

# **Narcolepsy in children**

**Relationship to the H1N1 influenza vaccination,  
association with psychiatric and cognitive  
impairments and consequences in daily life**

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Cover: the figure illustrates the role of hypocretin (HCRT) in the regulation of awake-sleep. The brain model is illustrated by Attila Szakács.

Narcolepsy in children – relationship to the H1N1 influenza vaccination, association with psychiatric and cognitive impairments and consequences in daily life

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To my angel and lovely wife, Valéria, and  
our wonderful daughters, Beatrix and Brigitta



# ABSTRACT

**Background/aims:** Narcolepsy is a lifelong sleep disorder with an onset most frequently in the second decade of life. The cardinal symptoms are excessive daytime sleepiness, cataplexy, hypnagogic and hypnopompic hallucinations sleep paralysis and disturbed nighttime sleep. The purpose of this thesis was to study a population-based cohort of children and adolescents with narcolepsy in western Sweden to determine the incidence and relationship with the H1N1 influenza vaccination, psychiatric comorbidity, cognitive profile, health-related quality of life, adaptive behavior and parenting stress.

**Methods:** We aimed to identify all individuals below 18 years of age who developed narcolepsy between January 1, 2000, and December 31, 2010. Post-H1N1 influenza vaccination (PHV) narcolepsy was considered in patients with clinical onset within 10 months of vaccination. Psychiatric comorbidity was investigated using a test battery of semi-structured interviews and screening tools. The cognitive assessments were made by a clinical psychologist using age specific Wechsler Scales. A narcolepsy-specific quality of life questionnaire, the NARQoL was generated based on statements from four focus groups comprising young people with narcolepsy and was used along with the generic KIDSCREEN questionnaire to assess the HrQoL in the study population. The Adaptive Behavior Assessment System was administered to measure adaptive skills in the children and the short form of the Parenting Stress Index questionnaire was used to measure parenting stress in their parents.

**Results:** The incidence of narcolepsy was 25 times higher in the period after the vaccination compared with the period before. The children in the PHV group had a lower age at onset and a more sudden onset than is generally seen. Psychiatric comorbidity was present in 43% of the patients in the PHV group; ADHD in 8/28, major depression in 6/30, general anxiety disorder in 3/30 and oppositional defiant disorder (ODD) in 2/30. In the non-post-H1N1 influenza vaccination (nPHV) narcolepsy group, 1/7 patients had ADHD in combination with ODD. The cognitive assessment showed decreased verbal comprehension and working memory in both patient groups. Parents in the PHV group rated significantly lower scores for adaptive behavior relating to conceptual and social composites. Parents also rated higher in “total stress”, “parent-child dysfunctional interaction” and “difficult child”, significantly so in the PHV group. The pilot NARQoL questionnaire consisted of two patient reported outcome modules: QoL and future perceptions. Test-retest reliability and convergent validity with the KIDSCREEN-10 was good. Children with narcolepsy had significantly diminished scores compared with controls on both the KIDSCREEN and NARQoL; the PHV children in all domains of the NARQoL. Furthermore, patients with psychiatric comorbidity had a significantly lower full-scale IQ, HrQoL and adaptive behavior compared with those without.

**Conclusions:** The H1N1 influenza vaccination with Pandemrix represents a precipitating factor for narcolepsy in children. The identified high prevalence of psychiatric comorbidity and cognitive difficulties highlights the importance of a careful psychiatric and neuropsychological follow-up. The NARQoL revealed a more globally affected QoL than previously reported. Impaired adaptive behavior and high levels of parenting stress indicate considerable impact on daily life.

**Keywords:** narcolepsy, incidence, children, psychiatric comorbidity, cognition, adaptive behavior, quality of life, parenting stress. ISBN: 978-91-628-9902-8 (print); ISBN: 978-91-628-9903-5 (PDF)

# POPULÄRVETENSKAPLIG SAMMANFATTNING

Narkolepsi är en livslång sjukdom som oftast debuterar under tonåren eller unga vuxenår. Sjukdomen karaktäriseras av uttalad dagsömnighet, attacker av kataplexi (plötslig förlust av muskelkontroll i vakenhet som oftast utlöses av starka känslor), hallucinationer och sömnparalys i samband med insomnandet och uppvaknandet samt störd nattsömn. Syftet med avhandlingen var att studera en populationsbaserad grupp av barn och ungdomar med narkolepsi i Västsverige, för att kartlägga relationen till H1N1 influensavaccination med Pandemrix, psykiatrisk samsjuklighet och kognitiv profil samt att studera livskvalitet och adaptiv förmåga hos de drabbade barnen och graden av föräldrastress hos deras föräldrar.

Målet var att identifiera alla barn och ungdomar under 18 års ålder som utvecklade narkolepsi mellan den 1 januari 2000 och 31 december, 2010. Urvalet av patienter baserades på klassificeringskoderna i den tionde svenska versionen av International Classification of Diseases (ICD-10) och de diagnostiska kriterierna för narkolepsi enligt International Classification of Sleep Disorders från 2005. Sluten och öppenvårdsregister granskades från lokala och regionala barnkliniker och barnhabiliteringar i Halland och Västra Götaland samt neurofysiologiska kliniker i Västra Sverige. H1N1 influensavaccination relaterad narkolepsi (post-H1N1 influensavaccination narkolepsi, PHV) ansågs föreligga hos patienter med klinisk debut inom 10 månader efter vaccination. För att undersöka psykiatrisk samsjuklighet användes följande validerade instrument som genererade diagnoser enligt DSM-IV kriterier: Development and Well-Being Assessment och Attention Deficit Hyperactivity Disorder Rating Scale. För att screena för autistiska respektive psykotiska symptom användes Autism Spectrum Screening Questionnaire och Positive and Negative Syndrome Scale. Den kognitiva bedömningen genomfördes av en psykolog med hjälp av åldersspecifika Wechslerskalor. Adaptiv förmåga undersöktes med Adaptive Behavior Assessment System och föräldrastress med hjälp av den korta versionen av Parenting Stress Index. Ett sjukdomsspecifikt livskvalitetinstrument utarbetades med hjälp av fyra fokusgrupper bestående av ungdomar med narkolepsi och testades med avseende på reliabilitet och validitet. Detta nya frågeformulär, NARQoL användes tillsammans med det generiska frågeformuläret KIDSCREEN för mätning av sjukdomsgruppens hälsorelaterade livskvalitet.

Narkolepsiincidensen var 25 gånger högre för perioden efter vaccinationen jämfört med tidsperioden före. Barnen i PHV-gruppen hade en lägre ålder vid insjuknandet (median 10 år) och en mer plötslig symptomdebut än vad som tidigare har beskrivits vid narkolepsi. I PHV-gruppen hade 43% av patienterna någon form av psykiatrisk sjukdom: 8/28 hade ADHD, samtliga huvudsakligen

bristande uppmärksamhet, 6/30 hade depression, 3/30 hade generaliserat ångestsyndrom och 2/30 hade trotssyndrom. I non-post-H1N1 influensavaccination narkolepsi (nPHV)-gruppen hade en av 7 patienter ADHD, huvudsakligen bristande uppmärksamhet och trotssyndrom. De båda patientgrupperna presterade genomsnittliga resultat beträffande total-IQ och perceptuell hastighet men hade nedsatt verbal förståelse och arbetsminne. Föräldrar till barn i PHV-gruppen rapporterade sämre adaptiv förmåga hos sina barn avseende konceptuella och sociala färdigheter jämfört med föräldrar till friska jämnåriga svenska barn. Föräldrar skattade också högre föräldrastress avseende ”total stress”, ”dysfunktionell interaktion mellan förälder och barn” och ”svårhanterbart barn”. Det nyutvecklade instrumentet NARQoL består av två icke överlappande moduler: livskvalitet och syn på framtiden. Test-retest reliabiliteten hos NARQoL och validiteten mot KIDSCREEN-10 var god. Både NARQoL och KIDSCREEN-10 visade försämrad livskvalitet jämfört med kontroller. Barnen i PHV-gruppen hade nedsatt livskvalitet inom alla områden av NARQoL och barnen i nPHV-gruppen inom domänen skola/koncentration. Patienter med narkolepsi och psykiatrisk samsjuklighet hade lägre total-IQ, livskvalitet och adaptiv förmåga jämfört med dem utan psykiatrisk samsjuklighet.

Sammanfattningsvis talar resultaten för att vaccination mot H1N1 influensa med Pandemrix är en utlösande faktor för narkolepsi hos barn och ungdomar. Ytterligare genetiska och immunologiska studier behövs för att identifiera den exakta mekanismen bakom H1N1- influensavaccininducerad narkolepsi. Den ökade förekomsten av psykiatrisk samsjuklighet och kognitiva svårigheter understryker vikten av en noggrann psykiatrisk och neuropsykologisk uppföljning. Det narkolepsispecifika livskvalitet frågeformuläret NARQoL har god reliabilitet och validitet och påvisade en mer globalt försämrad livskvalitet jämfört med vad som tidigare har rapporterats. Nedsatt adaptiv förmåga hos barnen med narkolepsi och ökade stress nivåer hos föräldrarna talar för en betydande påverkan på det dagliga livet. Fynden i denna avhandling belyser narkolepsisjukdomens komplexitet och vikten av en multiprofessionell vård av barn och ungdomar med narkolepsi och behov av stöd till deras föräldrar.





# LIST OF PAPERS

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

- I. Szakács, A. Darin, N. Hallböök, T. Increased childhood incidence of narcolepsy in western Sweden after H1N1 influenza vaccination. *Neurology* 2013 Apr 2;80(14):1315-21
- II. Szakács, A. Hallböök, T. Tideman, P. Darin, N.\* Wentz E.\* Psychiatric comorbidity and cognitive profile in children with narcolepsy with or without association to the H1N1 influenza vaccination. *Sleep* 2015 Apr 1;38(4):615-21
- III. Chaplin, JE. Szakács, A. Hallböök, T. Darin, N. The development of a health-related quality of life instrument for young people with narcolepsy: NARQoL. *Submitted to Health and Quality of Life Outcome, May 2016*
- IV. Szakács, A. Chaplin, JE. Tideman, P. Strömberg, U. Nilsson, J. Darin, N. Hallböök, T. A population-based study of health-related quality of life, adaptive behavior and parenting stress in children with narcolepsy with or without association to the H1N1 influenza vaccination. *Manuscript*

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# ABBREVIATIONS

ABAS: Adaptive behavior assessment system

AD: Autistic disorder

ADHD: Attention-deficit/hyperactivity disorder

ADHDRS: Attention-deficit/hyperactive disorder-rating scale

ANOVA: Analysis of variance

ASSQ: Autism spectrum screening questionnaire

CBCL: Achenbach child behavior checklist

CHQ: Child health questionnaire

CI: Confidence interval

CNS: Central nervous system

CSF: Cerebrospinal fluid

DAWBA: Development and well-being assessment

DISABKIDS: stands for disabled children and is a group of disease-specific instruments, developed by the DISABKIDS Group for the assessment of HRQoL in children and adolescents aged between eight and 18 years with various chronic disorders.

DSM-IV: Diagnostic and statistical manual of mental disorders, 4th edition

EDS: Excessive daytime sleepiness

EEG: Electroencephalography

FSIQ: Full-scale IQ

GABA: Gamma-aminobutyric acid

GHB: Gamma-hydroxybutyric acid

Hcr: Hypocretin

Hcrtr: Hypocretin receptor

HLA: Human leukocyte antigen

HrQoL: Health-related quality of life

ICC: Intra-class correlation coefficient

ICD-10: International classification of diseases, 10th edition

ICSD: International classification of sleep disorders

KIDSCREEN: A screening of children and young people and their parents regarding health-related quality of life

PHV: Post-H1N1 influenza vaccination narcolepsy

NARQoL: Narcolepsy quality of life questionnaire

NEPSY-II: Developmental neuropsychological assessment test battery

nPHV: Non-post-H1N1 influenza vaccination narcolepsy

MRI: Magnetic resonance imaging

MSLT: Medium sleep latency test

ODD: Oppositional defiant disorder

PAF: Principal axis factoring

PANSS: Positive and negative syndrome scale

PDD NOS: Pervasive developmental disorder not otherwise specified

PRI: Perceptual reasoning index

PS: Parenting stress

PSI: Processing speed index

PSI/SF: Parenting stress index, short form

PSG: Polysomnography

RAS: Reticular activating system

REM: Rapid eye movement

SD: Standard deviation

SDQ: Strengths and difficulties questionnaire

SOREM: Sleep onset REM

SPSS: Statistical package for the social sciences

VAESCO: Vaccine adverse event surveillance and communication

VCI: Verbal comprehension index

VSP: Vecu et sante percue questionnaire

WAIS-IV: Wechsler adult intelligence scale-fourth edition

WISC-IV: Wechsler intelligence scale for children-fourth edition

WMI: Working memory index

WPPSI-III: Wechsler preschool and primary scale of intelligence-third edition



# INTRODUCTION

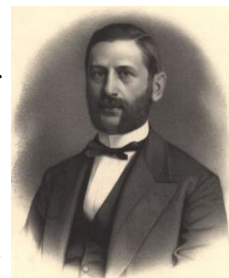
In the late fall of 2009, an increasing number of patients with narcolepsy were identified at our clinics in Halmstad and the Queen Silvia's Children's Hospital in Gothenburg. The patients appeared to have experienced a sudden onset of the disease that came within months after vaccination against the H1N1 influenza virus. Intrigued by these patients, a research project was set up to study whether there was a possible causal relationship between the vaccination and the onset of narcolepsy. We also wanted to determine whether we could find any associated impact on mental health or cognition and how the narcolepsy affected the children in their daily lives.

Narcolepsy often begins in adolescence and is almost as common as multiple sclerosis or Parkinson's disease in adults.[1, 2] It is characterized by the tetrad of excessive daytime sleepiness, cataplexy, sleep paralysis and hypnagogic/hypnopompic hallucinations. Excessive daytime sleepiness (EDS) is the main clinical diagnostic criterion for narcolepsy and most often the first symptom raising a suspicion of the disease.[3, 4] Sleep attacks have a sudden daytime onset, occur several times a day with an increased likelihood in connection with physical inactivity and are unavoidable, despite the patient's efforts to stay awake. The duration is generally short, although the sleep attacks are longer in children and don't have the same beneficial effects of sleep compared with adolescents and adults with narcolepsy. Cataplexy is the most specific clinical symptom of narcolepsy since it is extremely rare in other diseases. More than half the children with narcolepsy have cataplexy and the prevalence is higher in patients with longer disease duration and those with hypocretin-1 deficiency.[5, 6] Cataplexy is characterized by a sudden loss of muscle tone and deep tendon reflexes triggered by strong emotions, most often positive ones. All striated muscles, except the diaphragm, can be involved and it is not uncommon that only the facial muscles are affected, causing the protrusion of the tongue, dysarthria, facial flickering and head or jaw dropping. The duration of cataplexy varies from seconds to minutes and, even if rare, up to several hours, a condition named "status cataplecticus". Cataplexy can also occur in a more pronounced form that may resemble complex movement disorder.[7] Hypnopompic/hypnagogic hallucinations are auditory, visual or somesthetic hallucinations on awakening or on falling asleep and are present in approximately half the children.[3, 5] Sleep paralysis is equally common and entails an inability to move the limbs, the head or to speak either on awakening or on sleep onset, despite being fully conscious. It lasts from seconds to some minutes and can sometimes be interrupted by physical stimulation. Nocturnal sleep is fragmented in the majority of patients, with frequent awakenings and lower overall sleep duration.[5] Up to one third of the children also have other

sleep-related parasomnias, i.e. sleep terrors, sleepwalking and sleep talking.[8] Besides the typical symptoms, additional features may include weight gain and precocious puberty.[5, 9] The symptoms of narcolepsy vary to some extent, based on the patient's age. Clinical and polysomnographic findings indicate that the main symptoms of narcolepsy, EDS and cataplexy, improve in later adulthood, while nocturnal sleep disturbances can worsen with age.[10] However, there are no prospective studies that have examined the development of the main symptoms with age.

