per cent by 2 years of age and staying at that level thereafter. NREM and REM sleep alternate throughout the night 3–4 times. The amount of NREM sleep gradually lessens in successive sleep cycles, with SWS usually confined to the first two cycles. Conversely, the amount of REM sleep usually increases as the night progresses.

An important timer of sleep is the circadian clock which is located in the suprachiasmatic nucleus (SCN) of the hypothalamus [63]. The circadian clock also controls other biological rhythms including body temperature and cortisol production, with which the sleep-wake rhythm is normally synchronized. From an early age the sleep-wake rhythm has to be brought into line with the 24-hour day-night cycle (“entrainment”). In healthy 12 month-old children, sleep periods have largely shifted to night, and wakefulness to daytime, excepting, of course, daytime napping. The main cue (or “zeitgeber”) by which this is achieved is presumed to be light perception, while social cues, e.g., mealtimes and social activities, as well as ambient temperature and noise levels, and internal body signals such as hunger and temperature, are also
important. The hormone melatonin, mainly produced in the pineal gland during darkness, influences circadian rhythms via the SCN pacemaker, which in turn, regulates secretion of the hormone by relaying light information to the pineal gland.

### 2.3.2 Assessment of sleep

Subjective measures of sleep, such as sleep history, sleep-wake questionnaire, and sleep diary are based on information obtained from parents, caregivers, and/or children themselves. Objective, detailed, measures of sleep may be obtained through actigraphy and PSG. A careful sleep history, with respect to sleep problems, should describe its precise nature and development, any associated triggering or maintaining factors of the problem, impact of the sleep problem on the child and others, and also past and present treatments and their effectiveness [65]. The sleep history should also describe the child’s 24-hour sleep-wake schedule (school day weekend differences), sleep rhythm, overall amount of sleep each 24 hours, sleep associations, and sleep hygiene. Two additional measures, a sleep-wake questionnaire which gathers retrospective data, and a two-week sleep diary which gathers prospective data, provide supplementary information with regard to the child’s sleep-wake behaviour.

Actigraphy (movement-based computerised sleep-wake detection) is regarded as a reliable method for the assessment of sleep patterns related to timing, duration, and continuity of sleep [66]. Five or more nights of usable recordings are required in order to obtain accurate actigraph measures of sleep for children and adolescents [67]. Agreement rates in sleep-wake detection between actigraphy and PSG are in the 80–95% range. However, it has also been pointed out that some caution is needed when comparing actigraphy and PSG. As noted by Tryon “Actigraphy is a single-channel measurement system, whereas PSG is a multichannel measurement system. It is unlikely, even in principle, for a univariate system to fully duplicate a multivariate system unless the multivariate system is completely redundant, which PSG and actigraphy are not” [68]. The same author adds that some sleep-scoring softwares are better validated against PSG. Actigraphy does not measure physiologic sleep, as does PSG, it measures movement [69]. Moreover, it has been stated that actigraphy and sleep diary as complementary measures should always be used concomitantly in sleep assessment [70].

The gold standard of sleep assessment, the PSG, comprises monitoring of EEG, muscle activity and eye movements. Parallel registration of respiration, blood oxygen saturation levels and electrocardiography is often performed [71]. Common indications of PSG are suspicion of sleep disordered breathing, abnormal limb movements, episodic nocturnal phenomena, such as parasomnias which are frequent, violent, atypical, prolonged, or resistant to treatment, and unexplained daytime sleepiness [71].

### 2.3.3 Disturbed sleep in childhood

When a child has a sleep problem, it is important to attempt to ascertain the specific sleep disorder or underlying cause of the problem. A simplified characterization of sleep problems in children may divide those into the three basic types: difficulty falling
or staying asleep, sleeping too much, and disturbing behaviours during ongoing sleep [65]. The comprehensive International Classification of Sleep Disorders-Revised (ICSD-R) [72] characterizes sleep disorders as dyssomnias, parasomnias, sleep disorders associated with mental, neurological or other medical disorders, and, also, proposed sleep disorders. Dyssomnias are sleep disorders causing either difficulty in going to sleep or remaining asleep (sleeplessness, insomnia, night-wakings, circadian rhythm sleep disorders), or excessive sleepiness during the day. Parasomnias are disturbances that intrude into the sleep process, e.g., nightmares, night terrors, sleep walking and bedwetting. The third category of sleep disorders are sleep-related manifestations of psychiatric or medical conditions. Proposed sleep disorders are disorders needing further assessment.

2.3.4 Sleep patterns in school-age children

The school-age years are characterized by developmental maturation, circadian preference, and irregularity of sleep-wake schedules, and as the child approaches puberty, an increased discrepancy in sleep timing between school day and weekend [73, 74]. The average difference in bed- and get up times on school days and on weekends is approximately 60 minutes at age 10 years, and this discrepancy increases between ages 10 and 13 years [74]. The estimates of prevalence rates of sleep problems in school-age children vary substantially between different reports, possibly reflecting methodological differences between studies. An overall prevalence of parent-reported sleep problems is reported being as high as 37 per cent in the age group 6–12 years, with a 15 to 25 per cent prevalence of bedtime resistance, a 10 per cent prevalence of significant sleep onset delay and anxiety at bedtime, and a 10 per cent prevalence of teacher- and/or parent-reported daytime sleepiness [73]. However, it has been suggested that these figures might underestimate the magnitude of sleep problems during the school-age years, while parents may be unaware of and, thus, underreport sleep concerns at this age.

2.3.5 Relationship between emotional and sleep regulation

The relationship between emotional and sleep regulation [75] is bidirectional, emotional disturbance causing changes in sleep regulation as well as disturbed sleep can cause changes in the control of affect and attention [76]. This general link between emotional regulation and sleep regulation is even more apparent in the domain of clinical disorders of affect regulation [75]. Among depressed children and adolescents, 75% complain of insomnia, and 25% have symptoms of hypersomnia during the episode of depression [75]. Further, inadequate sleep results in alterations in affect and attention. Inadequate or disrupted sleep in children is related to increased irritability, lowered threshold for negative emotional responses, and less control of attention [75].
2.4 SLEEP IN PERVERSIVE DEVELOPMENTAL DISORDERS

Table 3 gives an overview of sleep research on subjects with PDD. Despite the numerous sleep studies in PDD, there is still a scarcity of data in regard to prevalence and persistence of disturbed sleep in subjects with high-functioning PDD, AS and HFA. Previous research on children as well as on adults with PDD has indicated a high frequency of sleep problems related to timing [57, 59, 77-80] initiation [57-59, 77, 80-89] maintenance [57, 59, 80-85, 87, 89, 90], and duration of sleep [59, 80, 87]. Existing sleep research on individuals with high-functioning PDD (n=17) has used both objective [PSG (n=4), actigraphy (n=4)], and subjective measures of sleep [sleep questionnaire and/or diary (n=9)]. As a limitation of these previous studies on subjects with high-functioning PDD, participants have had wide age ranges, only a few studies have been based on objective sleep measures (n=8), and several reports have included participants with factors possibly affecting sleep (medication).

Subjective measure-based research on individuals with high-functioning PDD has indicated:

- a high frequency of sleep problems [58, 59, 77, 80, 86, 87];
- difficulties initiating and maintaining sleep [58, 59, 77, 80, 87]; and
- aberrations in sleep timing and duration [59, 77, 80, 87].

Objective measure-based research has shown:

- difficulties initiating and maintaining sleep [57, 81, 84, 85, 88];
- aberrations in sleep timing [57];
- lower incidence of sleep spindles and/or poor REM sleep control [57, 81, 91]; and
- decreased NREM sleep [57].

Actigraphy-based research [88] has estimated more frequent presence of objective (according to actigraphic data) than subjective, caregiver-reported sleep disturbance in individuals with PDD/AS. In another study, 20 adults with AS showed frequent self-reported insomnia [58]. However, assessments by actigraphy [92] or PSG [93] of these 20 subjects with AS could not detect any difference from the healthy controls. Thus, there is some discrepancy in the findings of actigraphy-based research on subjects with PDD/AS.
Table 3. Sleep studies on children, adolescents and adults with PDD.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Subjects, methods</th>
<th>Findings with regard to sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ornitz 1972 [94]</td>
<td>A review article</td>
<td>A maturational delay in sleep, particularly in REM sleep</td>
</tr>
<tr>
<td>Tanguay 1976 [95]</td>
<td>16 children with PDD aged 36–62 months, and 30 controls aged 3–68 months. PSG</td>
<td>A maturational delay in REM sleep (similar to younger ages)</td>
</tr>
<tr>
<td>Hoshino 1984 [77]</td>
<td>75 children with PDD aged 3–15 yrs (24 were “relatively well-developed”) and 75 controls aged 3–11 yrs. Sleep questionnaire, one-month diary</td>
<td>65% sleep disturbance (past or present), poorly developed group showed higher rate of sleep disturbance than well-developed. The most common: difficulties initiating sleep. Irregular sleep-wake pattern</td>
</tr>
<tr>
<td>Elia 1991 [96]</td>
<td>4 children with PDD aged 10–15 yrs, 5 controls aged 9–17 yrs. PSG</td>
<td>Higher REM sleep density, an increased redundancy of REMs (a dysregulation of REM sleep)</td>
</tr>
<tr>
<td>Segawa 1992 [78]</td>
<td>27 children with PDD. Monthly or bimonthly diary assessment over the course of 4 years</td>
<td>Abnormality of the sleep-wake cycle is a primary and pathognomonic symptom of infantile autism. Improvement of the sleep-wake cycle preceded improvement of other symptoms of autism</td>
</tr>
<tr>
<td>Berthier 1992 [97]</td>
<td>2 adolescents with AS</td>
<td>Kleine-Levin syndrome in both cases</td>
</tr>
<tr>
<td>Richdale 1995 [80]</td>
<td>39 children with PDD aged 32 months–19 yrs (27 with high-functioning PDD aged 4–14 yrs). 58 controls aged 2–14 yrs. 14-day sleep diary and questionnaire</td>
<td>A high rate of sleep problems, particularly difficulties initiating and maintaining sleep, early morning waking</td>
</tr>
<tr>
<td>Author, year</td>
<td>Subjects, methods</td>
<td>Findings with regard to sleep</td>
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<tr>
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</tr>
<tr>
<td>Patzold 1998 [59]</td>
<td>38 children with PDD (7 of them with AS) aged 3–12 yrs, 36 controls aged 5–14 yrs. 14-day sleep diary</td>
<td>High rate of sleep problems (&gt; 60%), mainly bedtime resistance, difficulties initiating and maintaining sleep, longer night wakings, shorter sleep duration</td>
</tr>
<tr>
<td>Hering 1999 [79]</td>
<td>22 children with PDD aged 4–12 yrs. Sleep questionnaire, 8/22 with 72-hour actigraphy</td>
<td>Questionnaire: early sleep offset times, multiple and early night arousals Actigraphy: only early sleep offset times</td>
</tr>
<tr>
<td>Godbout 2000 [81]</td>
<td>8 persons with AS aged 7–53 yrs, 8 controls aged 7–61 yrs. PSG</td>
<td>Difficulties initiating and maintaining sleep: low amount of sleeping time in the first two-thirds of the night. Low incidence of sleep spindles, poor REM sleep control (disruptions of REM sleep)</td>
</tr>
<tr>
<td>Schreck 2000 [82]</td>
<td>55 children with PDD, 22 children with MR, 43 controls, 49 children receiving special education. A sleep questionnaire</td>
<td>Higher frequency of sleep problems in PDD higher dyssomnia- and parasomnia-scores</td>
</tr>
<tr>
<td>Elia 2000 [98]</td>
<td>13 children and adolescents with PDD aged 5–12 yrs, 5 controls aged 7–11 yrs, 7 subjects with fragile X aged 8–12 yrs. PSG</td>
<td>Compared to controls, PDD group showed shorter time in bed, sleep period time, and total sleep time. Compared to fragile X group, PDD group showed shorter first REM latency, less stage 1 sleep, shorter sleep period time</td>
</tr>
<tr>
<td>Honomichl 2002 [83]</td>
<td>100 children with PDD aged 2–11 yrs. Questionnaire and sleep diary</td>
<td>54% had sleep problems. Sleep patterns were stable over a 12-week period. Diary: prolonged sleep latency and more fragmented sleep</td>
</tr>
<tr>
<td>Thirumalai 2002 [90]</td>
<td>11 children with PDD aged 3–9 yrs. PSG</td>
<td>5/11 children diagnosed with REM sleep behaviour disorder</td>
</tr>
<tr>
<td>Author, year</td>
<td>Subjects, methods</td>
<td>Findings with regard to sleep</td>
</tr>
<tr>
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</tr>
<tr>
<td>Paavonen 2003 [84]</td>
<td>15 children with AS and insomnia aged 6–17 yrs. Open clinical trial with melatonin (14 days), 72-hour actigraphy three times</td>
<td>Melatonin improved sleep patterns, decreased sleep latency in 11/15, and also improved daytime behaviour</td>
</tr>
<tr>
<td>Tani 2003 [58]</td>
<td>20 adults with AS aged 19–34 yrs, 10 controls aged 18–34 yrs. Sleep questionnaire, diary</td>
<td>High frequency of insomnia in adults with AS (questionnaire: 18/20; diary: 15/20), also substantial psychiatric comorbidity</td>
</tr>
<tr>
<td>Daoust 2004 [91]</td>
<td>9 persons with AS/HFA aged 12–53 yrs, 8 age- and gender-matched controls. PSG</td>
<td>Lower beta activity during REM sleep (poor REM sleep control) Waking EEG: a higher left prefrontal theta activity</td>
</tr>
<tr>
<td>Tani 2004 [93]</td>
<td>20 adults with AS aged 19–34 yrs, 10 controls aged 18–34 yrs. PSG</td>
<td>No difference between AS and control groups.</td>
</tr>
<tr>
<td>Schreck 2004 [99]</td>
<td>55 children with PDD aged 5–12 yrs. Sleep questionnaire</td>
<td>Associations between: 1) shorter sleep duration and higher autism scores 2) shorter sleep duration, screaming during night and stereotypic behaviour 3) increased sensitivity to environmental stimuli in the bedroom, screaming at night and communication problems</td>
</tr>
<tr>
<td>Wiggs 2004 [85]</td>
<td>69 children with PDD aged 5–16 yrs. 2-week diary, actigraphy, sleep questionnaire</td>
<td>64% showed parent-reported sleeplessness, mostly difficulties initiating and maintaining sleep. No difference in actigraphic patterns between the children with and those without sleeplessness</td>
</tr>
<tr>
<td>Williams 2004 [89]</td>
<td>210 children with PDD aged 2–16 yrs. Sleep questionnaire</td>
<td>Difficulties initiating and maintaining sleep very frequent. Compared to those children without MR, children with MR showed more night wakings</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Subjects, methods</th>
<th>Findings with regard to sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tani 2005 [92]</td>
<td>19 adults with AS aged 19–34 yrs, 10 controls aged 18–34 yrs. Actigraphy</td>
<td>Similar actigraphic profile between AS and control groups.</td>
</tr>
<tr>
<td>Polimeni 2005 [86]</td>
<td>53 children with PDD aged 2–16 yrs, 52 children with AS aged 4–17 yrs, 66 controls aged 2–11 yrs. Sleep questionnaire</td>
<td>PDD and AS groups had more sleep problems than controls. Children with AS had higher scores of overall symptoms of sleep disturbance and more difficulties awakening.</td>
</tr>
<tr>
<td>Limoges 2005 [57]</td>
<td>27 persons with AS/HFA aged 16–27 yrs, 78 age- and gender-matched controls. Sleep questionnaire. 16 pairs: PSG</td>
<td>Symptoms suggestive to insomnia and/or a sleep phase advance. PSG: longer sleep latency, more frequent night wakings, lower sleep efficiency, decreased NREM sleep. Lower sleep spindle density (AS &lt; HFA).</td>
</tr>
<tr>
<td>Couturier 2005 [87]</td>
<td>23 matched pairs of children with high-functioning PDD and controls aged 5–12 yrs. Sleep questionnaire</td>
<td>78% had sleep problems, higher scores on subscales: sleep onset delay, sleep duration, sleep anxiety, and parasomnias.</td>
</tr>
<tr>
<td>Oyane 2005 [88]</td>
<td>15 subjects with PDD aged 15–25 yrs. Sleep questionnaire, diary, actigraphy</td>
<td>Objective sleep disturbance more common than subjective, 80% showed objective sleep disturbance (actigraphic latency &gt; 30 min and/or sleep efficiency &lt; 85%).</td>
</tr>
</tbody>
</table>
2.5 PARENTING CHILDREN WITH AS/HFA