## History of narcolepsy

Karl F.O. Westphal, a professor of psychiatry and neurology working in Berlin, gave the first known description of narcolepsy with cataplexy in the medical literature in 1877.[11] The term “narcolepsy” was proposed by Jean B. É. Gélinau, a French physician, in 1880, by combining the Greek words *νάρκη* (*narkē*, “numbness” or “stupor”) and *λήψις* (*lepsis*, “attack” or “seizure”).[12] Insights into the pathophysiology of narcolepsy came from clinico-pathophysiological studies of cases of the encephalitis lethargica epidemic that followed the Italian influenza epidemic in 1889-1890 and the Spanish H1N1 influenza epidemic in 1918. Patients had increased daytime sleepiness, reversal of the sleep/wake cycle, movement disorders and psychiatric symptoms. Von Economo studied the postmortem samples and correlated symptoms with necrosis in the posterior hypothalamic area, a region now known to contain most essential wake-promoting systems.[13] Subsequently, there has been an exponential development of knowledge during the following decades concerning the etiology, pathomechanism and comorbidities of narcolepsy (Figure 1).



Karl F.O. Westphal

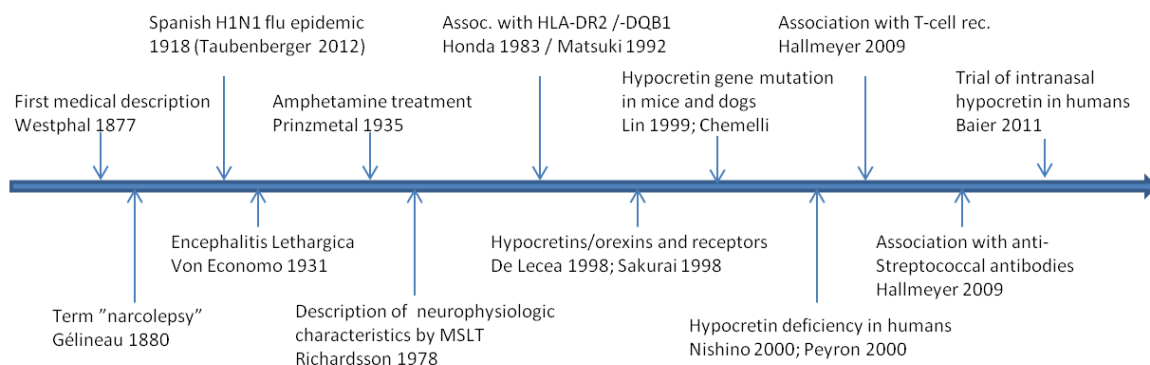


Figure 1. A few milestones in narcolepsy research



## Incidence of narcolepsy

Epidemiological research in general investigates the patterns, causes and effects of health and disease conditions in defined populations. It is also the cornerstone of public health, as it focuses on preventive health care. “Incidence” is an epidemiological term to describe the occurrence of a disease. It indicates the number of new disease cases in a given population during a defined period of time. In epidemiological research, population-based studies are often used to answer disease-related questions for a defined population. The results can usually be generalized to the entire population addressed in the study hypothesis, not only to the individuals included in the study. The selection of study population is crucial as it should be representative of all individuals in the *à priori* defined specific population.

Few studies have addressed the incidence of narcolepsy in children. In a study of children 0-19 years of age from Minnesota, the overall incidence of narcolepsy, with or without cataplexy, was estimated at 2.4/100,000 persons a year and 1.1/100,000 persons a year for narcolepsy with cataplexy.[14] The incidence of narcolepsy varies with age and is twice as high in the second decade of life compared with the third decade and more than three times higher than in the first and fourth decades.[14] Patients with a positive family history of narcolepsy have an up to 20- to 40-fold increase in the risk of having the disease and tend to have an earlier onset than those without a family history.[15, 16]

## Etiology

### Hypocretin-1 deficiency

The first report of hypocretin-1 deficiency in the cerebrospinal fluid of patients with narcolepsy with cataplexy was published in 2000 and, in the same year, a loss of hypocretin-1 neurons was found in the hypothalamus of patients with narcolepsy.[17, 18] Hypocretins/orexins were discovered in 1998, by two independent research groups, and are produced by a distinct group of 70,000 neurons in the lateral hypothalamus.[19, 20] One group called the peptides “hypocretins”, because of their hypothalamic localization and similarities to the hormone “secretin”, while the other group called the molecules “orexins”, due to their appetite-increasing effect. Two different peptides, hypocretin-1 and hypocretin-2, are cleaved from a precursor, preprohypocretin peptide, and bind to two different G-protein-coupled hypocretin receptors, Hcrtr 1 and Hcrtr 2. The role of hypocretin-1 in the regulation of wakefulness sleep is based on the

excitatory projections to monoaminergic neurons that promote wakefulness by stimulating cortical neurons.[21, 22] Monoaminergic neurons can be found in the locus coeruleus (noradrenergic), dorsal raphe nuclei (serotonergic), periaqueductal gray matter (dopaminergic) and tuberomammillary nucleus (histaminergic) of the brain and together they form the ascending reticular activating system. The hypocretinergic neurons, in turn, receive excitatory projections from the suprachiasmatic nuclei, responsible for the control of circadian rhythm, the limbic system that supports functions including emotion and behavior and the metabolic system that controls appetite and glucose metabolism.[23, 24] Inhibitory projections to hypocretinergic neurons, mainly GABAergic, derive primarily from the ventrolateral preoptic nucleus, which is the main sleep-inducing center.[24] Hypocretin-1 is thus a conductor which plays an important role in the interaction between the wakefulness-promoting monoaminergic system and sleep-promoting GABAergic system, thereby modulating the arousal threshold so that the individual is able to maintain adequate alertness.

A minority of patients with narcolepsy have normal levels of CSF-hypocretin-1. This group of patients has less frequent cataplexy and earlier onset of narcolepsy. A family history of narcolepsy is more common and the prevalence of HLA-DQB1\*0602 is considerably lower than in patients with low CSF-hypocretin-1 levels.[25] The etiology of narcolepsy without hypocretin-1 deficiency is much less known than that of narcolepsy with hypocretin-1 deficiency. One possible explanation could be that there are other disturbances in the hypocretin-1 signaling than hypocretin-1 deficiency. For example, a mutation in the gene encoding the hypocretin receptor 2 has been identified as the cause of the autosomal recessive canine narcolepsy.[26]

## **Genetic and autoimmune aspects of narcolepsy**

Narcolepsy is characterized by a strong linkage to certain human leukocyte antigen (HLA) types. The HLA system includes groups of genes encoding proteins found on the surface of cells that present antigens to T-lymphocytes. The strongest association has been found to HLA class II encoded HLA-DQB1, -DRB1 and -DQA1 haplotypes, which play a crucial role in triggering autoimmune responses. DQB1\*0602 is the primary candidate susceptibility gene for narcolepsy and is present in 85% of patients diagnosed with narcolepsy with cataplexy.[27] Subjects homozygous for DQB1\*0602 have a two to four times increased risk of developing narcolepsy when compared with DQB1\*0602 heterozygotes.[28] Furthermore, the risk in heterozygotes is modulated by the other DQB1 allele. The occurrence of the HLA-DQB1\*0602 allele is not limited to narcolepsy with cataplexy and is found in 12%-38% of the general European

population.[29] Together with case reports of patients with defined narcolepsy with cataplexy without the HLA-DQB1\*0602 allele, these findings indicated that a genetic predisposition to narcolepsy could not be fully explained by HLA allele association.[30] Epidemiological studies have found an association between narcolepsy and common upper airway infections, including those caused by streptococcus pyogenes, seasonal influenza and the influenza A virus.[13, 31, 32] Further studies have found a possible association between narcolepsy and several genes important in antigen processing, T-lymphocyte stimulation, neuronal surveillance and autoimmune diseases of the central nervous system.[33-35] These discoveries have contributed greatly to the understanding of how a genetic predisposition, in the form of specific HLA types, through an autoimmune reaction, could lead to the destruction of hypocretin-1-producing neurons. Two major hypotheses have been raised to explain the way infections or vaccination may induce the autoimmune-modulated destruction of hypocretin-1 neurons.[36] The first hypothesis is based on molecular mimicry involving antigen presentation in the context of DQB1\*0602, which would activate a population of cross-reactive T-lymphocytes present in predisposed individuals. The second hypothesis is bystander activation in which a generalized pro-inflammatory environment associated with infections could facilitate the destruction of hypocretin-1-producing neurons.

## **Symptomatic narcolepsy**

Narcolepsy can also be secondary to other neurological diseases (i.e. symptomatic narcolepsy). The most frequent causes in adults are CNS tumors, head trauma or demyelinating disorders.[37, 38] In children, the most common cause is CNS tumors, followed by hereditary diseases, i.e. Nieman-Pick disease Type-C and myotonic dystrophy Type 1.[39, 40] Other relatively rare causes are vascular disorders and encephalitis of infectious or autoimmune origin.[41, 42] However, the specific narcoleptic phenotype with clear-cut pathognomonic cataplexy and low CSF hypocretin-1 levels occurs very rarely.

## **Psychiatric comorbidity**

Psychiatric symptoms, including depressive mood and social anxiety, have been described in up to 30% of adult patients with narcolepsy compared with 10%-17% in the general population.[43, 44] A retrospective study of adult patients with narcolepsy identified a more than 8-15 times greater prevalence of attention-deficit/hyperactivity disorder (ADHD) during childhood than expected.[45] In children and adolescents, only one study has used standardized

methods to evaluate psychiatric comorbidity.[46] This study identified significantly higher scores on the Child Depression Inventory in patients compared with controls. Other studies have used medical records or follow-up questionnaires and described symptoms of mood disorders including depression occurring in 40% and behavioral disorders in 33-75% of pediatric patients with narcolepsy.[5, 47] According to one study, age at onset may have some implications for the prevalence of comorbid depression and anxiety, since these disorders were more prevalent in patients with postpubertal onset compared with those with prepubertal onset.[5] In one study, 89% of the parents reported concern about their child's irritability or emotional lability and 86% concern about academic performance.[48] A retrospective study comprising 51 children with narcolepsy with cataplexy revealed a higher prevalence of ADHD (inattentive type) compared with the general population.[5]

## **Cognition**

Adult patients with narcolepsy may attain a high performance in several cognitive domains, but, at the same time, they can exhibit difficulties in areas, such as attention, working memory, executive function, reward processing and decision-making.[49-52] These cognitive functions have been reported to affect tasks which require processing over a long period of time or during complex tasks demanding divided attention.[49] It has been hypothesized that patients with narcolepsy need to use a considerable amount of their attentional resources to maintain alertness and the attention needed for longer complex tasks suffers.[53] Difficulties with memory are present in up to 50% of adult patients.[54, 55] Neuropsychological studies have revealed primarily encoding memory problems, i.e. converting items of interest into a construct that can be stored within the brain [56], and more pronounced difficulties with verbal than with visual memory.[49] Several executive control impairments have been identified.[49, 57] Patients with narcolepsy need a longer time to complete a task and make more frequent errors during tests compared with controls.

Cognitive function in children and adolescents with narcolepsy has been sparsely studied. In general, sleep disruption is associated with a wide range of behavioral, cognitive and mood impairments in children.[58] In a controlled study of 157 mainly adult patients with narcolepsy, but also a smaller group of adolescents from 15 years of age, a self-report measurement of cognitive functioning was used. Significant difficulties were found in 26% of participants and the most affected areas were attention, delayed recall and memory.[59] Most of these difficulties were obvious even when controlled for age, sleepiness and psychotropic medication. Only one previous study has investigated cognitive functions in children and adolescents with narcolepsy using standardized

methods. This study enrolled twelve children and 11 of 12 had a full-scale IQ within the average range. Uneven cognitive profiles with a significantly higher verbal IQ than performance IQ were found in three patients and a higher performance IQ than verbal IQ in two patients.[60] Some studies using medical records and screening questionnaires have reported a higher prevalence of educational difficulties, including more frequent grade repetition and more school absences compared with controls.[5, 46, 61]

## Quality of life

The generic definition of quality of life (QoL) is the individuals' perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards and concerns.[62] Health-related quality of life (HrQoL) refers to domains of QoL that affect the health of a person. It is generally thought that the main domains of HrQoL are physical functioning, emotional state, performance of social roles, intellectual functioning and general well-being.[63] HrQoL is an important outcome, since it provides an individualized measurement of the disease impact on the patient's life and can thus contribute to personalized follow-up and treatment. HrQoL is usually measured with validated instruments such as questionnaires or semi-structured interview schedules. Self-reported HrQoL is, however, a subjective measurement and can also be affected by the social and cultural environment. In relation to the measurement of HrQoL in children, it has been stressed that appropriate goals that take account of developmental considerations need to be selected and that children have goals that are primarily related to the present.[64] Another point to consider is that some children and adolescents with severe disease may not have the necessary cognitive or communicative skills to express their preferences.

Studies of adult patients with narcolepsy have consistently found impaired HrQoL. Three of these studies report significantly decreased HrQoL in all domains.[65, 66] In one of the adult studies, 55% of the patients reported difficulties with school achievements and 37% reported that they had to give up working because of narcolepsy.[65] Irresistible sleepiness appears to be the main disabling symptom in the work field. Other negative effects of narcolepsy are reported in terms of poor relationships, with a higher rate of divorce and sexual dysfunction. The incidence of accidents, in automobiles as well as at home and at work is also increased.[66, 67] Another study found that in most patients the disease does not prevent high educational achievements and approximately 60% of the patients were capable of a regular occupation.[68] Drug treatment has a positive impact on HrQoL in narcoleptic patients, but other interventions could also be of value, such as social and mental support that can influence coping

mechanisms, thereby helping patients maintain their working and private relationships.[66] It appears that younger adult narcolepsy patients have more difficulties with social relationships and adjustment to their work environments and are more prone to depression than older patients.[66, 67] To our knowledge, only two studies have measured HrQoL in children with narcolepsy using validated questionnaires. One of these studies comprised a group of 42 children and a significant difference was found in mental health subscales but not in physical health subscales or global health compared with controls.[46] The other study evaluated 83 children with narcolepsy showing significantly lower general well-being, social functioning and school performance compared with controls.[61] The most affected areas were vitality and leisure whilst psychological well-being was not significantly affected.

Different stages of the disease, as well as different complications of the disease, may result in considerable differences in HrQoL. So, in order to assess the HrQoL concerns of a disorder, a disease-specific instrument is recommended, as it is more sensitive to changes.[69, 70] Disease-specific HrQoL methods and instruments give patients with a certain disease the opportunity to indicate the domains that are salient or meaningful to them in the context of their disease and HrQoL.[63] All studies of HrQoL in people with narcolepsy have been carried out without access to disease-specific instruments, as these have not yet been developed. In order to assess HrQoL in this group with new-onset narcolepsy, a disease-specific instrument was needed in order to be sensitive to the changes in lifestyle and future expectations.