Parenting children with PDD may engender sustained stress, which has been termed “burden of care” [100]. The caregiving process, in general, is affected by several factors such as socio-economic status, parental and child characteristics, coping strategies and social supports [101]. Several studies have examined factors that influence parental adaptation in families with children with high-functioning PDD [102-104]. Pakenham and colleagues used a family stress model (initial stressor and pile-up demands, appraisal, social support, coping strategies and adjustment) while assessing parental adjustment in families of children with AS [102]. The authors analysed the coping of 59 parents of children with AS in relation to two constructs, benefit finding and sense making, and indicated also the positive dimensions of parenting. In detail, 75 per cent of parents reported positive personality change (“increased tolerance of people, broader thinking”). Gray [104] examined the role of gender in relation to stressful events, and found that women were more vulnerable, using different coping strategies than men while coping with their child’s disability. Research [105] has also noted the role of individual differences, such as vulnerabilities and resources, seen as moderating factors between stressors and distress.

Parenting children with developmental disabilities, among them children with PDD and intellectual disability, may be associated with impairments in mental health, [106, 107] higher levels of stress [107-110] a sense of devaluation and blame [108] and also impairments in the physical functioning of the mothers and fathers [111, 112]. Weiss [106] reported that the majority of the parents of 20 children with PDD frequently experienced feelings of intense anger, guilt, depression or anxiety. Such feelings were manifested in psychosomatic problems, impulsive behaviour, sleeping difficulties, and anhedonia. Parental concerns in the families with children with high-functioning PDD are mainly issues related to the child’s adulthood and independent living [100, 113], mental health, victimization, skills deficits, and also to the lack of support and resources [113].

Regarding the relationship between stressful event and gender, Gray [104] compared well-being and coping between 32 mothers and 21 fathers of children with AS/HFA, and found that maternal emotional well-being was most severely affected. Mothers were the parent most likely to have experienced the negative impact of their child’s disability on their daily lives, and they received psychotherapy and medication due to distress, more frequently than fathers. Mothers felt considerable guilt and depression about their child’s disability, and in a few cases, they had also experienced strokes and other physical illnesses that they believed were linked to their child’s disability [104]. As noted by Gray, fathers displayed more suppressed feelings, even when they experienced considerable emotional distress. As a consequence, however, most of the fathers who claimed that they tried to suppress their feelings acknowledged that they often failed to do so [104]. Also Little [7] found that mothers of children with AS and NLD had higher rates of stress related to family problems and pessimism about their child’s future, higher rates of anti-depressant use, and higher rates of psychotherapy use than their spouses. Pakenham and colleagues [114] assessed maternal adjustment in 47 mothers caring for a child with AS, and found that better adjustment was predicted by higher levels of social support, emotional approach
coping, lower levels of child behaviour problems, stress appraisal, and passive avoidant coping. Moreover, mothers’ adjustment was related to the demographic factors, age and annual income, with older mothers showing better social adjustment, less severe depression, and better physical functioning.

Association between parental adaptation and health, with child characteristics such as age, the severity of the disability, and the extent of co-existing behaviour problems, has been pointed out also by other studies [115-117]. It has been suggested that co-existing behaviour problems in the child predict parental stress to a higher extent than the severity of the autistic symptoms [117].

Research has also examined personality traits in parents of children with PDD in an attempt to identify particular parental characteristics as possible expressions of a genetic predisposition to PDD. Wolff et al [118] found more schizoid traits, eccentricity and “social gaucheness” in parents, particularly in fathers, of 21 children with PDD, than in parents of 20 children with other handicaps. Other studies [119, 120] have also reported higher rates of traits expressed as aloofness, anxiety and rigidity [121] or anxiety and conscientiousness [122] among the parents of children and adults with PDD. One report [123], while assessing cognitive style in parents of children with AS, detected a particular cognitive style, reflected by superiority of “islets of ability” and subtle deficits on a mindreading test in these parents. Further, a review of 17 studies [124] showed that compared to parents of typically developing individuals, parents of persons with Down syndrome (DS), and parents of persons with MR of unknown aetiology, the parents of persons with PDD had more psychiatric difficulties. However, compared to parents of those with learning disabilities, and parents of children with psychiatric disorders, the parents of persons with PDD revealed significantly fewer psychiatric difficulties [124].

In summary, research on the parents of children with PDD indicates that many mothers of these children report impaired well-being, and that the mothers are more vulnerable to parenting stress than fathers.
3 OBJECTIVES

The introductory literature review indicates that several issues pertaining to the topic of sleep in childhood AS and HFA, and to the issue of the well-being of the parents of these children remain unclear. Thus, the main objectives of this thesis are to explore whether disturbed sleep is a characteristic aspect of childhood Asperger syndrome (AS) and high-functioning autism (HFA), and whether the raising of a child with AS/HFA is associated with impaired health-related quality of life (HRQL) in the mothers and fathers of these children.

More specifically, the aims are:

1. To examine frequency of globally assessed sleep problems, and sleep patterns related to timing, initiation, duration and maintenance of sleep in school-age children with AS/HFA and in a control group of typically developing children (Paper I)

2. To examine frequency of a wide range of specified sleep-wake behaviour in children with AS/HFA and in a control group of typically developing children (Paper II)

3. To examine frequency of insomnia, and associations between insomnia and behaviour problems in children with AS/HFA and in a control group of typically developing children (Paper II)

4. To examine if frequency of globally assessed sleep problems and sleep patterns related to timing, initiation, duration and maintenance of sleep develop differently in children with AS/HFA than in a control group of typically developing children over the course of 2−3 years (Paper III)

5. To examine HRQL in parents of children with AS/HFA and in parents of a control group of typically developing children (Paper IV)

6. To examine, merely within the AS/HFA group, associations between parental HRQL and child behaviour characteristics (Paper IV).
4 MATERIAL

4.1 SUBJECTS AT BASELINE (PAPERS I, II, IV)

4.1.1 Selection of the AS/HFA group

The AS/HFA group consisted of 32 children (mean age 10.8, range 8.5–12.8 years at baseline), of whom 28 were boys and 4 were girls. These 32 children were selected from a group of 122 children with a clinical diagnosis of AS, using a two-stage procedure (Figure 1).

122 children with AS

First selection stage
34 children were excluded: 5 due to epilepsy,
5 due to essential language delay, 4 due to
comorbid medical disorders, 20 due to
pharmacological treatment

88 children and their parents
received introductory letter

51 children and their parents
agreed to participate

Second selection stage
19 children were excluded:
15 due to pharmacological treatment,
4 due to intellectual disability

32 children participated at baseline

23 children participated at follow-up (2.5 years later)

Figure 1. A selection procedure and participation for subjects in the AS/HFA group.
The 122 children with a clinical diagnosis of AS, born between 1989 and 1992, were registered at three PDD-habilitation centers in Stockholm. In the first selection stage, the medical records of the 122 children with AS were reviewed by the author (H.A.) in order to exclude children with epilepsy, comorbid medical disorders, or ongoing medication, which are factors known to have impact on sleep [125-127]. In addition, essential language delay, which is inconsistent with ICD-10 diagnosis of AS, was used as an exclusion criterion in this selection stage. Thirty-four of the 122 children with AS were excluded: 5 due to epilepsy, 5 due to essential language delay, 4 due to comorbid medical conditions (2 had severe allergic complaints, 1 had ataxia, and 1 had ataxia with a visual impairment), and 20 due to pharmacological treatment (10 were taking psychostimulants, 8 were taking antidepressants, and 2 were taking neuroleptics). The initial review of the medical records did not indicate that any of the children had an intellectual disability.

In the second selection stage, the remaining 88 families were asked by mail to participate in the study. Fifty-one families expressed willingness to take part in the investigation. However, further communication between the author (H.A.) and the parents, along with a second review of medical records, resulted in 19 more exclusions in this stage of selection. Fifteen of the 19 children were excluded due to ongoing psychotropic medication (9 were taking psychostimulants, 3 were taking neuroleptics, and 3 were taking antidepressants). Also, 4 of the 19 children were excluded since further scrutinizing of the available information showed that an intellectual disability could not be ruled out. Furthermore, it was decided that children with a comorbid diagnosis of Tourette syndrome (n=3) were retained in the AS/HFA group. It was later found that the sleep data for these children, compared with the other children in the AS/HFA group, did not differ significantly. Consequently, 32 children with clinical diagnoses of AS constituted the AS/HFA group.

The clinical AS diagnoses of these 32 children were based on comprehensive multidisciplinary assessments (including neuropsychiatric examination, speech and communication testing, and neuropsychological testing) performed on average 40 months (range: 6−89 months) earlier by clinicians at child psychiatric and paediatric clinics. As indicated in the medical records, all of these 32 children with AS were of normal intellectual capacity according to one or more of four individually administered tests of cognitive ability (the Wechsler Intelligence Scale for Children [WISC-R], the Leiter International Performance Scale, the Wechsler Preschool and Primary Scale of Intelligence [WPSSI], or Griffiths' Development Scale). In the majority (n=21) of the cases, IQ was assessed using the WISC-R.

4.1.2 Diagnostic reassessment

Prior to sleep assessment, all of these 32 children with a clinical diagnosis of AS were subjected to a diagnostic reassessment, made by the research team, and mainly by the author (H.A.) [22]. The reassessment, which was based on interviews with parents and children, and on an additional review of medical records, showed that 13 children (11 boys and 2 girls) with a clinical diagnosis of AS displayed a history of essential language delay, and that they fulfilled criteria for autistic disorder (see Paper I, Appendix A1). Consequently, these 13 children were re-diagnosed with HFA. Nineteen
children (17 boys and 2 girls) from 32 with a clinical diagnosis of AS fulfilled ICD-10 research criteria for AS.

4.1.3 The issue of language delay

The initial aim of the present study was merely to study sleep patterns in children with a diagnosis of AS. According to the ICD-10 and the DSM-IV, there is a requirement of no clinically significant language delay in the diagnosis of AS. Consequently, during the earliest stages of the investigation, children with a clear indication of essential language delay in the medical records were excluded. However, the further diagnostic reassessment revealed that 13 out of the 32 children with the clinical diagnosis of AS displayed a history of early language delay and fulfilled the ICD-10 research criteria for autistic disorder. These children were retained in the sample, and the final aim of the study was changed in order to allow to explore sleep patterns of school-age children with both AS and HFA. The issue of language delay is also discussed in § 8.2.

4.1.4 Selection of the control group

The control group, 32 typically developing children (mean age 10.9, range 8.5–13.4 years), 28 boys and 4 girls were matched pairwise with the children in the AS/HFA group with respect to age, gender, residency, and actigraphy device. The controls were recruited via mainstream schools. In a first step of recruitment procedure, school nurses selected children of suitable age and gender who attended regular classes in mainstream schools and were without mental, developmental, or physical disabilities and long-term medication according to school medical records. In a second stage of recruitment of controls, a school nurse or the author (H.A.) telephoned the parents of selected children and asked whether the families were willing to participate in the study. An introductory letter was then sent to families who agreed to participate. The controls were not IQ tested.

4.1.5 Sociodemographic data

Descriptive data with regard to sociodemographics for children and parents in the AS/HFA and control groups are provided in Table 4. Statistical comparisons showed no difference between the groups, except the family status and school situation. Fewer children in the AS/HFA group than in the control group lived in nuclear families (65.6% vs. 87.5%, p < 0.05). Furthermore, all children in the control group, but only 13 of the children with AS/HFA attended regular classes in mainstream schools. Four of these 13 children with AS/HFA attending mainstream schools, received extra support from school assistants. Nineteen children with AS/HFA attended classes or schools for children with various special needs.
Table 4. Sociodemographic data for children and parents in the Asperger syndrome (AS)/high-functioning autism (HFA) and control groups.

<table>
<thead>
<tr>
<th></th>
<th>AS/HFA group (n=32)</th>
<th>Control group (n=32)</th>
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</thead>
<tbody>
<tr>
<td><strong>Gender of children N</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Boys</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td><strong>Age of children, mean</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(range) years</td>
<td>10.8 (8.5–12.8)</td>
<td>10.9 (8.5–13.4)</td>
</tr>
<tr>
<td><strong>School situation (children) N</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mainstream school</td>
<td>13</td>
<td>32</td>
</tr>
<tr>
<td>Special class or school</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td><strong>No. of children in family</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(range)</td>
<td>2.0 (1–4)</td>
<td>2.5 (1–4)</td>
</tr>
<tr>
<td><strong>Family status N</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuclear</td>
<td>21</td>
<td>28</td>
</tr>
<tr>
<td>Single parent</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>One step-parent</td>
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<td>2</td>
</tr>
<tr>
<td><strong>Age of parents, mean (range) years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mothers</td>
<td>42.4 (28–54)</td>
<td>40.3 (31–51)</td>
</tr>
<tr>
<td>Fathers</td>
<td>45.6 (35–64)</td>
<td>42.7 (35–53)</td>
</tr>
<tr>
<td><strong>High school education N (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mothers</td>
<td>20/31 (64.5)</td>
<td>19/30 (63.3)</td>
</tr>
<tr>
<td>Fathers</td>
<td>20/30 (66.6)</td>
<td>17/29 (58.6)</td>
</tr>
<tr>
<td><strong>Paid employment of parents N (%)</strong></td>
<td></td>
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</tr>
<tr>
<td>Mothers</td>
<td>23/31 (74.1)</td>
<td>28/30 (93.3)</td>
</tr>
<tr>
<td>Fathers</td>
<td>28/30 (93.3)</td>
<td>28/29 (96.5)</td>
</tr>
<tr>
<td><strong>On sick leave (for any illnesses) N (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mothers</td>
<td>3/31 (9.6)</td>
<td>1/30 (3.3)</td>
</tr>
<tr>
<td>Fathers</td>
<td>0/30</td>
<td>1/29 (3.4)</td>
</tr>
</tbody>
</table>
4.1.6 Parents

The AS/HFA group consisted of 31 mothers (mean age 42.4, range 28–54 years) and 30 fathers (mean age 45.6, range 35–64 years) to 32 children with AS/HFA. The control group consisted of 30 mothers (mean age 40.3, range 31–51 years) and 29 fathers (mean age 42.7, range 35–53 years) to 32 typically developing children (Table 4). The analysis did not show any statistically significant difference in parental demographic data between the AS/HFA and control groups.

4.2 SUBJECTS AT FOLLOW-UP (PAPER III)

At follow-up 23/32 children with AS/HFA were examined (mean age 13.7, range 11.7–15.5 years). Of these, 21 were boys and 2 were girls. Twenty-two of 32 children in the control group (mean age 13.6, range 11.2–15.8 years) were also examined, of these 20 boys and 2 girls. Complete sleep diary and actigraphy data were available for 21/32 children with AS/HFA (65.5% of the sample at baseline), and for 20/32 of the controls (62.5%). Within the AS/HFA group, of these 15 were children with AS and 6 children with HFA. A parental report of a global sleep problem was obtained for only 2 children with AS/HFA, and for 2 of the controls. The mean interval between baseline and follow-up was 2.5±0.4 years (range 2.2–3.7) for the AS/HFA group and 2.6±0.4 years (range 2.1–3.7) for the control group. Reasons for non-participation at follow-up included non-compliance of the child or family, or relocation.

With regard to sociodemographic data at follow-up, the school situation differed between children with AS/HFA and the control group. All of the control group, but only 14 children with AS/HFA attended regular classes in mainstream schools. Seven children with AS/HFA attended classes or schools for children with various special needs. Further, it should be acknowledged that at baseline, the presence of comorbid medical disorders and long-term pharmacological treatment, factors possibly affecting sleep [125-127], had constituted exclusion criteria. Forty-four children had been excluded from the AS/HFA group due to these exclusion criteria. However, in order to attain as great a follow-up sample as possible, these exclusion criteria were abandoned at follow-up. Hence, all children/families who were willing to remain in the study were included at follow-up. Consequently, 5 children with AS/HFA versus 4 from the control group showed medical problems at the time of follow-up [AS/HFA group: allergic symptoms (n=4), and diabetes type 1 (n=1) which had started around 1.5 yrs before the follow-up; versus control group: allergic symptoms (n=4)]. Moreover, 4 children with AS/HFA and 3 control children received pharmacological treatment at follow-up [AS/HFA group: anti-asthma medication (n=1), anti-asthma medication and melatonin (n=1), insulin and anti-asthma medication (n=1), antidepressant and melatonin (n=1). Control group: anti-asthma medication (n=3)].
5 METHODS

5.1 MEASURES OF SLEEP (PAPERS I, II, III)

5.1.1 Sleep questionnaire

A parental paediatric sleep questionnaire previously used in population-based studies of Swedish children [128-130], with satisfactory test/retest reliability, was utilized for a detailed survey of retrospective sleep-wake behaviour pertaining to the previous six months. Twenty-one items (items Q1–Q21) were categorized according to a 5-point rating scale (“never,” “rarely,” “once or twice per week,” “3 or 4 times per week,” and “at least 5 times per week”). The questionnaire used for this study also comprised additional items: a global question regarding whether the child had a current sleeping problem Q22, and questions about the following consequences of that sleeping problem: distress Q23, impaired daytime functioning in the child Q24, and a burden for the family Q25 (see Paper II, Additional file 1).

The questionnaire data presented in Papers I and III were based on the global question about whether or not the child was affected by sleeping problems, including parental response to an open-ended question about the nature of the child’s sleep problem. The questionnaire data presented in Paper II were based on information from Q1–Q25. Persistent sleep problem in Paper III was operationally defined as the presence of sleep problem in the child both at baseline and follow-up, according to parent endorsement of item Q22.

In Paper II questionnaire data were used in order to diagnose paediatric insomnia on the basis of the following DSM-IV-adapted criteria [131]:

1) the complaint is significant difficulty (defined by frequency, severity, and/or chronicity) in initiating or maintaining sleep. The difficulty is viewed as problematic by the child and/or a caregiver;
2) the sleep disturbance causes clinically significant impairment in school performance, behaviour, mood, learning, or development, for the child as reported by the child and/or a caregiver;
3) the sleep disturbance does not occur exclusively in the context of an intrinsic dyssomnia such as narcolepsy, restless legs syndrome, or sleep-related breathing disorders; a circadian rhythm disorder, or a parasomnia; and
4) the sleep disturbance is not attributable to either the direct physiologic effect of a drug or the abuse or misuse of a prescribed medication.
5.1.2 Child Sleep Diary

During one week, parents recorded six items of information: the time when the child went to bed (bedtime), the time in minutes required for the child to fall asleep (sleep onset latency), whether or not the child awakened at night (on a yes-no basis) (nighttime awakening), the time when the child woke up in the morning (get up time), parent’s estimation of the duration of the child’s nighttime sleep (total sleep time), and parent’s rating on a 5-point scale of the quality of the child’s nighttime sleep (sleep quality) (1=very poor, 2=quite poor, 3=neither poor nor good, 4=quite good, 5=very good).

5.1.3 Actigraphy

During the same week as the sleep diary, objective measures of sleep were evaluated by actigraphic monitoring. The actigraph used in the current project, Actiwatch (Cambridge Neurotechnology, Ltd, Cambridge, UK) is a self-contained mini computer the size of a wristwatch that is worn on the child’s non-dominant arm. It contains a piezoelectric accelerometer that records all movements exceeding the 0.05 g threshold, and translates these movements into electrical signals. Movements were sampled at the medium sensitivity level with the epoch length 30 sec and stored as activity counts per epoch in the Actiwatch’s 16-K memory. Data from the actigraph’s memory were thereafter downloaded to the Actiwatch Sleepwatch software [132, 133]. Bed- and get up times obtained from the child sleep diaries were manually entered into the software program. Sleep start was defined as the first minute after bedtime that was identified as sleep by the Actiwatch Sleepwatch algorithm and was followed by at least 10 consecutive minutes of recorded immobility. Sleep latency was defined as the latency before sleep start, following bedtime. Sleep end classified as the last epoch of immobility before the start of at least 10 minutes of consecutive activity. Actual sleep time was the calculated difference between sleep end and sleep start in minutes minus actual time spent awake during the sleep period. Number of night wakings was defined as a number of manually scored wakings lasting 5 minutes or longer, preceded and followed by at least 15 minutes of uninterrupted sleep [134]. Duration of night wakings was the total duration of these night wakings (≥5 min). Sleep efficiency was defined as the percentage of time spent asleep while in bed, and Actual time awake as the amount of time sent awake as determined by the algorithm.

All sleep diary and actigraphy variables were calculated for each child, and averaged into school day and weekend mean values, using the occurrence of school attendance the next day as the definition of a school day (school day: Sunday, Monday, Tuesday, Wednesday, Thursday; weekend: Friday, Saturday).
5.2 MEASURES OF CHILD BEHAVIOUR (PAPERS I, II, IV)

The Autism Spectrum Screening Questionnaire (ASSQ), a 27-item checklist for screening for AS and HFA in children 7–16 years of age [135], was used to evaluate the extent of autism-related symptoms in children with AS/HFA and also to screen for autism-related symptoms in the control group. Eleven items covering social interaction, 6 items covering communication problems, and 5 items covering aspects of restricted and repetitive behaviour were included. The remaining 5 items embrace motor clumsiness and other associated symptoms, including motor and vocal tics. Items are rated on a 3-point scale. Parent and teacher ASSQ versions have shown satisfactory test/retest reliability, inter-rater reliability, and validity [135].

The Strengths and Difficulties Questionnaire (SDQ), a 25-item checklist, was used in order to measure aspects of prosocial behaviour (social competence) and general behaviour problems in the child [136]. The SDQ probes behaviours and psychological attributes reflecting the child’s difficulties such as hyperactivity, emotional symptoms, conduct and peer problems, and also strengths, such as ability to act prosocially. All items are rated on a 3-point scale, and higher scores indicate higher rates of psychopathology, except the prosocial behaviour subscale, where the opposite is the case. A total difficulties score is constituted by the sum of scores on the 4 subscales of difficulties (hyperactivity, emotional symptoms, conduct and peer problems). Both parent [137] and teacher SDQ versions [136] have shown satisfactory reliability and validity.

5.3 MEASURES OF PARENTAL HRQL (PAPER IV)

The 12 Item Short-Form Health Survey (SF-12), a validated 12-item questionnaire was used to measure parental HRQL [138]. The SF-12 is a short instrument, covering the physical, emotional and social dimensions of health, and generating two scores, the Physical Component Summary (PCS-12), and the Mental Component Summary (MCS-12) score. In the current project, parental SF-12 scores of the parents of children with AS/HFA and of the parents of the typically developing controls were also compared to Swedish population means [139].

5.4 PROCEDURES FOR DATA COLLECTION

5.4.1 Sleep (Papers I, II and III)

Instruments to measure sleep (diaries, actigraphs and sleep questionnaires) were distributed to all families in conjunction with home visits, at both baseline and 2–3 years follow-up. Participants and their parents were instructed in the use of actigraphs and how to complete sleep diaries and sleep questionnaires. One week of parallel actigraphic and sleep diary recording commenced in conjunction with the first home visit. Following the monitoring period, actigraphs, sleep diaries and sleep
questionnaires were returned via a second home visit, a parental visit to the clinic, or by mail. At baseline, 62 participants, 30 children with AS/HFA and 32 children from the control group were monitored by sleep diary and actigraphy for 7 days, and 2 children with AS/HFA were monitored for 6 days. The current project used a pairwise matched design, thus, children within each matched pair were monitored within 2–4 weeks of one another using the same actigraphy device. Four different actigraphy devices were used, and the numbers of participants in each group were 9, 7, 8, and 8 pairs of children, respectively (Figure 2).

<table>
<thead>
<tr>
<th>AS/HFA group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
</tr>
<tr>
<td>32 children</td>
<td>32 matched pairs</td>
</tr>
<tr>
<td>32 children</td>
<td></td>
</tr>
<tr>
<td><strong>Measures:</strong></td>
<td></td>
</tr>
<tr>
<td>Sleep questionnaire</td>
<td></td>
</tr>
<tr>
<td>(AS/HFA: 32 vs. 32)</td>
<td></td>
</tr>
<tr>
<td>One-week sleep diary</td>
<td></td>
</tr>
<tr>
<td>(32 vs. 32)</td>
<td></td>
</tr>
<tr>
<td>One-week actigraphy</td>
<td></td>
</tr>
<tr>
<td>(32 vs. 32)</td>
<td></td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td></td>
</tr>
<tr>
<td>23 children</td>
<td>16 matched pairs</td>
</tr>
<tr>
<td>22 children</td>
<td></td>
</tr>
<tr>
<td><strong>Measures:</strong></td>
<td></td>
</tr>
<tr>
<td>Sleep questionnaire</td>
<td></td>
</tr>
<tr>
<td>(AS/HFA: 23 vs. 22)</td>
<td></td>
</tr>
<tr>
<td>One-week sleep diary</td>
<td></td>
</tr>
<tr>
<td>(21 vs. 20)</td>
<td></td>
</tr>
<tr>
<td>One-week actigraphy</td>
<td></td>
</tr>
<tr>
<td>(21 vs. 20)</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2.** Sleep assessment procedure at both baseline and follow-up for children in the AS/HFA and control groups. Interval between baseline and follow-up was: 2.5±0.4 (range 2.2–3.7 years) for the AS/HFA group and 2.6±0.4 (range 2.1–3.7 years) for the control group.