## **Adaptive behavior**

Normal adaptive behavior plays a crucial role in living independently and functioning safely and appropriately in daily life. Adaptive behavior includes abilities such as coping with social interactions and leisure activities, taking responsibility for one's own health care and safety and handling educational responsibilities. These skills are personal and age dependent, whereas different individuals may have different strengths and weaknesses in any or all of the main adaptive skills, resulting in an individual adaptive behavior profile. Several factors, such as development level and social environment, influence these skills. In addition, chronic illnesses can impair the patients' adaptive skills, resulting in an increased need for support from family members, social environment and health care. A careful assessment of an individual's profile of adaptive strengths and weaknesses is therefore important in order to provide the optimal support. A multitude of assessment scales have been constructed and the two most commonly used in children are the Vineland Adaptive Behavior Scale, which has

a more psychiatric and diagnostic profile, and the Adaptive Behavior Assessment Scale, which has a primary functional approach.

According to previous studies using medical record reviews and personal interviews, narcolepsy in adults has a greater impact on social (i.e. family relationship) and practical (i.e. occupational, health care orientation) adjustments compared with patients with other chronic illnesses such as cardiac disorders or diabetes.[67, 71] According to one study that enrolled adult patients with narcolepsy between 18-81 years of age, younger adults had more occupational difficulties compared with older patients. It is unclear whether the explanation is a more severe degree of narcolepsy related to the younger age or if it is easier for an elderly person to find more suitable working conditions.[67]

Difficulties with adaptive behavior have been reported by controlled studies using validated instruments, in children with neurological and psychiatric disorders.[72, 73] Moreover, impairments in different adaptive skills, especially social and communication skills, have been found to correlate with poorer school performance.[74] Adaptive behavior in children with narcolepsy has been investigated with a validated instrument in one previous study using the Achenbach Child Behavior Checklist. Significant impairments were found in social integration, school competence and participation in activities in over half the 12 included children.[60] Retrospective, hospital-based studies using non-validated questionnaires have also described social difficulties and poor school performance in a larger proportion of children with narcolepsy.[5, 46]

## **Parenting stress**

Parenting stress (PS) increases when demands and expectations exceed the resources available to the parents. It is assumed that there are four components to the stress in general: an external causal event, a cognitive appraisal of the event, coping mechanisms to reduce the impact of the event and reactions to the stress event.[75] Caring for young people with a chronic illness encompasses balancing typical familial responsibilities (i.e. employment, finances) with additional disease-related tasks. Parents of children with a chronic medical condition often have to overcome challenges associated with following a treatment regimen, coping with concerns about long-term consequences, having difficult discussions with the young people about their disease and navigating and serving as an advocate within a complex medical system. Another possible causal agent of parenting stress appears to be the children's behavioral problems associated to the chronic disease.[76, 77] These demands can be perceived by caregivers as overly burdensome and contribute to increased stress. Parenting stress can thus be regarded as an indirect measurement of the impact of narcolepsy on the

child's health and daily living. Higher PS has been reported in childhood chronic neurologic and psychiatric diseases, such as epilepsy and ADHD, compared with the parents of healthy children.[78, 79] The psychosocial functioning of caregivers managing a child with narcolepsy has only been studied in one previous study which found significantly poorer status compared with controls, but neither the level of PS nor which of the family members was affected was explored.[46]

## **Classification and diagnosis**

Sleep disorders are classified according to the International Classification of Sleep Disorders (ICSD), a diagnostic and coding manual produced by the American Academy of Sleep Medicine (AASM). The first revised edition from 2001 defined a single type of narcolepsy, described as a disorder of unknown etiology, with a lack of information regarding the pathology and familial pattern of the disorder.[80] The second edition from 2005 classified narcolepsy into “narcolepsy with cataplexy” and “narcolepsy without cataplexy” and regarded the HLA-DBQ1\*0602 subtype as being more specific to narcolepsy, especially to narcolepsy with cataplexy.[81] This symptom-based approach was sensible prior to the identification of hypocretin-1 deficiency as the cause of narcolepsy with cataplexy. In recent years, the “with cataplexy” terminology has been questioned, as a small group of patients with clear hypocretin-1 deficiency do not manifest cataplexy at the time of diagnosis.[6] A new approach to the subdivision of narcolepsy was therefore applied in the third edition of the ICSD in 2014 and the terminology has been changed to “Narcolepsy type 1” and “Narcolepsy type 2”.[82] Although hypocretin-1 deficiency is the hallmark of “Narcolepsy type 1”, the relative unavailability of hypocretin-1 assays to date has resulted in continued dependence on the identification of cataplexy to establish a Narcolepsy type 1 diagnosis.

The diagnosis is primarily based on the targeted clinical history and follows the International Classification of Sleep Disorders, 2nd edition.[81] To meet the diagnostic criteria, patients must have increased daytime sleepiness in combination with a pathologic polysomnography and medium sleep latency test (MST) or cataplexy or hypocretin-1 deficiency. A normal MSLT does not exclude the diagnosis of narcolepsy, since the sensitivity of an MSLT is 70%.[83] HLA typing provides further guidance, as HLA-DQB1\*0602 is present in more than 90% of subjects with narcolepsy with cataplexy.[3, 5] It is also mandatory that the increased daytime sleepiness and/or MSLT findings are not better explained by other causes such as other sleep disorders or the effect of medication. A lumbar puncture for the measurement of cerebrospinal levels of hypocretin-1 is recommended, especially in patients negative for HLA-



DQB1\*0602. MRI is usually performed to rule out some of the secondary causes of narcolepsy, i.e. tumors and multiple sclerosis, while an EEG differentiates cataplexy from epileptic seizures. Children with daytime sleepiness, cataplexy and progressive neurological impairment together with intellectual decline should be investigated for neurometabolic disorders such as Nieman-Pick disease Type-C. In the event of considerable hypersomnolence, it is important to exclude sleep-disordered breathing, delayed sleep phase syndrome and periodic leg movements during sleep.

## Treatment

The medical treatments available today are symptomatic. One major problem is that none of the drugs has an approved indication for the treatment of narcolepsy in children and adolescents. However, there are results from some studies and growing clinical experience which enable off-label usage.[5, 84] For the treatment of excessive daytime sleepiness, different stimulants are used, i.e. methylphenidate and modafinil. Stimulants are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the synaptic cleft, thereby increasing the level of alertness.[85, 86] Cataplexy is usually treated with antidepressants, nowadays mostly selective serotonin and/or noradrenaline uptake inhibitors which have better side-effect profiles than the older tricyclic antidepressants. Sodium oxybate is also used to reduce cataplexy but also to increase the duration of deep sleep which, in combination with fewer nighttime awakenings, results in an improved and less fragmented sleep architecture.[87-89] Sodium oxybate is an endogenous GABA metabolite that acts as a neurotransmitter in the CNS through GHB and GABA-B receptors and also has a modulating effect on dopaminergic and noradrenergic neurons.[90] The sedative effect is due to interaction with specific inhibitory GABA-B receptors.[91] Even if the exact mechanism by which sodium oxybate enhances wakefulness and reduces cataplexy is unknown, it is assumed that it is partly due to the stimulating effect on the locus coeruleus.[92]

Non-pharmacological treatment approaches in children with narcolepsy are regular exercise, optimized sleep habits and the avoidance of sleep deprivation. One or two scheduled daytime naps are often needed, as well as the reduction of very fast carbohydrates in the diet to reduce fluctuations in the level of alertness.

## AIMS

The main purpose of this thesis was to study a well-defined cohort of children and adolescents with narcolepsy within the framework of a series of population-based studies.

The specific aims of the different studies were

To determine the incidence and clinical features of narcolepsy in children and adolescents with or without correlation to the H1N1 influenza vaccination in western Sweden in order to study a possible relationship between the vaccination and narcolepsy – Study I

To examine psychiatric comorbidity and cognitive profile in children and adolescents with narcolepsy in western Sweden with or without correlation to the H1N1 influenza vaccination – Study II

To create and validate a disease-specific questionnaire by using focus groups and cognitive debriefing exercises to measure health-related quality of life – Study III

To measure HrQoL and adaptive skills in children and adolescents with narcolepsy in western Sweden and to analyze the level of parenting stress in their parents – Study IV

# **PATIENTS AND METHODS**

## **Study population**

### **Studies I, II and IV**

The geographic area studied was the western Swedish health-care region, with the counties of western Götaland and Halland. The at-risk population was calculated in children between two and 17 years of age and the ratio of boys to girls and the proportions by age-group population reflected the same demographic characteristics as the general distribution in Sweden. Residential and outpatient registers from local and regional pediatric clinics and child rehabilitation clinics were scrutinized. Written enquiries were sent to all outpatient pediatric clinics. Registers at the regional departments of neurophysiology in Gothenburg, Linköping and Lund were reviewed. The onset of narcolepsy was before 18 years of age and between January 1, 2000 and December 31, 2010. Patient selection was based on the classification codes of the Swedish version of the ICD 10.[93] The diagnostic criteria for narcolepsy according to the 2005 International Classification of Sleep Disorders were used.[94] Post-H1N1 influenza vaccination narcolepsy (PHV) was considered in patients with clinical onset within 10 months of vaccination and non-post-H1N1 influenza vaccination narcolepsy (nPHV) with onset unrelated to or after 10 months following vaccination. The search procedure is presented in Figure 2. The investigated population consisted of 53 patients of whom 43 were included in the different studies (Figure 2). Six patients of 43 were diagnosed after December 2010 but had onset of narcolepsy during the study period. These patients were included in Studies II and IV. Controls for measuring QoL and parenting stress in Study IV were recruited from elementary and high schools in the same counties. Age and gender matching was performed at group level.

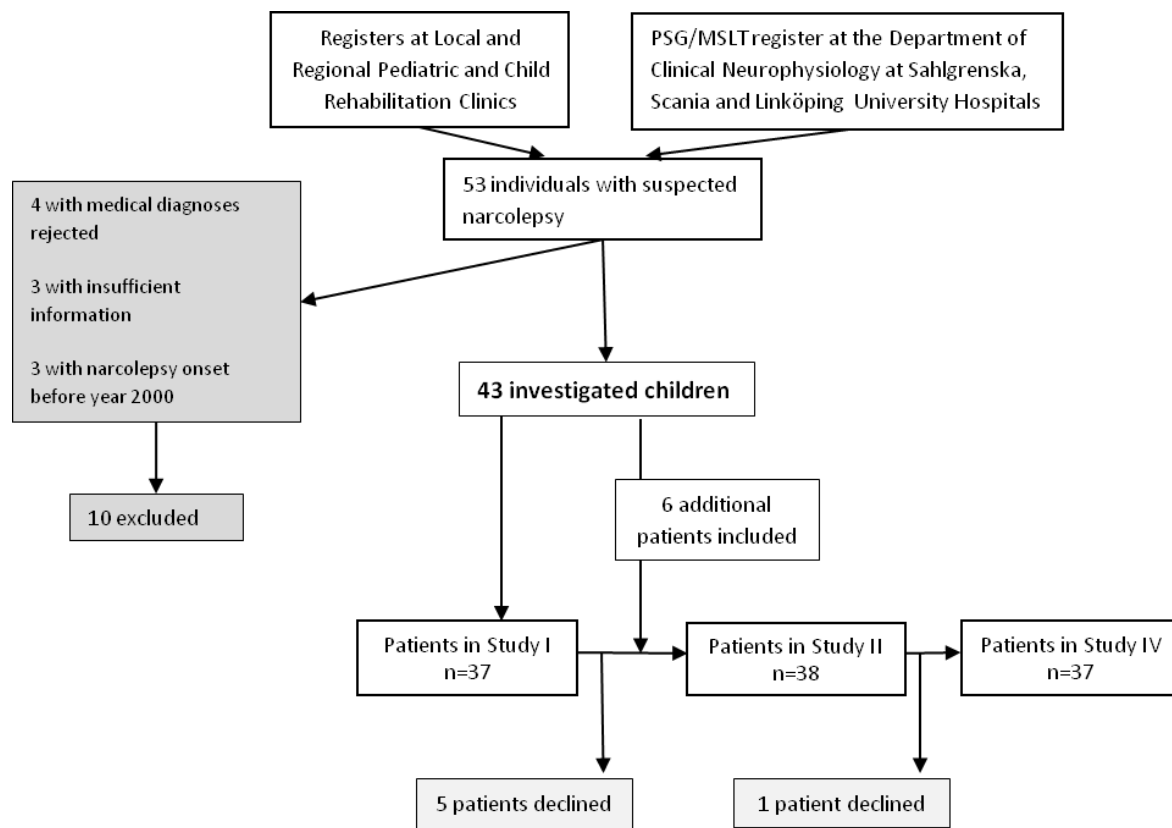


Figure 2. Search procedure for the identification of 43 children and adolescents with narcolepsy in western Sweden. MSLT: multiple sleep latency test; PSG: polysomnography

## Study III

In this study, four focus groups were created comprising children and adolescents with narcolepsy identified in the western Swedish health-care region, with the counties of western Götaland and Halland. The onset of narcolepsy was before 18 years of age and between January 1, 2000 and December 31, 2010. These focus groups consisted of 20 young people aged 8-18 years. Two additional focus groups were conducted with parents of these patients. A further 95 matched controls were recruited from a school-based population in the same counties.

## Methods

An overview of all the methods and instruments used in the different studies in the present thesis is given in Figure 3.