Due to drop-outs (AS/HFA: 11 vs. control-group: 12 cases), only 16 matched pairs remained in the study at follow-up. In addition, 5 separate subjects in the AS/HFA group and 4 subjects in the control group participated without their pairs at follow-up. The length of sleep recording at follow-up was as follows: 7 days for 16 children with AS/HFA versus 14 of the control group; 6 days for three children with AS/HFA versus five from the control group; and 5 days for two children with AS/HFA versus one from the control group.
5.4.2 Child behaviour (Papers I, II and IV)

The ASSQ and SDQ, both parent and teacher versions were distributed to all families simultaneously with the study of the children’s sleep patterns. Parents conveyed the relevant instruments to their children’s teachers. Teachers mailed the completed forms to the author (H.A.), and parent versions were returned via a second home visit, a parental visit to the clinic, or by mail.

5.4.3 Parental HRQL (Paper IV)

The SF-12, were distributed to the families at the first home visit, simultaneously with the study of children’s sleep patterns. If the parent (in this sample the father) did not live together with the child, the HRQL screening form was mailed to him. The questionnaires were returned via a second home visit, a parental visit to the clinic, or by mail.

5.4.4 Ethical considerations

Both baseline and follow-up investigations were approved by the Ethical Committee at the Karolinska Hospital, Stockholm, Sweden (Dnr 00-213, 03-320).
6 STATISTICAL ANALYSES

The project used a pairwise matched design, i.e., the children in the AS/HFA and the control groups were originally matched pairwise on age, gender, residency, and actigraphy device. Further, Papers I, II and IV were based on a cross-sectional study design in order to analyse sleep and parental HRQL data at baseline. Paper III used a longitudinal study design in an attempt to assess the change and development of sleep patterns from baseline to follow-up. Sample size estimations were performed in advance. Taking into account the assumed prevalence rates of sleep disturbances in both groups (AS/HFA: 60 vs. control: 10 %) [80], at least 17 children were required in both groups in order to detect differences with 80% power. This sample size was regarded as suitable to investigate the main research question, i.e., prevalence of globally assessed sleep problems in the AS/HFA and control groups.

Sociodemographic data and the frequency of occurrence of sleep-wake behaviours were groupwise compared, using standard statistical methods (Table 5). Further, the relationship between paediatric insomnia and child behavioural characteristics, and between paediatric insomnia and recent sleep patterns in Paper II were assessed using logistic regression. In Paper IV linear regression was used to analyse the relationships between parental HRQL and child behaviour.

Sleep diary and actigraphy data were obtained at both baseline (32 pairs of children) and 2–3 years follow-up (AS/HFA: 21/32 vs. control: 20/32). Thus, repeated measurements of sleep for each single individual were obtained at both time-points. All sleep variables for each child were averaged into school day and weekend mean values (see § 5.1.3). Sleep data were analysed as follows: In Paper I sleep patterns were compared between children with AS/HFA and the typically developing controls using repeated-measures analysis of variance (ANOVA), with group (AS/HFA vs. control) and day of the week (school day vs. weekend) as two within subject factors. In addition comparisons were carried out within the AS/HFA group: (1) between children with and those without sleep problems; and (2) between children with AS and children with HFA, using the presence or absence of parent-reported sleep problems, or these two diagnostic groups, respectively, as between subject factors in repeated measures ANOVA.

Paper III as a longitudinal assessment aimed at characterizing within individual changes in sleep patterns over time (2–3 years) in both groups, and to detect group differences in change of sleep patterns between the AS/HFA and control groups. Longitudinal data were unbalanced and incomplete due to missing data at follow-up (AS/HFA: 11 cases vs. control: 12 cases), thus, the most appropriate method to analyse such data was the linear mixed effects model [140, 141]. This model was chosen to adequately represent the average value of the sleep variable at both points of time in terms of covariates such as (1) group (AS/HFA and control); (2) time (baseline and follow-up); (3) baseline value; and (4) time interval between baseline and follow-up for each child. The model also accounts successfully for the observed pattern of dependence in these measurements. The fixed main effects of time, group, and interaction between time, and group, were investigated. Due to skewness in distribution in sleep variables, all data were log transformed before analyses to achieve approximate normality.
Table 5 displays a summary of statistical analyses, conducted in *Papers I-IV*. For more detailed descriptions of all these statistical analyses, see *Papers I-IV*. The Statistical Package for Social Sciences (SPSS) [142] and Stata [143] were used. Significance level $p < 0.05$ was regarded as statistically significant.

<table>
<thead>
<tr>
<th>Paper</th>
<th>Measures</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Sociodemographic data</td>
<td>t-test for paired samples</td>
</tr>
<tr>
<td></td>
<td>ASSQ</td>
<td>Wilcoxon test for paired samples</td>
</tr>
<tr>
<td></td>
<td>Parent report of a sleep problem</td>
<td>Repeated measures ANOVA</td>
</tr>
<tr>
<td></td>
<td>One-week diary</td>
<td>Pearson bivariate correlation</td>
</tr>
<tr>
<td></td>
<td>One-week actigraphy</td>
<td>Mantel-Haenszel test</td>
</tr>
<tr>
<td>II</td>
<td>Sociodemographic data</td>
<td>t-test for paired samples</td>
</tr>
<tr>
<td></td>
<td>A sleep questionnaire</td>
<td>Wilcoxon signed ranks test</td>
</tr>
<tr>
<td></td>
<td>One-week diary</td>
<td>Ordinal regression</td>
</tr>
<tr>
<td></td>
<td>One-week actigraphy</td>
<td>Logistic regression</td>
</tr>
<tr>
<td></td>
<td>ASSQ</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SDQ</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Sociodemographic data</td>
<td>Mann-Whitney test</td>
</tr>
<tr>
<td></td>
<td>Parent report of a sleep problem</td>
<td>Linear mixed effects model for repeated measurements</td>
</tr>
<tr>
<td></td>
<td>One-week diary</td>
<td></td>
</tr>
<tr>
<td></td>
<td>One-week actigraphy</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Sociodemographic data</td>
<td>Fischer’s exact test</td>
</tr>
<tr>
<td></td>
<td>SF-12 (MCS-12, PCS-12)</td>
<td>Mann-Whitney test</td>
</tr>
<tr>
<td></td>
<td>ASSQ</td>
<td>t-test for paired samples</td>
</tr>
<tr>
<td></td>
<td>SDQ</td>
<td>Linear regression</td>
</tr>
</tbody>
</table>

ANOVA = Analysis of Variance; ASSQ = the High-Functioning Autism Spectrum Screening Questionnaire; MCS-12 = Mental Component Summary; PCS-12 = Physical Component Summary; SDQ = the Strengths and Difficulties Questionnaire; SF-12 = 12 Item Short Form Health Survey.
7 RESULTS

*Paper I* presents comparisons of the frequency of parent-reported sleep problems, and sleep patterns (sleep diary and actigraphy) at baseline in the school-age children with AS/HFA and in the children of the control group. *Paper I* also presents within AS/HFA group assessments of sleep patterns whereby children with and those without parent-reported sleep problems, and children with AS and children with HFA are compared. *Paper II*, an extension of *Paper I*, details frequency of occurrence of a wide range of sleep-wake behaviour, and investigates rate of paediatric insomnia. *Paper II* also evaluates relations between paediatric insomnia, sleep diary and actigraphy variables, and, additionally, relations between insomnia and child behaviour. *Paper III*, longitudinally, evaluates whether sleep patterns develop differently in children with AS/HFA than in the control group of typically developing children over the course of 2–3 years. Finally, *Paper IV* focuses on parental HRQL, and associations between parental HRQL and child behaviour.

7.1 SLEEP PATTERNS AT BASELINE (PAPER I)

7.1.1 Parent-reported sleep problems

The odds ratio for parental report of global sleep problems in the AS/HFA group was 6.3 (95% CI: 1.8–21.4, p < 0.01). Nineteen children in the AS/HFA group (59.2%) and 3 of the children in the control group (9%) had parent-reported sleep problems. The sleep problems were perceived as mild in 10 of the children in the AS/HFA group (31.2%) versus 1 child in the control group (3.1%), and as definite in 9 of the children in the AS/HFA group (28.1%) versus 2 children in the control group (6.2%). The parents’ reply to an open-ended question revealed that bedtime resistance was a concern in 3 children in the AS/HFA group and for 1 child in the control group. Difficulties in falling asleep were reported for 12 children with AS/HFA, nighttime awakenings with difficulty in going back to sleep were described for 2 children with AS/HFA, restlessness during sleep was reported for 1 child with AS/HFA, “increased need for sleep” was described as a problem for 1 child in the AS/HFA group, and bed-wetting and nightmares were described as concerns for 1 child in the control group.

Further, sleep diary and actigraphic variables were compared between the children with and those without sleep problems in the AS/HFA group, using the presence of parent-reported sleep problems (dichotomized to *yes* and *no*) as the *between subject factors* in repeated measures ANOVA. Statistically significant differences between these two subgroups were found for diary-recorded sleep onset latency [F(1, 31)=6.2, p < 0.05] as well as for actigraphic sleep latency [F(1, 31)=6.1, p < 0.05]. Children with AS/HFA and sleep problems displayed 20.9 minutes longer sleep onset latency on school days, and 8.5 minutes longer sleep onset latency on weekends than those without sleep problems, according to sleep diary data. Actigraphic data revealed 13.9 minutes longer sleep latency on school days and 8.7 minutes longer sleep latency on weekends for the parent-reported sleep-disordered group. Children with sleep
problems and AS/HFA also showed more variable sleep latency, reflected in a higher standard deviation, according to both sleep diary and actigraphy data.

### 7.1.2 Timing and duration of sleep

Descriptive sleep diary data at baseline and at follow-up are presented in Table 6, and corresponding actigraphic data are presented in Table 7.  

Sleep diary data on bedtime, get up times, and total sleep time, as well as actigraphic data on sleep start, sleep end, and actual sleep time were used to determine the timing and duration of sleep. Sleep diary data displayed significant group-by-day interactions for bedtime \( F(1, 31)=7.04, p < 0.05 \) and get up time \( F(1, 31)=7.03, p < 0.05 \). Contrast analysis showed that the interactions depended on differences between children in the AS/HFA group and children in the control group at weekends. Compared to children in the control group, the children with AS/HFA had an average 39 minute earlier bedtimes and 40 minute earlier get up times at weekends (Table 6). Actigraphy data (Table 7) indicated statistically significant group-by-day interactions for sleep start \( F(1, 31)=11.52, p < 0.01 \) and sleep end \( F(1, 31)=7.82, p < 0.01 \). The interactions were due to the differences at weekends, children in the AS/HFA group showed an average 30 minute earlier sleep start time and an average 40 minute earlier sleep end time at weekends than the children in the control group. 

Both sleep diary (delayed bed- and get up times) and actigraphy (delayed sleep start and sleep end times) indicated a significant sleep phase delay in both groups at weekends. This phase delay was more pronounced for children in the control group. 

*Sleep duration* was measured by sleep diary data on total sleep time and actigraphic data on actual sleep time. Neither total sleep time, nor actual sleep time, differed between the children in the AS/HFA and the control groups.
Table 6. Sleep Diary variables of children with Asperger syndrome (AS) and high-functioning autism (HFA) and children in the control group at both baseline and follow-up.

<table>
<thead>
<tr>
<th>Sleep variable</th>
<th>Measurement</th>
<th>Day</th>
<th>Baseline</th>
<th></th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>AS/HFA (n=32)</td>
<td>Controls (n=32)</td>
<td>AS/HFA (n=21)</td>
</tr>
<tr>
<td>Bedtime</td>
<td>Time (PM)</td>
<td>School day</td>
<td>09:15 (34.9)</td>
<td>09:26 (35.6)</td>
<td>10:29 (86.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weekend</td>
<td>10:14 (54.3)</td>
<td>10:54 (59.5)</td>
<td>11:10 (66.8)</td>
</tr>
<tr>
<td>Sleep Onset</td>
<td>Mean (SD-min)</td>
<td>School day</td>
<td>31.7 (20.9)</td>
<td>17.2 (14.7)</td>
<td>25.8 (16.0)</td>
</tr>
<tr>
<td>Latency</td>
<td></td>
<td>Weekend</td>
<td>18.3 (13.7)</td>
<td>11.4 (10.3)</td>
<td>15.8 (11.2)</td>
</tr>
<tr>
<td>Get Up Time</td>
<td>Time (AM)</td>
<td>School day</td>
<td>07:05 (30.2)</td>
<td>07:11 (22.5)</td>
<td>07:15 (76.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weekend</td>
<td>07:56 (55.0)</td>
<td>08:36 (51.6)</td>
<td>08:37 (88.7)</td>
</tr>
<tr>
<td>Total Sleep Time</td>
<td>Mean (SD-min)</td>
<td>School day</td>
<td>542 (39.3)</td>
<td>556 (33.0)</td>
<td>490 (52.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weekend</td>
<td>553 (51.4)</td>
<td>566 (47.6)</td>
<td>525 (78.1)</td>
</tr>
<tr>
<td>Sleep Quality</td>
<td>Mean (SD)</td>
<td>School day</td>
<td>4.0 (0.6)</td>
<td>4.6 (0.6)</td>
<td>3.9 (0.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weekend</td>
<td>4.4 (0.6)</td>
<td>4.6 (0.6)</td>
<td>4.4 (0.6)</td>
</tr>
</tbody>
</table>
Table 7. Actigraphy variables of children with Asperger syndrome (AS) and high-functioning autism (HFA) and children in the control group at both baseline and follow-up.