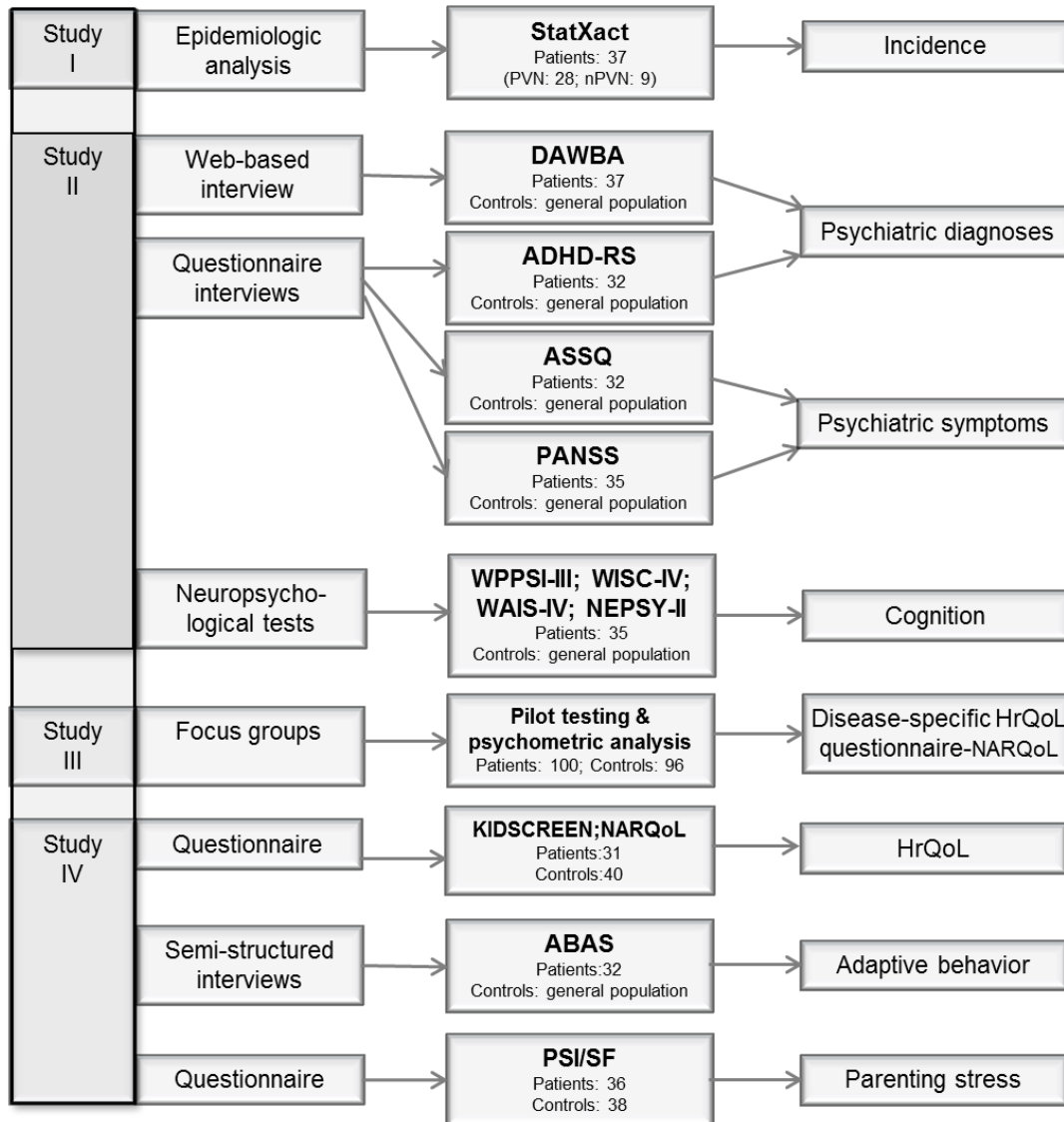


Figure 3. Methods used in the different studies in this thesis. Number of patients is given for each of the variables. Abbreviations: PHV, post-H1N1 influenza vaccination narcolepsy; nPHV, non-post-H1N1 influenza vaccination narcolepsy. The number of patients in Studies II and IV was fewer than 38 and 37 respectively, since all the patients did not require all the investigations to fulfill the criteria for narcolepsy according to the ICD-10. For abbreviations of the different tests, see the Method section of the thesis.

## **Study I**

Patient records at the different patient care centers (Figure 2) were reviewed to collect data on family history, past and previous illnesses, age at onset of symptoms, investigations, diagnosis and treatments. Information about the relationship in time with vaccination against H1N1 influenza was also collected. Children and parents were asked about symptoms of infection within a period of three months before the onset of narcolepsy. In Sweden, Pandemrix vaccine developed by GlaxoSmithKline was used; it contains inactivated, split influenza virus and the adjuvant SO3A (squalene, vitamin E and polysorbate).[95] Latency time was defined as the duration from the vaccination to the onset of narcolepsy. A sudden onset of symptoms was defined as onset within 12 weeks from vaccination in the post-vaccination group or a disease onset that could be dated within a 12-week period in the pre-vaccination group. In our study, children were assessed with actigraphy during a period of seven days prior to a multiple sleep latency test (MSLT). A CSF hypocretin-1 level below 200 pg/mL was considered abnormal.

## **Studies II and IV**

All patients participated in a research visit and were assessed by the same psychologist who performed an age-adapted intelligence test, online-based structured interview (DAWBA) and questionnaires described below. Age- and gender-matched controls have been included for measurements of HrQoL and parenting stress. For comparison, validated data on healthy Swedish children's and young people's cognitive functions and adaptive behavior were applied. Results from previous Swedish studies of the prevalence of different psychiatric disorders in the general population have also been used for comparison.

## **Psychiatric comorbidity**

To identify psychiatric comorbidity, a parental interview was conducted with the online-based Development And Well-Being Assessment (DAWBA) designed to generate psychiatric diagnoses according to the ICD-10 and the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV).[93, 96, 97] The final assignment of diagnoses was made by an experienced child and adolescent psychiatrist. The DAWBA has a relatively low sensitivity for autism and ADHD and we therefore included additional instruments for these disorders. The Autism Spectrum Screening Questionnaire (ASSQ) was used to screen for difficulties within the autism spectrum.[98] The Attention-Deficit/Hyperactive Disorder-

Rating Scale (ADHD-RS) was used to assign ADHD diagnoses.[99] If the onset of ADHD symptoms was after seven years of age, we defined it as ADHD with atypical onset. According to the DSM-5, published in 2013, after the present study had been conducted, the debut of ADHD symptoms has been raised to before 12 years. The onset of ADHD symptoms in our study population was after the debut of narcolepsy in all cases but one and was therefore diagnosed as an acquired variant of ADHD. The Positive And Negative Syndrome Scale (PANSS) was used to assess symptoms of psychosis.[100] The PANSS is only valid for adolescents and adults, but this instrument was considered the most suitable for screening purposes regarding psychotic symptoms in children.

## **Cognitive profile**

The cognitive assessments were made by a clinical psychologist using the Wechsler intelligence scales. We did not perform ratings of sleepiness, but all children were given the option to refuse testing if their current status was not suitable for testing. No one refused or interrupted the test and fewer than five patients needed a break of some minutes. Depending on the age of the patient, the appropriate Wechsler scale, WPPSI-III (Wechsler preschool and primary scale of intelligence-third edition), the WISC-IV (Wechsler intelligence scale for children-fourth edition) or the WAIS-IV (Wechsler adult intelligence scale-fourth edition), was used.[101-103] Values for the full-scale IQ (FSIQ), verbal comprehension index (VCI), perceptual reasoning index (PRI), processing speed index (PSI) and working memory index (WMI) were recorded. Executive functions such as initiation, cognitive flexibility and monitoring were examined with two subtests (animal sorting and word generation) from the developmental neuropsychological assessment test battery (NEPSY-II).[104]

## **Health-related quality of life**

For the measurement of HrQoL, the KIDSCREEN-10 and NARQoL questionnaires were used.[73, 105-107] The KIDSCREEN-10 questionnaire is a standardized instrument for screening, monitoring and evaluating HrQoL from the child's point of view with regard to physical, mental and social well-being. It is validated for children and adolescents between eight and 18 years. The mean index score is 100 in the general healthy child population. DISABKIDS is a group of disease-specific instruments, developed by the DISABKIDS Group for the assessment of HrQoL in children and adolescents aged eight to 18 years with various chronic disorders.[105, 108] The mean index score is between 41 and 51

points on a 0-100 scale in the general healthy child population. The NARQoL is a child/adolescent self-completion, disease-specific questionnaire for narcolepsy and it includes 15 questions assigned to three domains: emotional reaction, social confidence and school/concentration.[107] There are two additional domains related to future QoL consisting of six questions. The future domains capture future expectations and future limitations.

## **Adaptive behavior**

To assess the adaptive function skills, the Swedish version of the Adaptive Behavior Assessment System (ABAS-II) was used.[109] The ABAS-II provides a comprehensive assessment of the adaptive behavior of individuals aged five to 21 years and there are validated data on healthy Swedish children's and young people's adaptive behavior for comparison. The children's abilities are rated by parents in nine different skill areas which reflect different aspects of adaptive behavior, namely Communication, Community Use, Functional Academics, Home Living, Health and Safety, Leisure, Self-Care, Self-Direction and Social. Each skill area has a scaled score mean of 10, with a standard deviation of 3. The skill areas are grouped into three adaptive composites, Conceptual (Communication, Functional Academics, Self-Direction), Social (Leisure, Social) and Practical (Community Use, Home Living, Health and Safety, Self-Care), with a standard score mean of 100 and a standard deviation of 15. All nine skill areas are also combined into a General Adaptive Composite (GAC), with a standard score mean of 100 and a standard deviation of 15 which reflects the individual's overall adaptive functioning.

## **Parenting stress**

Parenting stress was evaluated with the short form of the Parenting Stress Index (PSI/SF) consisting of 36 questions screening for stress in the parent-child relationship.[110] The PSI/SF yields a total stress score from three scales: parenting distress (parental self-esteem), focusing on the parental distress related to parenting, parent-child dysfunctional interaction (parent-child interaction), focusing on the parents' perception that their child does not meet the parents' expectations, and difficult child (child self-regulation), focusing on the parents' perception of behavioral characteristics of children that make them either easy or difficult to manage.



## Study III

Four focus groups were conducted to identify relevant questions for the measurement of HrQoL in children and adolescents with narcolepsy. The focus group procedure followed a standardized approach, using a multi-stage method converging on specific QoL issues related to narcolepsy.[107, 111] This process was followed by cognitive debriefing and panel discussions to clarify patients' interpretations of the questions and their answers in order to refine the questions and ensure that all relevant topics were covered.[112] A pilot questionnaire which included the most relevant questions was constructed and was distributed by the Narcolepsy Association of Sweden, hospital outpatient clinics in the counties of western Götaland and Halland and via the closed Swedish narcolepsy Facebook group.[113] The questionnaire was also sent to students in two middle and two high schools in the counties of western Götaland and Halland. In all, 196 questionnaires were returned (100 patients and 96 controls) and analyzed for external reliability by conducting a test-retest. This was followed by exploratory data-driven factor analysis to explore the shared variance by the items. Several alternative structures were explored before the final 21-item version was determined as the best fit for the criteria. The last assessment was the validation process where the convergent validity was assessed against the KIDSCREEN questionnaire using bivariate correlation.

## Statistical analysis

### Studies I, II and IV

Data processing was performed with the Statistical Package for the Social Sciences (SPSS) version 21 statistical computer program.[114, 115] The annual average incidence was calculated for the entire study period between January 1, 2000 and December 31, 2010 (incidence period A), the period prior to the H1N1 influenza vaccine between January 1, 2000 and August 31, 2009 (incidence period B) and the period after the H1N1 influenza vaccination between October 1, 2009 and December 31, 2010 (incidence period C). The incidence was calculated by dividing the number of children with onset of narcolepsy during each study period by the annual average population at risk for the same period multiplied by the number of years for the same period. The population at risk for period B was  $9.75 \times 351,744$  individuals. The population at risk for period C was 424,028 individuals and the population at risk for Period A was B+C. The 95% confidence intervals were calculated with the exact method using CYTEL © StatXact.[114] The statistical calculations of the cognitive profile and adaptive

skills were performed with the independent one-sample t-test and correlations with Pearson's statistical test. A significance level of  $p = 0.05$  was used. We performed linear regression using the ANOVA test to determine the  $R^2$  factor showing how much variation in HrQoL, given as a percentage, is explained by age at testing.

### **Study III (psychometric testing)**

Data were analyzed using IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0.[114] Both principal components (PCA) and principal axis factor analyses (PAF) with Promax rotation were used to discover the underlying factor structure of the patient population responses ( $n=100$ ). Three criteria were used to determine the number of factors: scree plot, eigenvalue, and percentage of variance explained by the factors. A threshold factor loading of 0.5 was chosen as an indicator of a good item to factor fit. The best-fitting model identified from the exploratory factor analysis was subsequently submitted for confirmatory factor analysis on the combined patient and control data group ( $n=195$ ) using IBM SPSS AMOS for Windows version 20.0.0.1. Convergent validity was assessed by correlation to the KIDSCREEN-index-10 HrQoL questionnaire which acted as the conceptual construct for validation. To examine external reliability an intra-class correlation coefficient (ICC) was calculated on a test-retest of the questionnaire in a selected sample ( $n=38$ ). In addition, internal reliability was assessed by applying Cronbach's alpha.

### **Ethics**

Ethical approval for all the studies in this thesis was given by the Regional Board of Medical Ethics at the University of Gothenburg (ref: 246-11). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.[116] All patients, controls and their parents received a letter with information about the contents of the various studies and they all consented to participate. From this letter, it appeared that their participation or deflecting would not affect the clinical treatment or follow-up of the patients.

# RESULTS

## Baseline characteristics

An overview of the characteristics of the patients included in the studies in the present thesis is given in the table below (Table 1).

*Table 1. Demographics, clinical and laboratory characteristics in children and adolescents with narcolepsy with or without association to the H1N1 influenza vaccination*

Characteristics		nPHV group	PHV group	Total number of patients*
Gender	Female	6/8	16/34	22/42
	Male	2/8	18/34	20/42
Symptoms	Cataplexy	8/8	31/34	39/42
	Hallucinations	7/8	16/34	23/42
	Sleep paralysis	5/8	9/34	14/42
	Disturbed sleep	6/8	25/34	31/42
Actigraphy/MSLT	Positive	7/8	31/34	38/42
HLA-DQB1*0602	Negative	1/4	0/23	1/27 <sup>a</sup>
	Positive	3/4	22/23	25/27 <sup>a</sup>
CSF hypocretin-1	>110 pg/ml	0/4	1/34 <sup>b</sup>	1/38 <sup>a</sup>
	<110 pg/ml	4/4	33/34	37/38 <sup>a</sup>
Treatment	Methylphenidate	5/8	29/34	34/42
	Atomoxetine	1/8	2/34	3/42
	Modafinil	1/8	1/34	2/42
	Antidepressants	4/8	7/34	11/42
	Sodium oxybate	0/8	1/34	1/42
	No treatment	2/8	1/34	3/42

Number of patients is given for each of the variables. \* one of the 43 patients declined participation in more than the calculation of incidence of narcolepsy. <sup>a</sup>= the number of patients was fewer than 42 since all patients did not require all the investigations to fulfill the criteria for narcolepsy according to the ICSD 2005; <sup>b</sup> =121 pg/ml. Abbreviations: PHV, post-H1N1 influenza vaccination narcolepsy; nPHV, non-post-H1N1 influenza vaccination narcolepsy; CSF, cerebrospinal fluid; MSLT, multiple sleep latency test.

## Study I

In all, 37 patients developed narcolepsy during the entire study period from January 1, 2000 to December 31, 2010. Of these, nine patients had a disease onset during the period preceding the H1N1 influenza vaccination (nPHV group), giving an incidence of  $0.26 \times 10^{-5}$  (95% CI: 0.12-0.5). Twenty-eight patients had narcolepsy onset within 10 months from vaccination against H1N1 influenza, giving an incidence of  $6.6 \times 10^{-5}$  (95% CI: 3.4-8.1). The incidence for the entire study period is given in Figure 4.