<table>
<thead>
<tr>
<th>Sleep variable</th>
<th>Measurement</th>
<th>Day</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Baseline</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>AS/HFA (n=32)</td>
<td>Controls (n=32)</td>
<td>AS/HFA (n=21)</td>
<td>Controls (n=20)</td>
</tr>
<tr>
<td><strong>Sleep Start</strong></td>
<td>Time (PM)</td>
<td>School day</td>
<td>09:47 (40.1)</td>
<td>09:42 (32.5)</td>
<td>10:56 (89.7)</td>
<td>10:50 (50.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weekend</td>
<td>10:36 (54.6)</td>
<td>11:06 (58.7)</td>
<td>11:35 (67.4)</td>
<td>00:08 (53.7)</td>
</tr>
<tr>
<td><strong>Sleep Latency</strong></td>
<td>Mean</td>
<td>School day</td>
<td>32.2 (17.9)</td>
<td>15.7 (10.6)</td>
<td>28.8 (19.8)</td>
<td>19.4 (13.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weekend</td>
<td>21.5 (20.0)</td>
<td>11.4 (10.3)</td>
<td>23.3 (25.1)</td>
<td>18.7 (20.9)</td>
</tr>
<tr>
<td><strong>Sleep End</strong></td>
<td>Time (AM)</td>
<td>School day</td>
<td>07:00 (30.3)</td>
<td>07:04 (23.2)</td>
<td>07:09 (78.9)</td>
<td>07:08 (33.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weekend</td>
<td>07:51 (53.7)</td>
<td>08:31 (53.4)</td>
<td>08:24 (89.9)</td>
<td>09:00 (54.5)</td>
</tr>
<tr>
<td><strong>Actual Sleep Time</strong></td>
<td>Mean</td>
<td>School day</td>
<td>511 (34.7)</td>
<td>523 (35.0)</td>
<td>425 (37.4)</td>
<td>432 (49.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weekend</td>
<td>514 (44.4)</td>
<td>522 (42.5)</td>
<td>451 (56.2)</td>
<td>466 (42.4)</td>
</tr>
<tr>
<td><strong>No of Night Wakings</strong></td>
<td>Mean</td>
<td>School day</td>
<td>1.1 (0.7)</td>
<td>1.0 (0.9)</td>
<td>1.5 (0.7)</td>
<td>1.6 (0.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weekend</td>
<td>1.1 (0.9)</td>
<td>1.1 (0.8)</td>
<td>2.1 (0.8)</td>
<td>1.7 (0.8)</td>
</tr>
<tr>
<td><strong>Duration of Night</strong></td>
<td>Mean</td>
<td>School day</td>
<td>10.9 (8.5)</td>
<td>7.9 (6.7)</td>
<td>15.6 (10.1)</td>
<td>16.7 (11.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weekend</td>
<td>9.5 (10.3)</td>
<td>8.1 (6.5)</td>
<td>22.3 (10.3)</td>
<td>14.6 (8.1)</td>
</tr>
<tr>
<td><strong>Sleep Efficiency</strong></td>
<td>Mean</td>
<td>School day</td>
<td>87.1 (3.6)</td>
<td>90.3 (4.1)</td>
<td>81.1 (5.2)</td>
<td>82.8 (4.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weekend</td>
<td>88.6 (4.7)</td>
<td>90.1 (4.1)</td>
<td>79.7 (5.8)</td>
<td>82.8 (5.2)</td>
</tr>
</tbody>
</table>
7.1.3 Initiation and maintenance of sleep

Sleep diary data on bedtime and sleep onset latency (Table 6), and actigraphic data on sleep latency (Table 7) were used to determine the initiation of sleep. Sleep diary data showed a significant group-by-day interaction for sleep onset latency \( F(1, 31)=4.63, p < 0.05 \). The interaction mainly depended on difference on school days, children in the AS/HFA group required 15 minutes longer time to fall asleep than children in the control group. Further, actigraphic sleep latency differed between the two groups on school days \( F(1, 31)=21.62, p < 0.001 \) and at weekends \( F(1, 31)=6.81, p < 0.05 \). Children with AS/HFA had approximately 17 minutes longer sleep latency on school days, and 10 minutes longer sleep latency at weekends than the children in the control group.

Sleep diary data (Table 6, sleep quality) on night-time awakenings and sleep quality, and actigraphic data (Table 7) on number of night wakings \((\geq 5 \text{ min})\), duration of night wakings, and sleep efficiency were used to investigate the maintenance of sleep. Only two measures differed statistically significantly between the AS/HFA and the control groups: sleep quality on school days \( F(1, 31)=7.15, p < 0.05 \) and sleep efficiency on school days \( F(1, 31)=15.60, p < 0.001 \). On school days, children with AS/HFA showed poorer parent-rated sleep quality, and lower actigraphic sleep efficiency than corresponding children in the control group.

7.1.4 Sleep diary versus actigraphy

With regard to timing of sleep, the correlation between bedtime (diary) and sleep start time (actigraphy) on school days was: 0.89 (p < 0.001) in the AS/HFA group, and 0.95 (p < 0.001) in the control group. The correlation between get up time (diary) and sleep end time (actigraphy) on school days was: 0.99 (p < 0.001) in the AS/HFA group, and 0.98 (p < 0.001) in the control group. Regarding initiation of sleep, the correlation between sleep onset latency (diary) and sleep latency (actigraphy) on school days was: 0.80 (p < 0.01) in the AS/HFA group, and 0.55 (p < 0.01) in the control group. Correspondence in sleep duration, between total sleep time (diary) and actual sleep time (actigraphy) on school days was 0.73 (p < 0.01) in the AS/HFA group, and 0.64 (p < 0.01) in the control group.

7.1.5 AS/HFA differences in sleep patterns

Parents’ retrospective reports indicated that 11 of the 19 children with AS (57%), and 8 of the 13 children with HFA (61%) showed sleep problems. Statistical analysis of all diary and actigraphy data, with AS and HFA as between subject factors in repeated measures, ANOVA, did not provide evidence that the sleep of children with AS differed from the sleep of children with HFA.
7.2 SLEEP-WAKE BEHAVIOUR AT BASELINE (PAPER II)

Parent report indicated that the frequency of occurrence of two dyssomnia-related sleep-wake behaviours differed between participants in the AS/HFA and control groups. Children with AS/HFA had more difficulties initiating sleep (8 vs. 1 child/≥3 times/week; \( p < 0.01 \) Wilcoxon signed ranks test), and more signs of daytime sleepiness (6 vs. 0 child/≥3 times/week; \( p < 0.01 \)) during the previous six months. The frequency of other dyssomnia- or parasomnia-related sleep-wake behaviour (see Paper II, Table 1) did not differ between these two groups. The prevalence of parent-reported current sleeping problems (AS/HFA: 19 vs. control: 3 children, \( p < 0.01 \)) as well as consequent distress (AS/HFA: 12 vs. control: 1 child, \( p < 0.01 \)), impaired daytime function for the child (AS/HFA: 17 vs. control: 1 child, \( p < 0.001 \)), and parental burden (AS/HFA: 17 vs. control: 3 children, \( p < 0.05 \)) was statistically significantly higher among the children with AS/HFA.

7.3 PAEDIATRIC INSOMNIA (PAPER II)

Table 8 shows how the DSM-IV adapted criteria for paediatric insomnia, proposed by Glaze et al [131] (see § 5.1.1) were operationalized in the current project. While applying these criteria, it was noted that parent-reported significant sleeping problems were present in 19 children with AS/HFA and in three of the typically developing children. Further, 12/19 children in the AS/HFA group versus none in the control group had parent-reported difficulties initiating sleep, and/or night-time awakenings at least three times per week during the previous six months. Consequent distress or impaired daytime functioning of the child, or burden for the parents, was present in 10/12 children in the AS/HFA group, versus in none of the children in the control group.
Table 8. Operationalization of DSM-IV-adapted criteria for paediatric insomnia in 32 children with AS/HFA and in 32 children in the control group.

<table>
<thead>
<tr>
<th>Operationalized criteria</th>
<th>AS/HFA group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Parent report of a significant sleep problem</td>
<td>19/32</td>
<td>3/32</td>
</tr>
<tr>
<td>1.1. difficulty initiating sleep ≥ 3 t/week</td>
<td>8/19</td>
<td>0/3</td>
</tr>
<tr>
<td>1.2. night-time awakenings ≥ 3 t/week</td>
<td>6/19</td>
<td>0/3</td>
</tr>
<tr>
<td>1.3. difficulty initiating sleep and/or night-time awakenings ≥ 3 t/week</td>
<td>12/19¹</td>
<td>0/3</td>
</tr>
<tr>
<td>2. Parent-reported consequence of a sleep problem</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.1. distress for the child</td>
<td>7/12</td>
<td>0/0</td>
</tr>
<tr>
<td>2.2. impaired daytime function for the child</td>
<td>10/12</td>
<td>0/0</td>
</tr>
<tr>
<td>2.3. burden for the parents</td>
<td>10/12</td>
<td>0/0</td>
</tr>
<tr>
<td>3. Insomnia does not occur exclusively in the context of another sleep disorder</td>
<td>10/12</td>
<td>0/0</td>
</tr>
<tr>
<td>4. Insomnia is not attributable to the previous or current medication</td>
<td>10/12</td>
<td>0/0</td>
</tr>
</tbody>
</table>

¹From these 12 children with difficulties initiating sleep or night-time awakenings at least three times per week, 6/12 children had difficulties initiating sleep, 4/12 had night-time awakenings, and 2/12 had both difficulties initiating sleep and night-time awakenings at least three times per week.

Other underlying sleep disorders in cases with insomnia were ruled out by detailed assessment of parent-reported sleep-wake behaviours during the previous six months and recent actigraphic sleep patterns (see Paper II, Additional file 2).

An additional requisite of the definition was that the insomnia was not related to the use of medication. None of the children received any medication at baseline. Thus, altogether, 10/32 children in the AS/HFA group (31.2%) but none in the control group fulfilled the present criteria for paediatric insomnia, 5 of these 10 children only had difficulties initiating sleep, 3 had night-time awakenings, and 2 children had both difficulties initiating sleep and night-time awakenings. All of the children with insomnia were boys, their mean age was 10.8 years, 6 of them were diagnosed with AS, and 4 with HFA.
7.3.1 Insomnia and co-existing sleep-wake behaviours

Parent ratings showed that children with insomnia were more frequently accompanied by someone at onset of sleep (40% vs. 9.1%/≥ 3 times per week, p < 0.01), showed signs of anxiety at bedtime (40% vs. 0%/≥ 3 times per week, p < 0.01), and signs of daytime sleepiness (30% vs. 13.6%/≥ 3 times per week, p < 0.05) than those children without insomnia.

Whereas 3 children with and 3 without insomnia displayed parent-reported sleepiness at least 3 times per week, all sleep questionnaire, diary and actigraphy data were reviewed in order to identify possible sleep-related correlates of daytime sleepiness in these children [144]. With respect to the 3 children with insomnia, no evidence of any other sleep disturbance than the difficulties initiating or maintaining sleep was found. With respect to the 3 children without insomnia, one had tossing and turning during sleep at least 3 times per week, one napped at least 3 times per week, and in one child, any correlated sleep disturbance was not identified.

7.3.2 Insomnia and recent sleep patterns

One-week actigraphic monitoring compared the children with insomnia (n=10) and those without insomnia (n=22) regarding their sleep patterns. Children with insomnia had longer sleep latency on school days (43.9 ± 20.9 vs. 27.1 ± 14.0 min; logistic regression, p = 0.02) as well as at weekends (37.5 ± 27.0 vs. 14.3 ± 10.1 min; p = 0.01), delayed sleep start time on school days (10:10 ± 32.8 vs. 09:37 ± 39.7; p = 0.01), and delayed sleep end time at weekends (08:27 ± 62.6 vs. 07:34 ± 41.2; p = 0.008). Bedtime, actual sleep time, actual time awake, and sleep efficiency did not differ between the groups.

7.3.3 Relation between insomnia and daytime behaviour

Children with insomnia showed higher parent-rated ASSQ total score (26.4 vs. 18.5; p = 0.02; logistic regression), higher parent-rated SDQ emotional symptoms score (6.2 vs. 3.4; p = 0.009), higher parent-rated SDQ total difficulties score (20.4 vs. 14.8; p = 0.02), lower parent-rated SDQ prosocial behaviour score (4.9 vs. 7.0; p = 0.04), higher teacher-rated SDQ hyperactivity score (6.7 vs. 4.6; p = 0.04), and higher teacher-rated SDQ emotional symptoms score (4.8 vs. 2.8; p = 0.03) than children without insomnia.
7.4 LONGITUDINAL SLEEP PATTERNS (PAPER III)

7.4.1 Parent-reported global sleep problems

Parent-reported persistent sleep problems, i.e., sleep problems endorsed both at baseline and follow-up, occurred in 10/23 of the children in the AS/HFA group (43.5%) versus 1/22 in the control group (4.5%) (p = 0.003, Mann-Whitney test). Parental reply to an open-ended question indicated that bedtime resistance was a main concern for two children, anxiety at bedtime was reported for one child, difficulties initiating sleep for four children, and night-time awakenings for three children in the AS/HFA group. The parental main concern for the child in the control group with a persistent sleep problem was bedtime resistance. Six children in the AS/HFA group (26.1%) versus 16 children in the control group (72.7%) showed no parent-reported sleep problem, neither at baseline nor at follow-up.

7.4.2 Timing and duration of sleep

Descriptive data, mean values, and standard deviations of sleep diary variables, at both baseline and follow-up, are presented in Table 6 and of actigraphic variables in Table 7. Sleep diary data on bedtime, get up times, and total sleep time, as well as actigraphic data on sleep start, sleep end, and actual sleep time were used to determine the timing and duration of sleep. Linear mixed effects models analysis showed a statistically significant group effect for the weekend get up time [F(1, 101)=7.59, p < 0.01]. The findings corresponded to an average 40 min earlier get up times for the AS/HFA group at weekends, at both baseline and follow-up.