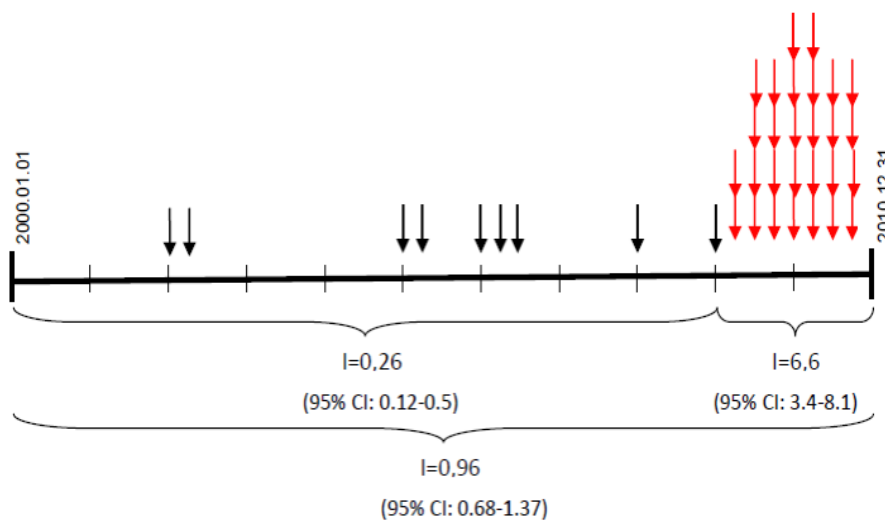


Figure 4. Incidence of narcolepsy in children aged 2-17 years in western Sweden between 1 January 2000 and 31 December 2010. Each arrow represents one patient. I; incidence figures/100,000/year before (black arrow) and after (red arrow) mass vaccination against H1N1 influenza started October 2009. The incidence in the period after vaccination compared with the period before was 25 times higher, giving a statistically significant difference ( $p < 0.000001$ ).

The median age at onset was 10 years (range 3-17) in the PHV group and 12.5 years (range 5-15) in the nPHV group. In the PHV group, the median latency time from vaccination to disease onset was 9.5 weeks (range 2-40). A similar analysis was not possible in the nPHV group due to a more subtle clinical onset. The diagnosis of narcolepsy was made with a median delay of one year (range 3 months to 2 years) from narcolepsy onset in the PHV group and of five years (range 1-8) in nPHV group. A family history of neurological disease was identified in five children in the PHV group and three children in the nPHV group of whom two had a parent with narcolepsy. Six children had a relative with ADHD, autism, bipolar disorder or an unspecified psychiatric disorder.

We investigated the presence of non-specific symptoms in the patients and found that, in the PHV group, 61% of the patients had weight gain and 57% had behavioral symptoms compared with 25% and 50% respectively in the nPHV group. A previous infection occurred in 8/36 children of whom six had H1N1

influenza vaccine-related narcolepsy. The infectious agent was a virus in four of the cases (gastroenteritis, upper respiratory infection, influenza and herpes zoster) and bacteria in the other four cases (borrelia, chickenpox, impetigo and suspected tonsillitis). The results of actigraphy/MSLT, HLA typing and CSF-hypocretin-1 measures are presented in Table 1.

## Study II

### Psychiatric comorbidity

Thirty-seven patients (21 female) were evaluated for psychiatric comorbidity. The median age at testing was 15.3 (range 6-25) years. In all, 14 of 37 (38%) evaluated patients had at least one psychiatric disorder. At group level, 13/30 (43%) of the patients with PHV narcolepsy and 1/7 (14%) with nPHV narcolepsy had at least one psychiatric disorder (Table 2).

Table 2. Psychiatric disorders according to the DSM-IV

Diagnosis	PHV group	nPHV group	Total no. of patients
Major depression*	6/30	0/7	6/37
Autistic disorder	1/30	0/7	1/37
Attention-deficit/ hyperactivity disorder	1/28	1/4	2/32**
Acquired Attention-deficit/ hyperactivity disorder***	7/28	0/4	7/32
General anxiety disorder	3/30	0/7	3/37
Oppositional defiant disorder	2/30	1/7	3/37
Eating disorder - not otherwise specified (anorectic type)	1/30	0/7	1/37

*Overlapping of diagnoses occurred in seven patients. \*= of six patients with major depression, one fulfilled the criteria for major depression including functional decline but some of the criteria overlapped with symptoms of narcolepsy; \*\*=32/37 patients were assessed by the ADHD-RS; \*\*\*=inception after onset of narcolepsy and seven years of age, all patients had the inattentive type.*

Interviews with the patients with ADHD and their parents revealed an onset after seven years of age (according to the DSM-IV criteria for ADHD, the onset of symptoms must occur before age 7; the DSM-5, which was launched in 2013, has changed the age of onset of symptoms to before age 12), in seven of them. The symptoms of ADHD in these patients started after the debut of narcolepsy. The ADHD criteria were met, even though they received concurrent treatment with psychostimulants due to narcolepsy. Screening for psychotic symptoms with the PANSS interview identified three patients in the PHV narcolepsy group with daytime hallucinations but without any other symptom of psychosis. Three patients, of whom two belonged to the PHV narcolepsy group, screened positive on the ASSQ. One of these three met the criteria for autistic traits, i.e. three criteria for autistic disorder according to the DSM-IV were met. The most frequent psychiatric symptom was temper tantrums, which occurred in 94% of the patients in the PHV narcolepsy group and 71% of the patients in the nPHV narcolepsy group.

## **Cognitive profile**

A cognitive assessment was performed in 35 children (19 female). The median age at testing was 13.8 (range 6-23) years. Lower verbal comprehension and working memory indexes were found in both the PHV (mean 92 and 89 respectively) and nPHV group (mean 95 and 93 respectively) but significantly so only in the PHV group compared with the normal mean index value of 100 (Table 3).

A difference of at least one standard deviation was found in 17/35 patients when comparing the PRI with the VCI where the VCI was lower. The FSIQ was found to be lower ( $p= 0.027$ ) in patients with a concurrent psychiatric disorder compared with patients without a psychiatric diagnosis (Figure 5).

Table 3. Results of cognitive assessments of 35 children with or without association to the H1N1 influenza vaccination

Cognitive domain	Group	N	Mean	Std. deviation	p-value <sup>a</sup>
Full-scale IQ	PHV	30	96.4	11.7	0.107
	nPHV	5	100.0	8.3	1.000
Verbal comprehension	PHV	30	91.9	9.4	0.000
	nPHV	5	94.8	8.2	0.230
Perceptual reasoning	PHV	30	105.4	16.1	0.077
	nPHV	5	107.2	12.9	0.279
Working memory	PHV	29 <sup>b</sup>	89.5	13.3	0.000
	nPHV	5	92.8	10.9	0.217
Perceptual speed	PHV	30	100.7	12.9	0.769
	nPHV	5	105.6	9.0	0.238

N: number of patients; PHV, post-H1N1 influenza vaccination narcolepsy; nPHV, non-post-H1N1 influenza vaccination narcolepsy; <sup>a</sup>= compared with the normal mean index value of 100; <sup>b</sup>= the number of patients was fewer than 30 since one patient did not complete the working memory test.

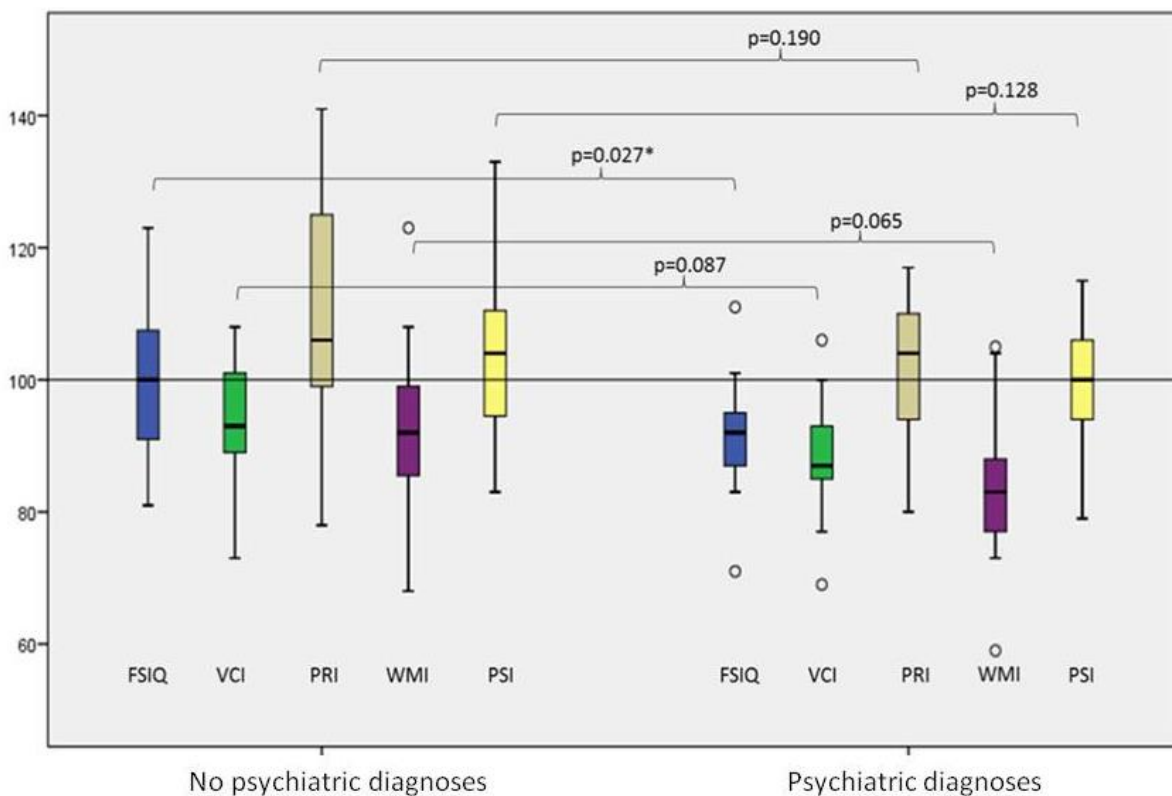


Figure 5. Comparison of the cognitive profile in children and adolescents with narcolepsy with and without psychiatric diagnoses. Abbreviations: FSIQ, full-scale IQ; VCI, verbal comprehension index; PRI, perceptual reasoning index; WMI, working memory index; PSI, processing speed index. \*= significance level  $p < 0.05$

## Study III

### Qualitative analysis

The focus group discussions revealed that parent groups tended to focus on the need for medical intervention, whereas the children and young people were more concerned with the effects of narcolepsy on their social life and life at school. The initial analysis of the transcribed statements produced a set of seven themes with 135 items of importance to the young people's concept of their QoL with narcolepsy: Emotional support, School performance, Social image, Concern about the future, Being limited by the condition, Personal energy and Disturbed sleep. The parent groups also produced seven themes with 109 items: Health and well-being, Independence, Friends, School, Leisure time, Family and Happiness/contentment with life. Panel discussions and cognitive debriefing resulted in a subset of 40 items with the greatest relevance to the conceptual model developed by the focus groups and these items constituted the pilot questionnaire (Figure 6). The pilot questionnaire was completed by 100 people with narcolepsy (59 girls), aged 8-18 (mean age=15.8) years, contacted via the hospital outpatient clinics, the Narcolepsy Society of Sweden and a closed Facebook group for patients with narcolepsy. They all had onset of narcolepsy following the H1N1 influenza vaccination. A further 95 matched controls were recruited from a school-based population in the same counties.

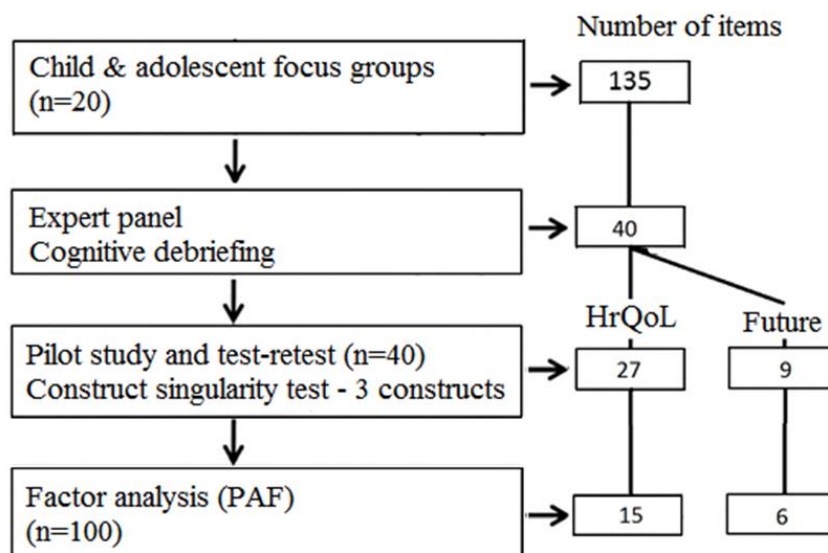


Figure 6. Stages of item reduction in the NARQoL questionnaire.



## Quantitative analysis

The returned 100 pilot questionnaires were checked for the assumption of normality. A test-retest procedure was carried out to test for internal reliability and showed good interclass correlation coefficients (ICC) (QoL=0.785; Future=0.741). Two distinct patient reported outcome modules were identified with items related to HrQoL and items related to future perceptions creating two modules. The HrQoL module consisted of three domains: emotional reaction, school/concentration and social confidence. The future module consisted of two domains: expectations and limitations. The structure for these modules and domains is given in Table 4.

*Table 4. HrQoL domains and factor structure of the NARQoL questionnaire.*

	Item num.	QoL			Future	
		Emotional reaction	School / concentration	Social confidence	Future Expectations	Future Limitations
Sadness	Q31	.771				
Feeling alone	Q25	.717				
Angry	Q32	.621				
Anxiety	Q26	.602				
Irritable	Q34	.537				
Able to concentrate	Q05		.708			
Awake when watching TV	Q39		.664			
Alert	Q11		.615			
Alert in School	Q14		.588			
Able to follow lessons	Q02		.577			
Staying awake	Q37		.545			
Feeling confident	Q29			.607		
Not giving up easily	Q20			.573		
Getting on with others	Q22			.488		
Lazy	Q04			.469		
Hopeful future	Q15				.990	
Possibilities	Q27				.611	
Problems in the future	Q06				.465	
After school	Q21					.613
Travel	Q24					.593
Driving licence	Q09					.539

*The item numbers refer to the respective questions in the Appendix that comprise NARQoL. Extraction method was the Principal Axis Factoring and the rotation method was the PROMAX with Kaiser Normalization.*

## Study IV

### Health-related quality of life

Health-related quality of life was evaluated in 27/31 (14 females) with a mean age of 15.1 (SD 3.9; range 8-20) years in the PHV group and four/six (3 females) with a mean age of 15.5 (SD 1.9; range 13-17) years in the nPHV group. As age- and gender-matched controls, 29 individuals (15 females) with a mean age of 13.0 (SD 3.3; range 8-19) years and 11 individuals (6 females) with a mean age of 16.0 (SD 2.3; range 11-20) years were included.

Measurements with both KIDSCREEN and the NARQoL showed significantly decreased HrQoL in both the PHV and nPHV groups (Table 5). All five domains of the NARQoL were significantly decreased in the PHV group compared with controls, but only the school/concentration domain was significantly decreased in the nPHV group.