Analyses also showed statistically significant time effects for school day bedtime [F(1, 101)=39.84, p < 0.001], weekend bedtime [F(1, 101)=9.05, p < 0.01], weekend get up time [F(1, 101)=5.59, p < 0.05], school day sleep start time [F(1, 101)=38.99, p < 0.001], weekend sleep start time [F(1, 101)=12.43, p < 0.01], school day total sleep time [F(1, 101)=17.39, p < 0.001], school day actual sleep time [F(1, 101)=66.09, p < 0.001], and weekend actual sleep time [F(1, 101)=17.46, p < 0.001]. The time effects for school day and/or weekend bed- and get up times corresponded to an average 60-70 minute delay in school day/weekend bedtimes for both groups (Table 6, Figure 3), and to an average 40 minute delay in weekend get up times for both groups at follow-up (Table 6, Figure 4). The time effect for total sleep time on school days corresponded to an average 50 minute shorter total sleep time on school days for both groups at follow-up (Table 6, Figure 4). Also, actigraphy data showed a sleep phase delay: an average 60 minute delay in sleep start times for both groups on school days as well as at weekends at follow-up (Table 7, Figure 5). Moreover, the actual sleep time decreased across time, 86 minutes in the AS/HFA group, and 91 minutes in the control group on school days, and 63 minutes in the AS/HFA group versus 56 minutes in the control group at weekends (Table 7, Figure 6).
Figure 3. Change in bedtimes on school days (upper figure) and weekends (lower figure) from baseline to follow-up for participants in the AS/HFA and control groups.
Figure 4. Change in get up times at weekends (upper figure) and total sleep time on school days (lower figure) from baseline to follow-up for participants in the AS/HFA and control groups.
**Figure 5.** Change in sleep start times on school days (upper figure) and weekends (lower figure) from baseline to follow-up for participants in the AS/HFA and control groups.
Figure 6. Change in actual sleep times on school days (upper figure) and weekends (lower figure) from baseline to follow-up for participants in the AS/HFA and control groups.
7.4.3 Initiation and maintenance of sleep

Sleep diary data on bedtime and sleep onset latency, and actigraphic data on sleep latency were used to determine the initiation of sleep.

There was a statistically significant group effect for actigraphic school day sleep latency \[F(1, 101)=5.30, p < 0.05\], i.e., the AS/HFA group had longer sleep latency on school days both at baseline and at follow-up. There was no evidence of a time effect or of a two-way interaction between group and time for the sleep initiation measures. Thus, sleep initiation measures did not change with time, neither in the AS/HFA nor in the control groups.

Sleep diary data on sleep quality, and actigraphic data on number of night wakings \((\geq 5 \text{ min})\), duration of night wakings \((\geq 5 \text{ min})\), and sleep efficiency were used to investigate the maintenance of sleep. Statistically significant time effects were found with respect to: the number of night wakings \((\geq 5 \text{ min})\) on school days \[F(1, 101)=14.92, p < 0.001\] and at weekends \[F(1, 101)=10.72, p < 0.01\], the duration of night wakings \((\geq 5 \text{ min})\) on school days \[F(1, 101)=20.34, p < 0.001\] and at weekends \[F(1, 101)=13.16, p < 0.01\], and, the sleep efficiency on school days \[F(1, 101)=44.54, p < 0.001\] and at weekends \[F(1, 101)=35.91, p < 0.001\]. The number and duration of night wakings increased (Table 7, Figures 7, 8), and sleep efficiency decreased (Table 7, Figure 9) in both groups over the course of 2–3 years. There was no evidence of a group effect or of a two-way interaction between time and group for any of the sleep maintenance measures.
Figure 7. Change in the number of night wakings on school days (upper figure) and weekends (lower figure) from baseline to follow-up for participants in the AS/HFA and control groups.
Figure 8. Change in the duration of night wakings on school days (upper figure) and weekends (lower figure) from baseline to follow-up for participants in the AS/HFA and control groups.
Figure 9. Change in sleep efficiency on school days (upper figure) and weekends (lower figure) from baseline to follow-up for participants in the AS/HFA and control groups.
7.5 PARENTAL HRQL (PAPER IV)

7.5.1 Maternal HRQL

Mothers in the AS/HFA group reported lower PCS-12 score, i.e. poorer physical health, than mothers in the control group (44.7 vs. 52.5), while controlling for mother’s and child’s ages (Table 9). The PCS-12 Swedish norm for 40–44-year-old females is 51.2 [139]. Thus, the score for the control group resembles data from the norm population mean, while the score for the AS/HFA group is lower than the norm population mean. The MCS-12 score, reflecting the mental health status, did not differ between mothers of the AS/HFA and control groups (49.1 vs. 52.0). The MCS-12 Swedish norm for 40–44-year-old females is 52.4 [139].

Table 9. Physical (PCS-12) and Mental Component Summary (MCS-12) scores and PCS-12/MCS-12 differences between mothers and fathers of the AS/HFA and control groups.

<table>
<thead>
<tr>
<th>SF-12 score</th>
<th>AS/HFA</th>
<th>Control</th>
<th>β</th>
<th>SE</th>
<th>p</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mothers' PCS</td>
<td>44.7 (10.8)</td>
<td>52.5 (7.4)</td>
<td>-8.5</td>
<td>2.4</td>
<td>0.001</td>
<td>-13.3</td>
</tr>
<tr>
<td>Mothers’ MCS-12</td>
<td>49.1 (11.1)</td>
<td>52.0 (9.6)</td>
<td>-2.7</td>
<td>2.7</td>
<td>0.32</td>
<td>-8.2</td>
</tr>
<tr>
<td>Fathers’ PCS-12</td>
<td>49.8 (6.9)</td>
<td>53.0 (6.8)</td>
<td>-2.1</td>
<td>1.8</td>
<td>0.24</td>
<td>-5.7</td>
</tr>
<tr>
<td>Fathers’ MCS-12</td>
<td>51.3 (7.8)</td>
<td>53.6 (6.1)</td>
<td>-2.7</td>
<td>1.9</td>
<td>0.16</td>
<td>-6.5</td>
</tr>
<tr>
<td>PCS-12 difference(^1)</td>
<td>4.7 (13.8)</td>
<td>-0.3 (9.1)</td>
<td>6.9</td>
<td>3.1</td>
<td>0.03</td>
<td>0.6</td>
</tr>
<tr>
<td>MCS-12 difference(^1)</td>
<td>2.8 (11.7)</td>
<td>0.5 (11.0)</td>
<td>1.5</td>
<td>3.1</td>
<td>0.64</td>
<td>-4.8</td>
</tr>
</tbody>
</table>

Each row is a separate linear regression with the SF-12 score as the dependent variable. The independent variables were: group (AS/HFA vs. control), parental age, age of the child.

\(^1\) PCS-12/MCS-12 differences were calculated as following: Fathers’ PCS-12 (MCS-12) minus Mothers’ PCS-12 (MCS-12). Positive values indicating better health for the father.

AS = Asperger syndrome; HFA = High-Functioning Autism
No. of participants: 31 mothers and 30 fathers in the AS/HFA group vs. 30 mothers and 29 fathers in the control group.

7.5.2 Paternal HRQL

Neither PCS-12 (49.8 vs. 53.0) nor MCS-12 scores (51.3 vs. 53.6) differed between fathers of the AS/HFA and control groups, while controlling for father’s and child’s ages (Table 9). The PCS-12 Swedish norm for 40–44-year-old males is 51.4 and the MCS-12 norm is 53.8 [139].
7.5.3 Gender differences in HRQL

The PCS-12 score difference between mothers and fathers among the parents in the AS/HFA group was statistically significantly greater than the difference among the parents in the control group (Table 9). Thus, the mothers in the AS/HFA group reported poorer physical health status than the fathers. The MCS-12 score difference between mothers and fathers was similar between parents in the AS/HFA group and parents in the control groups.

7.5.4 Relation between parental HRQL and child behaviour

Parental HRQL was not related to the parent or teacher-rated ASSQ scores of the child. However, there were statistically significant relationships between maternal HRQL and SDQ scores of the child (Table 10). Higher PCS-12 score – indicating better physical health of the mother – was related to a higher teacher-rated prosocial behaviour score, i.e. better social competence of the child. Further, a higher MCS-12 score – indicating better mental health of the mother – was related to higher scores of parent-rated prosocial behaviour, and lower scores of parent-rated hyperactivity and conduct problems in the child. There was no association between paternal MCS-12/PCS-12 scores and SDQ scores of the child.

Table 10. Relationships between Mothers’ Physical (PCS-12) and Mental (MCS-12) Component Summary scores and the teacher- or parent-rated SDQ scores of the child within the AS/HFA group

<table>
<thead>
<tr>
<th>Relationship</th>
<th>β</th>
<th>SE</th>
<th>z</th>
<th>p</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother’s PCS-12 teacher SDQ prosocial</td>
<td>1.8</td>
<td>0.8</td>
<td>2.1</td>
<td>0.03</td>
<td>0.11</td>
</tr>
<tr>
<td>Mothers’ MCS-12 parent SDQ prosocial</td>
<td>1.5</td>
<td>0.7</td>
<td>2.1</td>
<td>0.04</td>
<td>0.07</td>
</tr>
<tr>
<td>Mothers’ MCS-12 parent SDQ hyperact.</td>
<td>-1.9</td>
<td>0.9</td>
<td>-2.2</td>
<td>0.03</td>
<td>-3.76</td>
</tr>
<tr>
<td>Mothers’ MCS-12 parent SDQ conduct¹</td>
<td>-8.8</td>
<td>3.5</td>
<td>-2.5</td>
<td>0.01</td>
<td>-15.68</td>
</tr>
</tbody>
</table>

General Linear Model. Dependent variable: Mothers’ PCS-12 or MCS-12 score; Independent: Mother’s age, age and gender of the child. ¹Due to skewness, the logarithmic value of parent SDQ conduct score was used. SDQ = the Strengths and Difficulties Questionnaire; AS = Asperger Syndrome; HFA = High-Functioning Autism.
No of participants: 31 mothers and 30 fathers.
8 DISCUSSION

The main findings of the present thesis are discussed and clarified in the following sections: sleep patterns at baseline (8.1); AS versus HFA (8.2); sleep-wake behaviour at baseline (8.3); paediatric insomnia at baseline (8.4); longitudinal sleep data (8.5); parental HRQL (8.6); and relation between maternal HRQL and child behaviour (8.7). The final sections cover the issues of generalisability of the findings (8.8); and conclusions and future research questions (8.9).

8.1 SLEEP PATTERNS AT BASELINE

8.1.1 Parent-reported sleep problems

Sixty per cent of the school-age children with AS/HFA were deemed by their parents to have a current sleep problem at baseline. Such a finding is in accordance with data from previous research on children with high-functioning PDD [59, 80, 86, 87, 89]. As well reports by Richdale & Prior [80] as those by Patzold et al [59] Polimeni et al [86] Couturier et al [87] Williams et al [89], and Wiggs & Stores [85] presented all similar rates of sleep problems in PDD, high-functioning PDD. Moreover, the nature of sleep disturbance in the current study, mainly difficulties initiating and maintaining sleep, is consistent with previous research. Thus, both previous and the present findings indicate that disturbed sleep is a characteristic aspect of childhood AS/HFA. Concerning the mechanisms underlying the sleep disturbance in PDD, it has been argued whether difficulties with perception of social cues, particularly at younger ages, may cause difficulties with the entrainment of circadian rhythms and synchronisation of sleep-wake rhythm [59, 80], or whether sleep disturbance is related to particular PDD features [99] (see Table 3). Segawa and colleagues view abnormal sleep-wake cycle as a primary and pathognomic symptom of PDD [78], related to dysfunction of the brainstem aminergic neurons [145]. Limoges and colleagues consider sleep disturbance as a salient feature of the PDD phenotype [57]. Also the neuropsychiatric deficits inherent to AS and coexistent mood disorders [58, 59], and/or aberrant sensory processing [146-148] may predispose to disturbed sleep in AS/PDD.

The occurrence of parent-reported sleep problems in AS/HFA in the present study corresponded also in some aspects to the sleep diary and actigraphy data. The children with parent-reported sleep problems had longer and more variable sleep latencies on school days and weekends than those children without sleep problems. Good correspondence between the presence of parent-reported sleep problems, and sleep diary and actigraphy data provides support to previous suggestions with regard to parental accuracy in perception of problem sleep in their children [83].
8.1.2 Timing and duration of sleep

Both subjective (sleep diary) and objective (actigraphy) measures displayed significant group differences in the timing of sleep, children with AS/HFA having earlier bed-, sleep start- and get up times at weekends than those in the control group. While comparing the present findings with data from previous research, it should be noted that previous studies on children with high-functioning PDD: firstly they have been based mainly on subjective sleep measures (except an open clinical trial with melatonin on children with AS [84], one actigraphic report [85], and one PSG-based study [81]); secondly they have included participants with wide age ranges; and thirdly they have not included separate analyses for sleep patterns on school days and sleep patterns at weekends. Research on adolescents and adults with AS and/or HFA, has, however, included separate sleep variable analyses on school day/working day and weekends.

At least three previous studies on high-functioning PDD have found signs indicative of aberrations in sleep timing. Firstly, Richdale & Prior [80] used sleep diary and questionnaire, and estimated earlier wake up times for children with high-functioning PDD, compared with those in the control group. Secondly, Patzold et al [59] using the same measures as Richdale & Prior detected later sleep start times in the PDD group than in the control group. Thirdly, Limoges and colleagues [57] compared sleep patterns between adolescents and adults with AS/HFA and healthy control persons by sleep questionnaire and PSG, and found earlier bedtimes on school days and on weekends, and earlier get up times on school days, namely, soft signs of a sleep phase advance in AS/HFA. Thus, the current finding of earlier sleep timing at weekends in AS/HFA is consistent with data of Richdale & Prior [80] and Limoges et al [57], but differs from the results of Patzold et al [59].

The possible causes of the earlier sleep timing in AS/HFA can be related to good parenting, including regular routines and beneficial sleep hygiene, or to good collaboration between parents and professionals at the PDD-habilitation centers. Parents may have used an optimal sleep routine including earlier bedtimes with a clear intention of helping their child fall asleep. The role of regular sleep routines and good sleep hygiene for solving sleep problems in children with disabilities has been emphasized by several authors [77, 149]. Another explanation of the earlier bedtimes in the AS/HFA group might be that these children were generally more sleepy at bedtime than those in control group (see § 7.2).