*Table 5. Disease-specific HrQoL in 31 patients with narcolepsy with or without association to the H1N1 influenza vaccination.*

Quality of life	PHV group					nPHV group					
	Narcolepsy patients		Control group			Narcolepsy patients		Control group			
	No	Mean (SD)	No	Mean (SD)	p-value	No	Mean (SD)	No	Mean (SD)	p-value	
KIDSCREEN	27	64(16)	29	83(11)	0.000*	4	68(17)	11	83(9)	0.040*	
NARQoL	Emotional reaction	27	65(22)	29	87(11)	0.000*	4	66(42)	11	86(16)	0.409
	Social confidence	27	69(17)	29	84(15)	0.001*	4	84(12)	11	87(11)	0.703
	School/concentration	27	51(23)	29	89(10)	0.000*	4	56(10)	11	88(13)	0.001*
	Expectations	27	59(25)	29	88(10)	0.000*	4	67(40)	11	82(12)	0.509
	Limitations	27	76(24)	29	94(10)	0.001*	4	71(28)	11	86(11)	0.359

*Health-related quality of life, measured with the KIDSCREEN and NARQoL questionnaires, was filled in by the patients. The different main and sub-domains are reported with mean values. A statistical comparison was performed with the mean scale score for the age- and gender-matched control group. Abbreviations: PHV, post-H1N1 influenza vaccination narcolepsy; nPHV, non-post-H1N1 influenza vaccination narcolepsy; No., number, SD; standard deviation, \* significant difference compared with the control group. The level of statistical significance was  $p < 0.05$ .*

Further analyses were performed at sub-group level to identify factors with a negative impact on HrQoL. There were no differences in HrQoL between genders. Patients with psychiatric comorbidity in the PHV and nPHV groups had lower emotional reaction domain index on the NARQoL (mean  $58 \pm 16$  versus  $73 \pm 15$ ,  $p=0.033$ ) and social confidence domain index (mean  $52 \pm 23$  versus  $71 \pm 19$ ,  $p=0.035$ ) compared with patients without psychiatric comorbidity.

Higher age at testing was correlated to decreased KIDSCREEN index and NARQoL (emotional reaction and social confidence domains) in the PHV group compared with controls ( $R^2=0.21-0.37$ ,  $p=0.002-0.006$  versus  $R^2=0.02-0.07$ ,  $p=0.083-0.410$ ). (Figure 7).

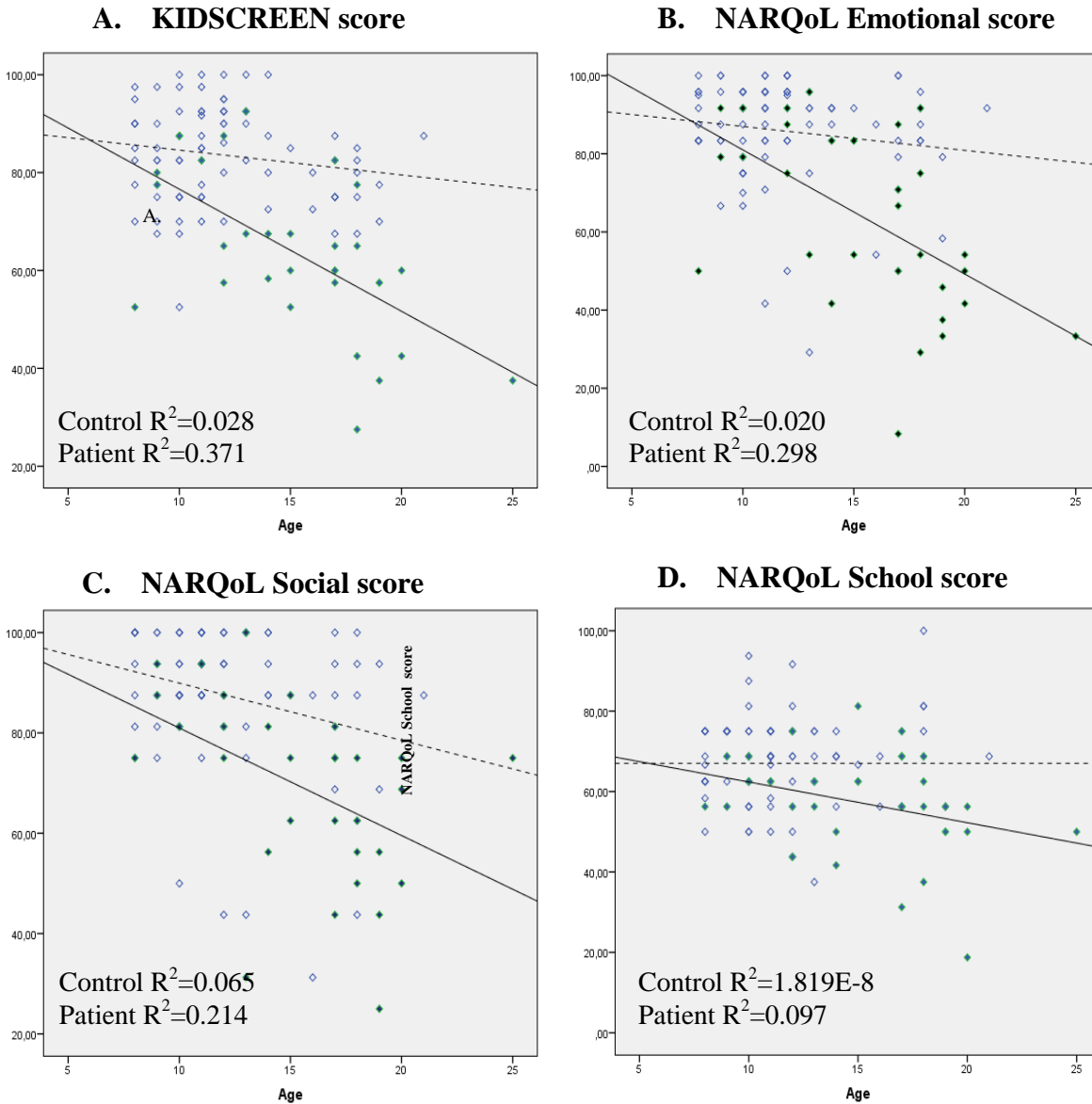


Figure 7. Correlation of HrQoL and age at testing. Correlation of HrQoL measured with A. KIDSCREEN, B. NARQoL emotional domain, C. NARQoL social domain, D. NARQoL school domain and age of testing in patients with narcolepsy after H1N1 influenza vaccination (filled rhombs, continuous line) and healthy controls (empty rhombs, dotted line). The coefficient of determination,  $R^2$  (R squared), is given for each of the HrQoL domains.

## Adaptive behavior

Adaptive behavior was rated by the parents of 28/31 patients (13 females) with a mean age of 13.9 (SD 4; range 6-19) years in the PHV group and 4/6 (3 females) with a mean age of 15.5 (SD 1.9; range 13-17) years in the nPHV group who completed the questionnaire. Validated data on healthy Swedish children's and young people's adaptive behavior were used for comparison.

Table 6. Adaptive behavior in 32 patients with narcolepsy with or without association to the H1N1 influenza vaccination.

Adaptive behavior	PHV group					nPHV group					
	Narcolepsy patients		Control group			Narcolepsy Patients		Control group			
	No.	Mean (SD)	No.	Mean (SD)	p-value	No.	Mean (SD)	No.	Mean (SD)	p-value	
General Adaptive Composite	28	92(18)	-	100	0.018*	4	105(18)	-	100	0.598	
Conceptual	Total Conceptual Score	28	91(19)	-	100	0.018*	4	105(15)	-	100	0.535
	Communication	28	8.9(3.0)	-	10	0.058	4	9.3(3.1)	-	10	0.753
	Functional Academics	28	9.4(3.3)	-	10	0.386	4	11.1(1.5)	-	10	0.170
	Self-Direction	28	7.2(3.6)	-	10	0.000*	4	9.2(3.1)	-	10	0.797
Social	Total Social Score	28	86(18)	-	100	0.000*	4	100(18)	-	100	0.929
	Social	28	8.4(3.1)	-	10	0.012*	4	9.6(2.4)	-	10	0.851
	Leisure	28	6.7(3.9)	-	10	0.000*	4	10.0(3.1)	-	10	0.925
Practical	Total Practical Score	28	95(18)	-	100	0.166	4	106(16)	-	100	0.432
	Community Use	28	9.3(3.3)	-	10	0.281	4	11.2(1.4)	-	10	0.059
	Home Living	28	7.1(4.3)	-	10	0.001*	4	12.3(2.7)	-	10	0.078
	Self-Care	28	8.8(3.9)	-	10	0.112	4	9.9(3.4)	-	10	0.710
	Health and Safety	28	11.3(3.4)	-	10	0.044*	4	13.0(3.2)	-	10	0.076

Adaptive behavior was rated by parents using the second version of the Swedish Adaptive Behavioral Assessment Scale (ABAS-II). The different adaptive composites and skill areas are reported with mean values. A comparison was made with the mean scale score for the Swedish healthy pediatric population, (mean 100 for the composite scores and 10 for the different skill areas). Abbreviations: PHV, post-H1N1 influenza vaccination narcolepsy; nPHV, non-post-H1N1 influenza vaccination narcolepsy; No., number, SD; standard deviation, \*Significant difference compared with the control group. The level of statistical significance was  $p < 0.05$ .

The general adaptive composite score and the total conceptual and social composite scores were significantly lower in the PHV group compared with controls (Table 6). None of the adaptive skills was lower in the nPHV group compared with controls. Male gender was associated with lower adaptive skills, significantly so regarding social skills, in the PHV group compared with females (mean  $79 \pm 18$  versus  $96 \pm 16$ ,  $p=0.019$ ). Psychiatric comorbidity was associated with lower conceptual composite scores compared with patients without psychiatric comorbidity (mean  $79 \pm 18$  versus  $95 \pm 18$ ,  $p=0.048$ ).

## Parenting stress

Parenting stress was rated by the parents of 31/31 patients (14 females) with a mean age of 13.4 (SD 3.9; range 5-19) years in the PHV group and 5/6 (3 females) with a mean age of 16.3 (SD 3.4; range 11-20) years in the nPHV group who completed the questionnaire. As age- and gender-matched controls, 26 individuals (11 females) with a mean age of 13.0 (SD 4.3; range 5-20) years and 12 individuals (7 females) with a mean age of 15.0 (SD 3.4; range 11-20) years were included.

We found that the parents of children in the PHV group rated significantly higher parenting stress on all sub-scales compared with controls, except for the “parenting distress score” (Table 7). All stress scores apart from parenting distress were also found to be higher in the nPHV group compared with controls but without reaching statistical significance.

*Table 7. Parenting stress in the parents of 36 patients with narcolepsy with or without association to the H1N1 influenza vaccination*

Parenting stress	PHV group					nPHV group				
	Narcolepsy patients		Control group			Narcolepsy patients		Control group		
	No.	Mean (SD)	No.	Mean (SD)	p-value	No.	Mean (SD)	No.	Mean (SD)	p-value
Total Stress Score	30	87(27)	25	64(22)	0.001*	5	65(18)	12	61(22)	0.744
Parenting Distress	31	25(9)	26	22(9)	0.256	5	17(2)	12	22(9)	0.265
Parent-Child Dysfunctional Interaction	30	28(11)	26	21(11)	0.021*	5	22(8)	12	19(9)	0.445
Difficult Child	30	35(11)	25	23(7)	0.000*	5	26(9)	12	21(8)	0.270

*Abbreviations: PHV, post-H1N1 influenza vaccination narcolepsy; nPHV, non-post-H1N1 influenza vaccination narcolepsy. \* p-value <0.05 was considered significant*

The parents of 13 children with psychiatric comorbidity in the PHV and nPHV groups obtained higher scores on all parenting stress scales compared with those without comorbidity in the same groups, but the difference was not significant. No differences in the parental stress ratings were seen between the genders of the children or age at testing.

# DISCUSSION

## Increased incidence of narcolepsy related to H1N1 influenza vaccination

In this population-based study, we found a 25 times higher incidence in the period after vaccination against H1N1 influenza (6.6/100,000 individuals per year) compared with the period before (0.26/100,000 individuals per year). We did not find any other possible explanation for the increase in incidence than the vaccination against the H1N1 influenza. Information about the worldwide incidence of narcolepsy is limited, especially in children. The pooled incidence in children 5-19 years of age in six European countries before the period of H1N1 influenza vaccination has been estimated at 0.57/100,000 individuals a year.[117] This is higher than our baseline incidence, but a comparison between the studies is difficult due to broad CIs, different populations and study design.

Our finding of a 25-fold increase in narcolepsy incidence following the H1N1 influenza vaccination is higher than the 6.6-fold increase reported by the Swedish retrospective national cohort study.[118] The higher incidence in our study may be due to the population-based study design providing a higher probability of identifying all patients in the two studied counties compared with the national cohort study that used a case inventory design involving all six health-care regions in Sweden.

Our results are higher than those reported in several other studies of the incidence of narcolepsy in children and adolescents following vaccination with the ASO3 adjuvant containing H1N1 influenza vaccine (Pandemrix). An increased incidence has also been detected in other Nordic countries, ranging from a 17.0-fold increase in Finland to a 1.9-fold increase in Denmark.[47, 117-119] A 6.6- to 14.4-fold increase has also been reported by the VAESCO group in six European countries,[120-122] while a 4.6-fold increase was found in Quebec.[123] There appears to be a correlation between the incidence of narcolepsy and the vaccine coverage in the population, which was 65% and 75% in Sweden and Finland respectively, while only 20% of individuals with chronic diseases and underlying conditions were vaccinated in Denmark.[124-126]

Our findings suggest a causal relationship between the increased incidence of narcolepsy and immunization against H1N1 influenza. Almost 70% of the children (19/28) in our cohort became ill quite abruptly within 12 weeks of vaccination. The PHV group had more severe clinical symptoms, with more frequent weight gain and a higher prevalence of psychological symptoms than the nPHV group. An abrupt onset and a more severe clinical picture, i.e. unusual

severe sleepiness, cataplexy and weight gain in children with H1N1 influenza vaccine-associated narcolepsy, have also been reported in other studies.[47, 127] The correlation with Pandemrix vaccination in our study population is further strengthened by the absence of other trigger factors. Furthermore, none of our patients had an abnormal MRI or other abnormalities suggesting a secondary cause of narcolepsy. Only 6/28 patients in the PHV group had a previous infection within three months before the H1N1 influenza vaccination. Preceding infections or other trigger factors were not looked for in the national report from Sweden or the VAESCO group. The Finnish study reported that influenza-like illness was present in 4/50 post-vaccination patients but without evidence of clinically important infections.[47]

All investigated patients in our study had decreased hypocretin-1 levels in CSF (< 200 pg/ml).[25] All but one had CSF hypocretin-1 levels <110 pg/ml compatible with ICSD-2005 diagnostic criteria. One patient had a CSF hypocretin-1 level of 121 pg/mL. This patient had no cataplexy but she fulfilled all other criteria for diagnosis of narcolepsy. Our findings suggest that, in children with HLA-DQB1\*0602, Pandemrix vaccination may initiate or precipitate narcolepsy with cataplexy. The exact mechanism by which Pandemrix vaccine is able to cause narcolepsy is still unclear, but several factors have been suspected of being involved in the development of an autoimmune reaction. The AS03 adjuvant in the vaccine could potentially catalyze a molecular mimicry between virus antigens in the vaccine and hypocretin-1-producing neurons by inducing a strong immune response.[128] A recent study identified detergent-induced antigenic changes of viral nucleoprotein in Pandemrix. An increased number of antibodies to the same nucleoprotein were also found in DQB1\*0602-positive children with vaccine-related narcolepsy.[129] It has been hypothesized that infection with streptococcus pyogenes at the time of the vaccination induces a specific immune response and facilitates the permeability of the blood-brain barrier, thereby potentially exposing hypocretinergic neurons to the immune system.[130] Significantly elevated antibody titers against streptococci have been identified in Pandemrix-related narcolepsy patients.[131]

## **Increased psychiatric comorbidity and deviant cognitive profile in narcolepsy**

### **Psychiatric comorbidity**

To our knowledge, this is the first study to use the DSM-IV criteria and validated screening instruments in order to diagnose psychiatric comorbidity in childhood

narcolepsy. A total of 37 patients with narcolepsy were investigated and 14 of them (38%) had one or more psychiatric diagnoses. Major depression was present in 20% of our patients with PHV narcolepsy compared with the 5.8% one-year prevalence of major depression in the general Swedish adolescent population.[132] Previous retrospective studies have reported depressive symptoms in 25-40% of children and adolescents with narcolepsy.[5, 133] None of these studies included PHV narcolepsy patients or used DSM-IV criteria, which makes a comparison difficult. In our study, ADHD was present in 29% of the patients with PHV narcolepsy and the diagnostic criteria were met despite ongoing treatment with stimulants. This is a four times higher prevalence than in healthy Swedish children at the age of six to seven years.[134] Our results are similar to those reported in a cross-sectional study of 108 French children and adolescents with narcolepsy with or without cataplexy using the same instrument as in our study (ADHD-RS). In that study, clinically significant levels of ADHD symptoms were present in 23% of patients compared with 5% of controls.[135] Oppositional defiant disorder (ODD) was also more common in our study population (8%) than in child estimates from 25 studies reporting a point prevalence of ODD of 3.3%, according to DSM-III-R or DSM-IV criteria for children 18 years or younger.[136] ODD is frequently secondary to ADHD and this was the case in our three patients with ODD. They were all older than 11 years of age, which is less common among patients with ODD.[137] Psychotic symptoms were absent in all our patients. Psychiatric comorbidity was higher in the PHV group (43%) compared with the nPHV group (14%), but the small number of patients in the nPHV group makes comparison difficult. Two other studies have included children with H1N1 influenza vaccination-related narcolepsy and they did not find any differences in the prevalence of depressive symptoms or ADHD compared with the non-H1N1 influenza vaccination-related narcolepsy group.[133, 135]

The mechanisms behind the co-occurrence of narcolepsy and psychiatric disorders are still unclear. Co-existent psychiatric disorders in narcolepsy may be due to the hypocretin-1 deficiency, secondary to the disturbed sleep and hypersomnia, or a reaction to the consequences of the disorder. Hypocretinergic neurons have complex projections and interactions with several brain areas related to psychiatric disorders.[21] Hypocretin-1 has been described to regulate the function of the amygdala and serotonergic raphe nuclei which are important in the pathogenesis of depression.[138, 139] Patients with depression have been found to have a substantial limitation in the diurnal variation of CSF hypocretin-1 levels and an improved variation was seen in patients who responded to treatment with antidepressants.[140] Significantly lower CSF hypocretin-1 levels have also been found in patients with major depressive disorder who had recently attempted suicide.[141] In addition, the intracerebroventricular infusion of hypocretin-1 in animal models reduced depressive behavior and increased the



proliferation of neurons in the hippocampus which are well known for modulating the affective status.[142]

Functional MRI studies (fMRI) have found that, in young adults with narcolepsy with hypocretin-1 deficiency, hypothalamic activation is reduced, while amygdala activation is exaggerated during the response to positive emotions.[143] In addition, reduced activity has been found in the prefrontal cortex and nucleus accumbens, brain areas receiving projections from hypocretinergic neurons and known for their crucial role in the regulation of emotions. Some of these changes correlated with the degree of depressed mood.[144] Only a few studies provide an insight into a possible link between narcolepsy and ADHD. A high density of hypocretin-1 projection has been found to reticular formation and nucleus locus coeruleus, both of which have several catecholaminergic projections to the prefrontal and superior parietal cortex.[21] A dysfunction in these centers has been correlated to deficits in vigilance and sustained attention in patients with ADHD.[145, 146] Changes in activation in the executive cortical networks localized in the prefrontal cortex have been demonstrated in studies of patients with narcolepsy using fMRI, event-related potentials and cognitive evoked potentials.[147] These areas are known as the main locations of the attention system and are diminished in children with ADHD.[148]

Sufficient sleep is defined as the amount necessary to permit optimal daytime functioning and insufficient sleep can be a risk factor for psychiatric illness.[149] A meta-analysis incorporating 86 studies of 35,936 healthy school-age children (5-12 years old) found that children with shorter sleep duration had more internalizing (i.e. depressive and anxiety symptoms) and externalizing (i.e. hyperactive or antisocial behavior) problems.[150] The risk of developing a behavior characterized by hyperactivity-impulsivity has been estimated to be three times higher in pre-school children who have had insufficient sleep during the preceding three years. A lack of sleep could thus be a factor that aggravates ADHD symptoms in children with narcolepsy. Up to 70% of otherwise healthy children with major depression have nocturnal sleep disturbances and there is a correlation between the severity of sleep disturbance and the severity of depression.[151] However, sleep disturbance is one of the criteria for depression, which means that depression often leads to difficulties with sleep, particularly insomnia.[97] Children with anxiety problems have been shown to have even more nocturnal awakenings than children with depression and less slow-wave sleep compared with controls as well as children with depression.[152] Disturbed sleep was found in the majority (81%) of our study population.[153] There are no studies addressing the correlation between disturbed sleep and psychiatric comorbidity in patients with narcolepsy. It has been hypothesized that sleep is essential in maintaining the appropriate reactivity of the affect regulation system by resetting the neuronal networks and reprocessing recent

emotional experiences.[154] Sleep deprivation can lead to poor emotional regulation by reducing the threshold at which negative emotions (such as irritation and frustration) are expressed.[155] In line with this hypothesis, increased amygdala reactivity has been described in sleep-deprived adults.[156]

Daytime sleepiness itself could possibly contribute to the increased prevalence of psychiatric comorbidity, as it has been shown in otherwise healthy children.[157] Patients with idiopathic hypersomnia have a significantly higher prevalence of anxiety and depression than controls.[158] In a study that included children with narcolepsy as well as hypersomnia alone, there were no differences in the rates of depressive or hyperactive symptoms between these two clinical groups and the authors suggested that hypersomnia could be the main underlying cause of the observed psychiatric problems.[46] Children with narcolepsy and comorbid ADHD have been reported to be sleepier during the day and to have longer reaction times compared with those patients with narcolepsy without comorbid ADHD.[135] Similar results have been demonstrated in a meta-analysis indicating that children with ADHD, who were otherwise healthy, had significantly higher daytime sleepiness compared with healthy controls.[159] All patients with ADHD in our study had the predominantly inattentive type. It has been hypothesized that, among children with narcolepsy, daytime sleepiness and insufficient nighttime sleep may lead to impaired attention and a higher prevalence of the predominantly inattentive type of ADHD, similar to what has been described in primary hypersomnia.[47, 49]

Long-lasting symptoms of daytime sleepiness, cataplexy and disturbed nighttime sleep in narcolepsy cause considerable psychosocial stress [46, 60, 160] and it has been reported that children with narcolepsy can be stigmatized and isolated.[161] These factors may increase the risk of developing depressive symptoms as a reaction on narcolepsy as a chronic disease. Patients with narcolepsy are exposed to stressors in a chronic manner and the risk of more severe and prolonged symptoms, such as major depressive disorder and generalized anxiety disorder, may therefore be increased.

## **Cognitive profile in narcolepsy**

We used the validated and age-appropriate Wechsler Intelligence Scales to explore any cognitive difficulties in the investigated 35 patients. Statistically significant impairments were found regarding verbal comprehension and working memory in the PHV group. Cognitive function in children with narcolepsy unrelated to the H1N1 influenza vaccination has been studied in two previous studies showing normal full-scale IQ, verbal IQ and performance IQ.[60, 162] A difference between the PRI and VCI, where the VCI was lower by at least 1 SD, was found in half our patients. This indicates that patients with

narcolepsy have a relative strength in processing visual information but weaknesses in learning, remembering and retelling new information. A similar cognitive profile was reported in both the previous studies.[60, 162] Adults with narcolepsy have uniformly presented a normal general cognitive function.[50, 55] Although there is some disagreement about how well adult patients perform within the different cognitive sub-domains, there is evidence of impaired attention, memory, executive and verbal functions.[49, 51] We found a lower FSIQ in patients with a concurrent psychiatric disorder. A low FSIQ has been reported to be associated with increased psychiatric comorbidity in otherwise healthy young children.[163]

The exact mechanism behind the cognitive difficulties in patients with narcolepsy is unknown. One possible explanation could be a combined effect of primary and secondary mechanisms, as outlined in the discussion above about psychiatric comorbidity. There are well-defined projections of hypocretin-1 neurons and a high density of hypocretin-1 receptors in the prefrontal cortex and hippocampus, two areas that are important for learning and memory.[21] In addition, studies of the intracerebroventricular administration of hypocretin-1 in rodents showed an increase in the building of synapses in the hippocampus and improved learning, consolidation and memory.[164, 165] A change in the function of the prefrontal cortex in narcolepsy has been detected by neurophysiological investigations including event-related potentials and has been interpreted as being related to the observed alterations in cognitive attentive processing.[166] Functional MRI studies have also demonstrated changes in frontal cortical and limbic areas.[143, 167]

Sleep deprivation in children can also lead to cognitive difficulties, especially regarding verbal function and memory processing.[168] An experimental study of 9- to 12-year-old children demonstrated a positive correlation between sleep duration and both memory and reaction time.[169] The results of another study suggested that even a modest yet chronic reduction of just one hour of sleep nightly in pre-school children can impair a child's language acquisition and the consolidation of new words into memory, resulting in a lower cognitive performance at school entry.[170] It has been hypothesized that, during slow-wave sleep, a homeostatic downregulation of synapses takes place, preventing the saturation of limbic and neocortical networks that could otherwise lead to cognitive and emotional difficulties.[171] This process is considered to be even more pronounced in children than in adults.[172] Optimal sleep duration is also crucial for memory consolidation through the reactivation of neuronal networks that encode information during the antecedent awake period during the day.[173] During this process, temporary memory in the hippocampus is transferred to the neocortex for long-term memorization. The stability of the attentional network in the frontoparietal cortex is also dependent on an optimal amount of sleep.[174]

Sleep deprivation can lead to EEG-verifiable “local sleep” in different cortical areas, resulting in cognitive impairments in the awake state.[175]

Daytime sleepiness may secondarily lead to the impairment of attention, which in turn leads to difficulties with working memory.[49] Adult patients with narcolepsy have greater subjective cognitive difficulties that can be verified by different neuropsychological tests.[176] This can be partly explained by the patients’ potential to increase and maintain their attention during short and simple tests to some extent, while they fail in everyday situations that are more time consuming, complex and rich in distracting stimuli.[176] Neurophysiological studies in patients with excessive daytime sleepiness have demonstrated lapses in attention during wake-state periods characterized by brief sleep intrusions (microsleeps) that are identifiable on EEG.[177] Neuroimaging studies have found the thalamus to be important in the allocation of attentional focus during tasks with high cognitive demands.[177] Taken together, these findings suggest that disruptions in hypocretin-1 signaling, combined with the secondary effects of narcolepsy, may have a deleterious effect on cognitive function.

## **NARQoL – a disease-specific HrQoL instrument**

To our knowledge, the NARQoL is the first disease-specific HrQoL instrument for children and adolescents with narcolepsy. The instrument was found to have a high internal reliability coefficient, Cronbach’s alpha was 0.785 for QoL and 0.741 for Future. The NARQoL also had a high correlation to KIDSCREEN ( $r_s=0.865$ ), indicating good construct validity. From a content and face validity aspect, the NARQoL is designed as a disease-specific module to be used alongside a generic HrQoL such as DISABKIDS and to achieve accurate HrQoL quantification with regard to the psychosocial burden of the condition. There are seven other DISABKIDS condition-specific modules for children and adolescents with chronic disorders, i.e. epilepsy and cerebral palsy.[178] These modules were developed cross-nationally and have a Cronbach’s alpha of 0.71-0.90 which is similar to the reliability coefficient of the NARQoL. The construction of the NARQoL with two divisions is also similar to that of the other DISABKIDS modules permitting comparisons of the HrQoL of patients with narcolepsy with that of other patients suffering from chronic conditions.

Patients in our focus groups were concerned that narcolepsy gave rise to difficulties in everyday life that could potentially lead to pronounced limitations in the future. The inclusion of a future aspect in a QoL instrument is beyond the traditional model, but it has also been explored by others and can be described as an impairment of “belonging, being and becoming”.[179] In our model, Being

and Belonging come within the concept of QoL, the Emotional and Social domains, whereas the Becoming concept is more likely to be captured by the Future domains. It has been suggested that this could be a sign that young people are particularly sensitive to difficulties which impinge on their future plans.[179] The Future domain does not correlate with the accepted domains of HrQoL, the Emotional and Social domains, because the future concerns of children and adolescents with narcolepsy are not related to their current state of HrQoL. Nevertheless, because of the responses from the focus groups, we chose also to include this domain as a separate concept.

There are several advantages to a disease-specific instrument. In general, an illness-specific measurement is more sensitive to changes in disease-related parameters or treatment than generic instruments.[180] It also provides measurements of HrQoL without any relationship to the severity of the disease, whereby even patients with milder disease obtain a more equitable rating compared with a generic instrument that measures HrQoL related to disease severity. Studies of other chronic diseases using generic instruments have shown a discrepancy between the perception of HrQoL by medical staff and patients, which leads to a lower level of satisfaction with medical care.[105] The NARQoL can be used as a tool to assess the patient-reported outcomes of narcolepsy treatment and to analyze the aspects of the condition that have the greatest effect on the patient. This will facilitate the provision of personalized care and thus increase patient satisfaction. Used in association with DISABKIDS, the NARQoL provides not only a disease-specific measurement of HrQoL but also comparisons with other chronic disorders in children.

## **Implications of narcolepsy for HrQoL, adaptive behavior and parenting stress**

### **HrQoL**

We have identified two previous studies of HrQoL in children with narcolepsy and both used generic instruments. One of these studies used the parent report, the 50-item Child Health Questionnaire (CHQ). The children's HrQoL was compared with normative data for the scale.[46] In the other study, different versions of the Vecu et Sante Percue questionnaire (VSP) were used for self-rated HrQoL in adolescents (VSP-A) and children (VSP-E) and parentally rated HrQoL in their children (VSP-P). The results were compared with those of matched controls.[61] In contrast to the above-mentioned studies, the current study was population based and we used a disease-specific HrQoL instrument, the NARQoL. A total of 31 patients in our study cohort performed a self-

estimated measurement of HrQoL using the NARQoL. Patients in the PHV group obtained significantly lower HrQoL scores with KIDSCREEN and with all the domains of the NARQoL, emotional reaction (mean 65), social confidence (mean 67) and school/concentration (mean 71). A direct comparison of these data with the two previous studies of children and adolescents with narcolepsy is difficult because of the use of different questionnaires and the generic nature of the other instruments. However, our findings confirmed the decrease in HrQoL in emotional reaction found using the CHQ[45] and decreased HrQoL in social confidence and school/concentration functioning found in the study using the VSP-A/E/P.[61] The findings from the NARQoL, however, indicate lower scores in all HrQoL domains and suggest a more global impact. The reason why a greater impact is recorded by the NARQoL than previous instruments is most probably the utilization of a disease-specific questionnaire which has a domain structure designed for the assessment of the HrQoL issues specifically affecting patients with narcolepsy, thereby capturing the emotional and psychological burden of narcolepsy missed by a generic questionnaire. The patients with psychiatric comorbidity had considerably lower emotional and social index scores than those without psychiatric comorbidity. A negative impact of psychiatric disorders on HrQoL has also been demonstrated in one earlier study of children.[61] A more global impact on HrQoL, in both the emotional reaction and social confidence domains, has also been reported in several studies of adults with narcolepsy.[64, 65] In addition, studies of adults have consequently reported educational problems and lower employment rates, which could be related to poorer school performance due to difficulties with working memory and verbal comprehension, as was shown in our Study II. The school domain was the most affected of all the domains on the NARQoL and appears to be a major contributory factor to the globally impaired quality of life in our cohort of patients. This highlights the importance of school achievements in the context of HrQoL and preparation for adult life. Our study addressed an additional aspect of HrQoL, the future outlook of the adolescents, which has not been investigated in earlier studies. This module also revealed lower scores compared with controls and thus demonstrates increased anxiety about the future in children with narcolepsy. Another interesting finding was that higher age was associated with lower HrQoL in both the PHV group and the nPHV group, as well as in the control group. One of the previous studies has addressed this issue, but did not find this association.[61] The HrQoL profile of the nPHV group was very similar to that of the PHV group. It was only in the school domain that a significant difference was found between the nPHV group compared with controls. These results were confirmed by significantly lower index scores in the KIDSCREEN in both narcolepsy groups compared with controls, suggesting that children with narcolepsy have greater problems at school.