The duration of sleep did not differ between children in the AS/HFA and the control groups in the present study. This finding differs from previous research on children with high-functioning PDD [59, 80, 87] indicating shorter sleep duration in individuals with PDD than in those in the control group. As noted earlier, the discrepancy between the current findings and the findings from previous research may be related to methodological issues; previous research has included participants of wider age ranges, and has not included separate school day and weekend analyses. However, it cannot be ruled out that the limited statistical power of the present study made detection of a genuine difference in sleep duration impossible.
8.1.3 Initiation and maintenance of sleep

The finding of prolonged sleep latency in AS/HFA in the present study resembles data from previous research on children and adults with high-functioning PDD. The mean sleep latency, on average half an hour on school days, is remarkably similar to the findings reported by Richdale & Prior [80] Patzold et al [59] Paavonen et al [84], and Limoges et al [57]. As mentioned earlier, previous studies on children have not included separate analyses for sleep latency on school days and sleep latency at weekends. Research on adults with AS [58], has, however, included such analyses, and presented mainly working day difference, also with longer values of sleep latency in AS than in the present study [92].

Possible hypothetical explanations of the prolonged sleep latency in childhood AS/HFA might be: anxiety or high physiological arousal; more problematic daytime behaviour; fear; rigidity; resistance to changes; and/or altered circadian pattern of melatonin [59, 80, 84]. Anxiety and arousal factors, as possible cause of difficulties initiating sleep in high-functioning PDD were pointed out by Richdale & Prior (1995) [80], confirmed further by Patzold et al [59], Couturier et al [87], Paavonen et al [84], and Tani and colleagues [58]. Research on adults with PDD has also indicated altered melatonin secretion [150, 151], and, melatonin treatment on children with AS and insomnia has resulted in a decrease of sleep latency [84].

Further, the maintenance of sleep at baseline differed between the AS/HFA and the control groups, in the current study, in only two aspects; slightly lower sleep quality, and sleep efficiency, in AS/HFA on school days. Importantly, there were no group differences in the number and duration of night wakings. The last finding differs from previous research [59, 80] which has presented longer lasting night wakings for children with high-functioning PDD compared to children in control groups.

8.2 AS VERSUS HFA

Diagnostic re-assessment in the frame of the current study showed that 13/32 children with a clinical diagnosis AS had a history of early language delay, and fulfilled ICD-10 criteria for childhood autism. Such discrepancy between the clinical diagnosis of AS and the requirement of “no clinically significant cognitive or language delay in AS” in the ICD-10 might illustrate that there still exists some lack of consensus regarding aspects of diagnostic criteria in the field of PDD. As mentioned earlier (see § 2.1.3), prior to the inclusion of AS as an “official diagnosis” in ICD-10 and DSM-IV, several sets of diagnostic criteria for AS were available [34], amongst others also those presented by Gillberg & Gillberg in 1989 [16]. Research in Sweden, based on the above-mentioned criteria, has estimated the prevalence between 0.9 and 3.6 per 1.000 children for AS [35, 36]. Thus, the existence of several sets of diagnostic criteria for AS may also have influenced the clinicians in Sweden. It needs also to be acknowledged that behavioural manifestations may be similar for AS and HFA during adolescence, despite differences in the early speech development [152]. Thus, it is possible that the issue of language delay was not taken into consideration by clinicians while assessing cases who later came to participate in the present study. Nevertheless, despite differences in early language development, the children in both AS and HFA groups
showed severe impairments in social interaction, communication, and restricted behavioural repertoire (see Paper I, ASSQ Data and Appendix A1).

Neither subjective nor objective measures of sleep in the present study could detect any difference between AS and HFA subgroups. Only one of previous reports has conducted separate comparisons between AS and HFA. Limoges and colleagues [57] compared sleep questionnaire and PSG data between 6 subjects with AS and 10 subjects with HFA, and established lower sleep spindle density in AS. Some caution is needed while comparing the present findings and the findings of Limoges et al since different methods were utilized in these studies (actigraphy vs. PSG). Moreover, it might be that the limited statistical power of the present study made the detection of differences in sleep data between the AS and HFA subgroups impossible. However, despite this limitation, the present sleep data adds to the knowledge about possible similarities between AS and HFA [37, 153, 154].

8.3 SLEEP-WAKE BEHAVIOUR AT BASELINE

In the current analysis, two dyssomnia-related sleep-wake behaviours were more frequent in children with AS/HFA, namely difficulties in initiating sleep, and daytime sleepiness. Similar to present findings, Couturier et al [87] have presented higher rates of difficulties initiating sleep in children with high-functioning PDD (n=23) than in age- and gender-matched controls (n=23). However, compared to the present report, Couturier et al also found higher scores of sleep anxiety, parasomnias, and shorter sleep duration in children with PDD. Discrepancy between the findings may be related to the methodological issues; e.g., inclusion of participants with wider age range (5–12 years) and pharmacological treatment (70%) by Couturier et al. High rate of medication in the PDD sample of Couturier et al might also be related to the high rate of psychiatric comorbidity and/or sleep disturbance in these children.

Almost one fifth (6/32) of the children with AS/HFA, and none of those in the control group, showed parent-reported daytime sleepiness in the present report. Such rate of daytime sleepiness in AS/HFA at age 10 is in accordance with some previous studies [85], but differs from others [59, 80, 87]. For example, Wiggs & Stores [85] found that one fourth of the PDD sample aged 5–16 years showed signs of daytime sleepiness and/or drowsiness. However, neither Richdale & Prior [80] nor Patzold et al [59] could ascertain higher rates of daytime sleepiness in children with high-functioning PDD compared to those in control groups. Further, it is worth noting that daytime sleepiness in the present study was assessed only by one informant, a parent. Previous research has suggested the use of multiple informants (child, parent, teacher) when assessing a child’s behaviour [155, 156].

Daytime sleepiness during childhood is considered to be often caused by insufficient sleep (impaired quantity), sleep fragmentation (impaired quality), and increased need for sleep [144]. Based on the present findings (see § 7.3.1), one can speculate as to whether daytime sleepiness in cases with insomnia (n=3) was related to inadequate sleep on school days. Among the children without insomnia (n=3), one had restless sleep, one napped at least 3 times per week, and in one child, no sleep disturbance that could potentially account for the daytime sleepiness could be identified. Excessive napping in pre-adolescents can be related to inadequate sleep
hygiene [157]. Since excessive sleepiness in pre-adolescents is quite uncommon, and a potentially serious problem [73, 158], the topic of daytime sleepiness in childhood AS/HFA needs examination in future studies. Further research on sleepiness should also include reports from multiple informants, and objective sleep measures such as PSG, including Multiple Sleep Latency Test.

8.4 PAEDIATRIC INSOMNIA AT BASELINE

A recent consensus paper (2006) points out that there is a great need to understand and be able to effectively treat paediatric insomnia, particularly in high-priority populations such as children with neuropsychiatric disorders [159]. Compared to insomnia in adults which is considered to be a reasonably well-understood condition, paediatric insomnia is thought to be less well understood [159]. According to the recent consensus, paediatric insomnia is defined as “repeated difficulty with sleep initiation, duration, consolidation, or quality that occurs despite age-appropriate time and opportunity for sleep and results in daytime functional impairment for the child and/or family” [159]. One third of the school-age children with AS/HFA in the present study, but none of those in the control group, fulfilled the current criteria of paediatric insomnia. Such high frequency of insomnia in AS/HFA resembles and extends further data from previous research [58, 84, 147]. Paavonen et al [84] examined the effectiveness of melatonin in 15 children with AS and insomnia aged 6−17 years, and found decreased sleep latency, and improvement of emotional and behavioural symptoms with melatonin. Two other Finnish studies on adults with AS [58, 147] presented high frequency of insomnia in AS, and it was speculated whether insomnia in adult AS frequently commences in childhood. The current findings provide support for this view.

Concerning coexistent sleep-wake behaviours, children with insomnia in the current report were more often accompanied by another person at onset of sleep, had more signs of anxiety at bedtime, and more signs of daytime sleepiness than those children without insomnia. These findings resemble data from previous research on children with chronic insomnia. Ivanenko and colleagues [160] examined effectiveness of melatonin in 32 children with insomnia and psychiatric disorders [ADHD (50%), anxiety disorder (25%), affective disorders (9%), and developmental delay (9%)], and presented a similar rate of anxiety at bedtime in insomnia as the present study: 40%. However, children in the report by Ivanenko et al also showed higher rates (62.5%) of daytime sleepiness than cases in the present study (30%). The discrepancy between the findings could be related to methodological issues such as wider age range (2–18 yrs), presence of comorbid medical disorders (asthma and diabetes), and pharmacological treatment in the study by Ivanenko et al.

Children with insomnia, within the AS/HFA group in the present study, showed higher scores of parent-rated autistic symptoms than those without insomnia. Schreck et al [99] has similarly pointed toward the associations between autistic symptoms, sleep disturbance and shorter sleep duration in children with PDD. Moreover, insomnia in the current report was also related to higher scores of parent- and teacher-rated SDQ emotional symptoms, i.e. psychosomatic complaints, fears, worries, anxiety and depression [136]. Research has demonstrated relationships between anxiety, depression and difficulties initiating and maintaining the state of sleep [58, 75, 80, 130], and
between depression and prolonged sleep latency [76]. However, determination of cause and effect regarding associations between insomnia and emotional problems is widely considered to be difficult. Sleep deprivation in itself may produce daytime emotional distress [161]. Also the interaction between insomnia and behavioural symptoms may be bidirectional [75, 76, 131] or it may be mediated by other factors such as physiological or cognitive hyperarousal [162]. Research on adults with insomnia has indicated higher levels of physiological, as well as emotional and cognitive over-arousal [162].

Wicklow & Espie [163] demonstrated that thinking about sleep and the anticipated consequences of poor sleep, along with general problem-solving were the strongest predictors of objective sleep latency. Drawing on these findings, it may be speculated whether some children with AS/HFA suffer from cognitive over-arousal, reflected in certain intrusive repetitive thoughts about sleep or school work, which could delay the initiation of sleep. As well clinical experiences as the finding of the current study that children with insomnia showed more anxiety at bedtime and were more often accompanied by someone at onset of sleep, may support such a speculation.

Research on adults has also speculated about the role of predisposing, precipitating, and perpetuating components in the development of insomnia [162]. Predisposing factors include anxiety and worry, and precipitating factors acute stress, conflict, or environmental change. Perpetuating factors, further, are related to sleep environment, poor sleep hygiene (too much time in bed, without sleep). It has also been speculated whether the particular disposition to anxiety in persons with AS and HFA [48, 60] increases their vulnerability to insomnia. Tani et al [58] noted that neuropsychiatric deficits inherent of AS predispose these individuals both to insomnia and to anxiety and mood disorders. The high predisposition to insomnia in AS/HFA was also evident in the present study.

8.5 LONGITUDINAL SLEEP DATA

The present results demonstrated that both children with AS/HFA and typically developing children in the control group were subjected to significant age-related changes in sleep timing, duration, and maintenance over a 2–3 year period. The current finding of a sleep phase delay, an average 60 minutes in bed- and sleep start times during the whole week, and an average 40 minutes in get up times on weekends, resembles data from previous research. Laberge et al [74] examined change of parent-reported sleep patterns in 588 boys and 558 girls with typical development, and also found an average 60 minute delay in bedtimes during the whole week, and 50 minutes delay in get up times at weekends at age 13 compared to age 10. Further, both subjective and objective measures in the present report indicated shorter sleep duration at age 13. An average 60 minute decrease in a total sleep time (diary) on school days is consistent with the findings by Laberge et al [74]. Approximately 90 minute decrease in actual sleep time (actigraphy) on school days, and 60 minutes at weekends, resembles data from a report on Japanese schoolchildren (school day: 94 minutes vs. weekend: 47 minutes) [164]. Present findings, in respect to less efficient sleep at age 13, are in accordance with data from two Japanese actigraphic studies [164, 165].
The high persistence rate (43%) of parent-reported sleep problems in AS/HFA in the present study is comparable with findings from previous studies. Hoshino et al [77] reported an average 11-month persistence of sleep disturbance in children with high-functioning PDD (n=24), and Honomichl and colleagues [83] indicated that the sleep disturbance persisted at least 12 weeks in children with PDD (n=100). Also Paavonen et al noted the high continuity of sleep disturbance in children with AS [84]. The current persistence rate, 43%, is slightly lower than the figure 63%, presented by Wiggs & Stores on children with PDD [85], and higher than the figure 12%, provided for children with typical development [166].

The present finding that one fourth of the AS/HFA sample did not have any sleep problems longitudinally, over 2–3 years, exceeds somewhat figures presented by previous research. Richdale & Prior [80] found that 11 per cent (3/27) of the high-functioning PDD group had neither past nor current sleep problems. The discrepancy between the findings of the present study and the study by Richdale & Prior can be related to methodological issues; the wider age range of participants in the previous report, and differences in time intervals.

The present data might also indicate that subtle differences in sleep timing (earlier get up times during weekends in AS/HFA, at both baseline and follow-up) exist between children with AS/HFA and the typically developing children in the control group, and that these differences may be persistent over time. This finding resembles data from previous cross-sectional research on children and adults with high-functioning PDD [57, 80]. Both Richdale & Prior [80] and Limoges et al [57] reported earlier bed- and/or get up times in subjects with high functioning PDD/AS/HFA, than in subjects in the control groups. Limoges et al even proposed that a subtle sleep phase advance may be common in persons with AS/HFA. Current results, showing earlier get up times at weekends for children with AS/HFA, might lend some support to this proposition. However, compared to the previous studies, the current investigation applied a longitudinal design.

In regard to possible causes of earlier sleep timing in children with AS/HFA, the issue of maturational delay should be taken into consideration, i.e., the children of the present AS/HFA sample have a timing of sleep which to some extent resembles that of younger children. Honomichl et al [83] assessed the short-term stability of sleep patterns of children with PDD, and proposed that childhood PDD was associated with maturational delay. Related to this view, research has also shown a maturational delay in REM sleep in persons with PDD [94, 95], or a poor REM sleep control in those with AS/HFA [81, 91]. Ornitz discussed [94] whether a maturational delay in the differentiation of REM sleep is related to a maturational delay in the development of complex motor patterns and in the modulation of sensory input in children with PDD. Godbout [81] suggested further that there is a poor REM sleep control in persons with AS, possibly related to impaired daytime cognitive functioning.

The persistence of prolonged actigraphic sleep latency on school days in children with AS/HFA in the present report corroborates and extends the findings from previous cross-sectional research. The maintenance of prolonged sleep latency can be related to the persistence of earlier mentioned causes of prolonged sleep latency in those with AS/HFA, for example those with anxiety, high physiological arousal, more problematic daytime behaviour, fear, rigidity, resistance to changes, and altered circadian pattern of melatonin.
8.6 PARENTAL HRQL

The present study displays that mothers, but not fathers, caring for school-age children with AS/HFA report poorer physical well-being. Previous research has shown impairments in mental [7, 104, 114] as well as in physical health of mothers of children with high-functioning PDD or AS/NLD [104, 114]. Gray [104] and Little [7] examined parental stress and health of children with AS/HFA or AS/NLD, and indicated higher rates of mental health problems in mothers than fathers of these children. Gray also noted that, in a few cases, mothers of children with AS/HFA had experienced strokes or other physical illnesses that they believed were linked to their child’s disability. Also Pakenham and colleagues indicated the poor subjective health status in mothers of children with AS [114]. Thus, similar to findings of Gray and Pakenham et al, mothers experienced poorer self-reported physical health in the present study. However, further absence of differences in maternal mental well-being in the present report is in contrast to the findings of the previous research [7, 104, 107, 111, 112, 114, 167-170]. Could there be any way of explaining the present findings of relatively good mental, but poor physical well-being among the mothers of children with AS/HFA? Previous research [106] has noted that psychosomatic problems were common manifestations of stress related to caregiving in parents of children with PDD. Based on their findings, Magana et al [171] discussed whether mothers of adult children with mental illness were particularly vulnerable to physical health problems. From another standpoint, one might speculate as to whether the poorer self-rated maternal physical health in the AS/HFA group could be associated with particular personality traits. From a strictly theoretical perspective, a discrepancy between mental and physical health in these mothers could be related to the presence of alexithymic traits, meaning a reduced ability to engage in explicit emotional processing. A relationship between alexithymic personality and somatization has been reported [172, 173], and research has indicated higher rates of alexithymia in adults with AS [174]. Alexithymic traits may also be associated with impaired recognition of facial expressions of emotions [175], and limited research on parents of children with AS [123] has indeed demonstrated the subtle deficits on a mindreading test (the Reading the Mind in the Eyes Test). Thus, hypothetically, it might be possible that parents of children with AS/HFA have more alexithymic traits. Nevertheless, it should be carefully noted that the present study did not perform any assessment of personality profile or cognitive style in the parents of children with AS/HFA.

Debating over the possible mechanisms underlying the gender difference in parents’ self-rated physical health in AS/HFA, the issue of traditional gender expectations [103], and consequent higher levels of caregiver burden in mothers should be taken into consideration. As stated by Gray [103]: “There are traditional gender expectations that dictate that the mother will have more responsibility for child raising.” Also studies by Little [7] and Gray [104] have pointed to the gender differences in the responsibility of caring for a child with AS/HFA or AS/NLD. Gray reported that “Relatively few of the fathers reported a high degree of involvement in child raising” [104]. This view could also have been reflected by higher rates of non-employment among mothers of these children in the present report (26%) as well as in the studies by Little (38%), and Gray (50%) [104].
8.7 RELATION BETWEEN MATERNAL HRQL AND CHILD BEHAVIOUR

Present results have shown that maternal, but not paternal health in the AS/HFA group was related to child behaviour characteristics. The self-rated mental health of mothers was related to the symptoms of hyperactivity and conduct problems in the child. Also mothers’ physical and mental health was related to the level of prosocial behaviour, according to the SDQ, of the child. These findings are in line with suggestions from previous research. Hastings examined 18 couples, biological parents of school-age children with PDD [115], and noted that maternal stress was related to child behaviour problems as well as to partner’s mental health symptoms (anxiety, depression). Also, in a further report on preschool children with PDD, Hastings and colleagues [117] showed that mothers’ well-being was predicted by their children’s behaviour problems and by their partner’s depression. Thus, the finding of a relationship between maternal health and child behaviour characteristics in the present report corroborates the conclusions from previous research. However, unlike these two previous reports [115, 117], the present study did not examine the relationships between self-reported health in mothers and fathers. One possible mechanism underlying the relationship between maternal health and child behaviour might be the increased involvement by mothers in the care of their child with PDD [104, 115, 116]. As noted by Gray: “Mothers were also the parents who were most likely to be held responsible for their child’s behaviour, both by their husbands and by people outside the family.” Another possible mechanism can be related to the use of different coping strategies by parents [104, 117].

As noted earlier (see § 2.5), coexisting behaviour problems in a child could be more stressful for its parents than the severity of the core autistic symptoms [117]. Thus, the present finding that mothers’ health was related to the extent of general behaviour problems (SDQ: hyperactivity, conduct), and not to the degree of autistic symptoms in the child (ASSQ) may be consistent with suggestions from other authors. However, the current report also indicated a relationship between maternal health and the prosocial behaviour of the child (ability to be considerate, to share, to be helpful and to be kind to younger children) (SDQ). It needs to be acknowledged that the prosocial behaviour score of the SDQ (5 items) only covers limited aspects of autistic symptoms and social competence.

Finally, it is important to emphasize that caring for a child with PDD includes also positive parental perceptions [113, 117]. Little & Clark [113] described how parents of children with AS/NLD created a positive bias related to their child which enabled them to gain a sense of control that fuelled optimism in their parental task. Hastings et al [117] pointed further at the positive dimensions of parenting, particularly for mothers of children with PDD. Also Pakenham and colleagues noted the positive aspects of parenting children with AS [102]. By speculating further, it may be the case that such “positive bias” existed also in mothers of the children with AS/HFA in the present study, consequently reducing maternal stress, burden, and mental health complaints. Moreover it has been debated whether AS/HFA is necessarily a disability [176]. Baron-Cohen proposes that a more neutral term “difference,” instead of “disability,” may be utilised to describe AS and HFA [176]. Also Pakenham et al [102] used the term “difference” while describing children with AS.
8.8 GENERALISABILITY OF THE FINDINGS

8.8.1 How representative is the sample?

In similarity to other highly selected clinical samples, it cannot readily be ascertained whether the present sample of individuals with AS/HFA is representative of children with AS/HFA in general. At least two types of selection biases with respect to sleep may have affected the present sample. On the one hand, it is possible that more families with children with AS/HFA, and disturbed sleep, accepted the offer to participate in the study about sleep. On the other hand, baseline exclusion criteria resulted in the selection of children without comorbid medical disorders and/or pharmacological treatment (see § 4.1.1). It is well established that medication as well as comorbid medical disabilities can affect sleep [125-127]. Severely sleep-disturbed children who received medication for sleep problems were probably excluded from the present sample. Although none of the excluded children received medication for sleep, some of them received psychotropic medication, and could have been troubled by severe sleep problems. Hence, the two described types of selection biases may have worked in two directions, including children with parentally perceived sleep problems and simultaneously excluding severely sleep-disturbed individuals. Approximately one third (35/90) of the non-selected PDD sample in the present study received pharmacological treatment. The medication rate among non-selected cases in the present study, 38%, is lower than the figure, 55%, presented by other research [177]. The discrepancy may be related to methodological issues; a previous study included participants with somewhat older age. Moreover, it needs to be acknowledged that in 37/90 cases of the present report, medication data were missing, due to non-response to the introductory letter.

It should be noted that all of the 32 children with AS/HFA showed severe impairments in social and behavioural functioning. A review of the medical records as well as data from the interviews with parents and children (see Paper I, Appendix A1) indicated a pervasive impairment in the children’s behaviour. Also parent and teacher-rated ASSQ (see Paper I, ASSQ data), and SDQ data (see Paper II, Table 3) in different settings (home, school) showed high rates of autistic features and behavioural problems in these children.

Further, concerning the control group, there is a possibility of a selection bias, namely the inclusion of “extremely healthy” children. As stated in § 4.1.4: “In a first step of recruitment procedure, school nurses selected children of suitable age and gender who attended regular classes in mainstream schools and were without mental, developmental, or physical disabilities and long-term medication according to school medical records.” It might be possible that the school nurses turned first to the children with cooperative and motivated parents, in more healthy families. Such a suggestion may also be supported by the high frequency of nuclear families among the control families (28/32) (see Table 4). However, it is worth noting that despite strict exclusion criteria at the first stage of the recruitment procedure (baseline), 5/21 children in the AS/HFA group and 4/20 children in the control group showed medical problems at the time of the follow-up (see § 4.2). A high rate of medical problems (mainly allergic) at follow-up could probably contradict the possibility of “extreme healthy” controls.
Consequently, it can be concluded that the present AS/HFA sample, and the control sample, well represent children with AS/HFA and their typically developing peers. Sociodemographic data as well as comparability of sleep data to other studies provides support for this view.

8.8.2 Is the design suitable?

The pairwise matched design ensured that any difference between cases and controls was not a result of differences in the matching variables (age, gender, residency, actigraphy device) [178]. As stated by Bland & Altman: “We match to ensure that controls and cases are similar in variables which may be related to the variable we are studying but are not of interest in themselves” [178]. Thus, the present study did not focus on the effect of age, gender, residency, or actigraphy device on sleep pattern. Since there is an interdevice variability in the sensitivity of different actigraphs [179, 180], this issue was taken into consideration by pair matching (see § 5.4.1). However, as a disadvantage of pair matching, it was not possible to assess the effects of these matching variables. Moreover, there is a clear predominance of males to females among subjects with PDD [181]. As a consequence mainly boys were included in the present project. A longitudinal design (Paper III) was applied in order to examine continuity and development of sleep patterns over a 2–3 year-period. Possible attrition bias was evaluated by comparing sleep patterns at baseline between children who participated at follow-up and children who did not participate. Comparisons showed that drop-outs had an average 35 minute earlier bedtime (diary) on school days, 34 minute earlier sleep start time (actigraphy) on school days, and better sleep quality (diary) during a whole week compared to the non-drop-outs.

The present sample size (32 matched pairs) was regarded as sufficient to examine the main research question, namely the prevalence of globally assessed sleep problems. However, it should be acknowledged that the present study may be underpowered while evaluating some other, less frequent differences in respect to sleep and parental well-being between the AS/HFA and the control groups.

Despite the above-mentioned restrictions related to the small sample size, it seems that pairwise matched design is a good choice while examining sleep and parental well-being in childhood AS/HFA.

8.8.3 How appropriate are the measures?

Actigraphy is regarded as a valid and reliable method in sleep assessment, both in short-term and long-term intervals [66, 68, 182]. The present one-week actigraphy registration made it possible to perform separate school day/weekend analyses. With respect to disadvantages of actigraphy, it needs to be acknowledged that the method is less useful for documenting wake in individuals with quiet wakefulness (insomnia) [183]. A disadvantage of the one week parallel actigraphy and sleep diary in the present study is that a one-week period is too short an interval to sufficiently represent a child’s sleep. The need for at least 14 days of sleep diary recording, in order to obtain valuable information, has been pointed out [184].
Good correspondence between subjective (sleep diary) and objective (actigraphy) measures of sleep in the present study (see § 7.1.4) is both in support of [185, 186] and in contradiction [163] to the results of other studies. Gaina and colleagues [185] presented comparable correlation figures for sleep timing and duration, but lower for sleep latency (0.49) than the present study (AS/HFA: 0.80 vs. control: 0.55). Wicklow & Espie [163] also presented weaker correlation figures for sleep latency (0.41) and sleep duration (0.52) than the present report. Higher correspondence figures for sleep latency in the present study could be related to the methodological issues. There is a possibility that the use of shorter epoch length in the present study (30 sec) (previous studies: 60 sec) led to greater scoring precision, and, consequently, to more accurate estimation of sleep latency [187, 188]. Related to this, research has noted the high variability in activity patterns within a minute for a child [189, 190], and indicated the possible underestimation of physical activity with longer epoch lengths (e.g., 60 sec) [180, 190]. Consequently, the impact of epoch length on estimates of activity, and sleep-wake variables in children, needs clarification in further studies.

Another reason for good correspondence between diary and actigraphy in the present study might be related to the high motivation and cooperation of parents of children with AS/HFA. High motivation may be related to greater accuracy while completing sleep diaries. Corkum et al indicated in a previous report on children with ADHD that high parental motivation was related to good correspondence between diary and actigraphy data [186].

The sleep questionnaire, as well as the behavioural screening forms used in the present study, have shown satisfactory reliability and/or validity in Swedish child population-based samples [128, 135, 137]. The use of two informants (ASSQ, SDQ) made it possible to examine a child’s behaviour in two settings (home, school) as suggested by previous research [155, 156].

Parental HRQL was measured by a well-validated instrument, SF-12 [191]. The SF-12 represents the 8 health concepts (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health), and discriminates well between different physical and mental conditions [138]. The SF-12 has been previously used to measure well-being in caregivers for relatives suffering from different chronic medical conditions [192, 193]. However, it should be mentioned that there might be a bias in measuring subjective perceptions. A limitation of the present project is that poor physical health was not examined, or verified, by review of medical records.

In conclusion, the measures to explore sleep, behaviour and parental well-being, seem to provide a suitable generalisability of the present findings.
Asperger syndrome and high-functioning autism in school-age children are characterized by:

- high rates of parent-reported sleep problems
- prolonged sleep latencies on school days and weekends, and earlier sleep timing (bed- and get up times) at weekends
- high rates of difficulties initiating sleep and daytime sleepiness
- high rates of insomnia, commonly associated with hyperactivity and emotional symptoms
- persistence of parent-reported sleep problems, prolonged sleep latencies on school days, and earlier sleep timing (get up times) at weekends over the course of 2–3 years
- impaired self-rated physical health in the mothers of these children
- associations between maternal health and coexisting behaviour problems, such as conduct and hyperactivity problems of the child.

In summary, the findings of this thesis indicate that disordered sleep is a common and significant symptom in childhood AS/HFA, and that mothers of children with AS/HFA frequently report impaired physical well-being.

Future research in the area of childhood AS/HFA may among other issues address the need for:

- investigations of insomnia and daytime sleepiness by use of polysomnography
- development of methods and routines for early screening of disturbed sleep
- further studies of associations between sensory processing and sleep, and
- further assessments of the health-related quality of life, and related aspects, of the parents of these children.
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