## **Adaptive behavior**

Based on our earlier findings of psychiatric comorbidity and cognitive difficulties, we assumed in this study that the children and adolescents with narcolepsy would demonstrate more difficulties in adaptive functioning compared with the general Swedish child population. We used the ABAS-II questionnaire that focuses on basic adaptive skills with an everyday behavior approach. In our study, the parents of children in the PHV group rated significantly lower mean indices for the general adaptive composite (mean 92), conceptual (mean 91) and social (mean 86) composite scores compared with the general population. These findings are strengthened by our findings of decreased social confidence and a decrease in the school/concentration domain in the disease-specific HrQoL questionnaire, the NARQoL. Our findings are also in line with those of a previous study of 12 children aged between 7-16 years, where the Achenbach Child Behavior Checklist (CBCL), which is more focused on adaptive behavior in a psychiatric context, was used.[60] They found very high levels of behavior and adjustment problems, including somatic complaints, withdrawal and mood disturbance, attention problems and social problems.[60] The social difficulties could be related to either fear of stigmatization due to daytime sleepiness and cataplexy or difficulties with self-direction and structural planning.[51, 60] In our study, we found that patients with psychiatric comorbidity had lower conceptual composite scores than those without psychiatric comorbidity. In addition, lower adaptive functioning in the areas of socialization, communication and daily living has previously been reported in children with ADHD of the inattentive type.[181]

## **Parenting stress**

To our knowledge, this is the first study to address parenting stress in narcolepsy. Compared with matched controls, we found a higher “total stress score” in the parents of children in the PHV group. Significantly higher scores were detected regarding the “parent-child dysfunctional interaction score” and “difficult child score”. Our results are in line with those of studies of parenting stress in other neurological disorders, i.e. epilepsy.[182] There is also agreement with another study that addressed the impact of narcolepsy using the Strengths and Difficulties Questionnaire (SDQ), which focuses on behavioral problems, with a few questions addressing the impact on the family. This study found a significantly greater impact on the family in both children with narcolepsy and children with excessive daytime sleepiness compared with controls. The pattern of parenting stress found in our study, where the “parenting distress” subscale was least affected, may suggest that the stress burden stems mainly from

exogenous factors, i.e. the child's behavior and interaction with its parent, and to a lesser extent from endogenous factors, such as parental self-esteem. Similar correlations between parenting stress and children's behavior has been reported in children with sleep apnea.[183] In our study, increased parenting stress was more likely in the children with psychiatric comorbidity. This is also described in studies of children with other chronic neurological disorders.[78] Parents of children in the nPHV group also obtained increased stress scores except on the "parenting distress" subscale and without significance. This could be due to the small number of patients in this group.

## **Strengths and limitations**

One general limitation of the studies included in this thesis is the small sample size in the nPHV group, which limits the opportunity to perform statistical analyses and comparisons with the PHV group. The study design in Study I makes it difficult to compare clinical symptoms between the PHV and nPHV groups. The absence of a control group in Study II is another limitation. However, available population-based data on healthy Swedish children provided an opportunity to make comparisons. We used strict DSM-IV criteria for the diagnosis of psychiatric comorbidities. Using these stringent criteria may have resulted in some of patients with psychiatric symptoms not being highlighted. Due to the rarity of narcolepsy, the study sample was also relatively small in Study III. Physical wellbeing is often regarded as important in the measurement of quality of life, but it was not included in the disease-specific NARQoL questionnaire, since the focus groups did not regard it as an important issue. The NARQoL should therefore be used in combination with a generic HrQoL questionnaire where perceived physical health items always are included. Parental ratings of HrQoL were not made in Study IV, which could be a disadvantage. However, good agreement between parent and patient ratings of HrQoL in children and adolescents with narcolepsy has been demonstrated in a previous study.[61] Another weakness is that parenting stress was measured with the PSI/SF questionnaire at all ages, in spite of the fact that validity has not been fully established for children of older ages. The overall strengths in the performed studies are the population-based study design and a well-described cohort of children and adolescents with narcolepsy both with and without association to the H1N1 influenza vaccination. The use of validated diagnostic instruments and diagnosis according to the DSM-IV added further strengths to Studies II and IV. In Study IV, we also used the validated disease-specific NARQoL questionnaire and age- and gender-matched control groups. Psychiatric comorbidity was carefully investigated, providing a unique opportunity to identify its impact on cognitive functions, HrQoL, adaptive behavior and parenting stress.



## CONCLUSIONS

In this population-based study with a well-described cohort of children and adolescents with narcolepsy both with and without association to the H1N1 influenza vaccination, we found a 25 times higher incidence in the period after vaccination against H1N1 influenza compared with the period before. The children with Pandemrix-associated narcolepsy had a lower age at onset and a more sudden and pronounced onset than is generally seen. H1N1 influenza vaccination with Pandemrix is a precipitating factor for narcolepsy in children in combination with HLA-DQB1\*0602. Further genetic and immunological studies are needed to identify the exact mechanism behind H1N1 influenza vaccine-induced narcolepsy. We identified psychiatric comorbidity in 43% of the children with Pandemrix-associated narcolepsy and increased difficulties within verbal performance and working memory. This highlights the importance of a careful psychiatric and neuropsychological follow-up of all children and adolescents with narcolepsy. A narcolepsy-specific HrQoL instrument called the NARQoL was developed. HrQoL was tested with both the NARQoL and a generic QoL questionnaire and was found to be more globally affected when tested with the NARQoL. No previous studies have investigated the adaptive behavior of children with narcolepsy associated with the H1N1 influenza vaccination. Adaptive skills were tested using the ABAS-II questionnaire that focuses on basic adaptive skills with an everyday behavior approach. The parents of children in the PHV group rated significantly lower mean indices for the general adaptive composite, conceptual and social composites compared with the general population. These findings are strengthened by the decreased social confidence and a decrease in the school/concentration domain in the disease-specific HrQoL questionnaire, the NARQoL. The parents report on impaired adaptive behavior in their children and high parenting stress indicates a considerable impact on daily life. Psychiatric comorbidity showed a further impact on cognitive functions, HrQoL, adaptive behavior and parenting stress. Finding in this thesis highlight the complexity of narcolepsy and the need of a multiprofessional health care.

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# APPENDIX

## NARQoL questionnaire



UNIVERSITY OF  
GOTHENBURG

Datum: \_\_\_\_\_

### NARQoL- Att leva med narkolepsi

Frågeformulär för unga  
8 – 18 år  
Svenska (SE)

Hej

Hur mår du? Hur känner du dig? Det här är vad vi vill att Du ska svara på.

Vi vill att Du läser varje fråga noggrant. Vilket svar tänker Du först på? Kryssa för det alternativ som Du tycker passar bäst.

**OBS! Dubbelsidiga blad!**

Namn:	_____	
Födelseår:	_____	
Kön: Pojke	<input type="checkbox"/>	<input type="checkbox"/>

**Ifyllt formulär skickas till:**

Attila Szakacs  
Barnkliniken  
30185 Halmstad  
Mail: attila.szakacs@regionhalland.se

**Om Du tänker på förra veckan...**

1. Kände Du dig frisk och i god form?	Inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Sådär <input type="radio"/>	Mycket <input type="radio"/>	Jättemycket <input type="radio"/>
2. Kände Du dig full av energi?	Aldrig <input type="radio"/>	Sällan <input type="radio"/>	Ibland <input type="radio"/>	Ofta <input type="radio"/>	Alltid <input type="radio"/>
3. Kände Du dig ledsen?	Aldrig <input type="radio"/>	Sällan <input type="radio"/>	Ibland <input type="radio"/>	Ofta <input type="radio"/>	Alltid <input type="radio"/>
4. Kände Du dig ensam?	Aldrig <input type="radio"/>	Sällan <input type="radio"/>	Ibland <input type="radio"/>	Ofta <input type="radio"/>	Alltid <input type="radio"/>
5. Hade Du tillräckligt med tid över för dig själv?	Aldrig <input type="radio"/>	Sällan <input type="radio"/>	Ibland <input type="radio"/>	Ofta <input type="radio"/>	Alltid <input type="radio"/>
6. Kunde Du göra det Du ville på fritiden?	Aldrig <input type="radio"/>	Sällan <input type="radio"/>	Ibland <input type="radio"/>	Ofta <input type="radio"/>	Alltid <input type="radio"/>
7. Behandlade din förälder/dina föräldrar dig rättvist?	Aldrig <input type="radio"/>	Sällan <input type="radio"/>	Ibland <input type="radio"/>	Ofta <input type="radio"/>	Alltid <input type="radio"/>
8. Hade Du kul med dina kompisar?	Aldrig <input type="radio"/>	Sällan <input type="radio"/>	Ibland <input type="radio"/>	Ofta <input type="radio"/>	Alltid <input type="radio"/>
9. Gick det bra för dig i skolan?	Inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Sådär <input type="radio"/>	Mycket <input type="radio"/>	Jättemycket <input type="radio"/>
10. Kunde Du vara uppmärksam (i skolan)?	Aldrig <input type="radio"/>	Sällan <input type="radio"/>	Ibland <input type="radio"/>	Ofta <input type="radio"/>	Alltid <input type="radio"/>

**Hur mår du rent allmänt?**

- Utmärkt
- Mycket bra
- Bra
- Ganska bra
- Dåligt

Q1	Jag känner mig misstrodd.	Stämmer inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Ganska bra <input type="radio"/>	Mycket <input type="radio"/>	Stämmer helt <input type="radio"/>
Q2	Jag hänger med på lektioner.	Aldrig <input type="radio"/>	Sällan <input type="radio"/>	Ibland <input type="radio"/>	Ofta <input type="radio"/>	Alltid <input type="radio"/>
Q3	Jag tror jag kommer att jobba med det jag vill i framtiden.	Stämmer inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Ganska bra <input type="radio"/>	Mycket <input type="radio"/>	Stämmer helt <input type="radio"/>
Q4	Jag känner mig mer lat än andra.	Stämmer inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Ganska bra <input type="radio"/>	Mycket <input type="radio"/>	Stämmer helt <input type="radio"/>
Q5	Jag kan sitta still och koncentrera mig.	Stämmer inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Ganska bra <input type="radio"/>	Mycket <input type="radio"/>	Stämmer helt <input type="radio"/>
Q6	Jag ser hinder för mig i framtiden.	Stämmer inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Ganska bra <input type="radio"/>	Mycket <input type="radio"/>	Stämmer helt <input type="radio"/>
Q7	Jag tror att mina lärare blir irriterade på mig.	Stämmer inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Ganska bra <input type="radio"/>	Mycket <input type="radio"/>	Stämmer helt <input type="radio"/>
Q8	Jag sover under dagen.	Inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Sådär <input type="radio"/>	Mycket <input type="radio"/>	Jätte- mycket <input type="radio"/>
Q9	Jag tror jag kommer att få körkort.	Stämmer inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Ganska bra <input type="radio"/>	Mycket <input type="radio"/>	Stämmer helt <input type="radio"/>
Q10	Jag känner att jag får den hjälp jag behöver.	Stämmer inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Ganska bra <input type="radio"/>	Mycket <input type="radio"/>	Stämmer helt <input type="radio"/>

Q11	Jag håller mig vaken när jag läser.	Stämmer inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Ganska bra <input type="radio"/>	Mycket <input type="radio"/>	Stämmer helt <input type="radio"/>
Q12	Jag känner att jag kommer att få bra skolbetyg.	Stämmer inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Ganska bra <input type="radio"/>	Mycket <input type="radio"/>	Stämmer helt <input type="radio"/>
Q13	Jag drar mig undan på rasten.	Inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Sådär <input type="radio"/>	Mycket <input type="radio"/>	Jättemycket <input type="radio"/>
Q14	Jag har problem med att vara vaken hela tiden i skolan.	Stämmer inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Ganska bra <input type="radio"/>	Mycket <input type="radio"/>	Stämmer helt <input type="radio"/>
Q15	Allt kommer att bli bra med mig i framtiden.	Stämmer inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Ganska bra <input type="radio"/>	Mycket <input type="radio"/>	Stämmer helt <input type="radio"/>
Q16	Jag upplever att alla retar en person som inte kan hålla sig vaken.	Stämmer inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Ganska bra <input type="radio"/>	Mycket <input type="radio"/>	Stämmer helt <input type="radio"/>
Q17	Jag orkar fysiskt hänga med andra jämnåriga.	Aldrig <input type="radio"/>	Sällan <input type="radio"/>	Ibland <input type="radio"/>	Ofta <input type="radio"/>	Alltid <input type="radio"/>
Q18	Det är/blir svårt för mig att behålla en pojkvän/flickvän.	Stämmer inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Ganska bra <input type="radio"/>	Mycket <input type="radio"/>	Stämmer helt <input type="radio"/>
Q19	Jag undviker fester/kalas.	Inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Sådär <input type="radio"/>	Mycket <input type="radio"/>	Jättemycket <input type="radio"/>
Q20	Jag ger lätt upp.	Inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Sådär <input type="radio"/>	Mycket <input type="radio"/>	Jätte ofta <input type="radio"/>

Q21	Allt kommer att bli sämre när jag lämnar skolan.	Stämmer inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Ganska bra <input type="radio"/>	Mycket <input type="radio"/>	Stämmer helt <input type="radio"/>
Q22	Jag har lätt att komma överens med andra.	Stämmer inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Ganska bra <input type="radio"/>	Mycket <input type="radio"/>	Stämmer helt <input type="radio"/>
Q23	Jag upplever saker (hallucinationer) som oroar mig.	Inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Sådär <input type="radio"/>	Mycket <input type="radio"/>	Jättemycket <input type="radio"/>
Q24	Jag kommer inte att resa så mycket som andra.	Stämmer inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Ganska bra <input type="radio"/>	Mycket <input type="radio"/>	Stämmer helt <input type="radio"/>
Q25	Jag känner mig ensam.	Inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Sådär <input type="radio"/>	Mycket <input type="radio"/>	Jättemycket <input type="radio"/>
Q26	Jag får ångest.	Inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Sådär <input type="radio"/>	Mycket <input type="radio"/>	Jättemycket <input type="radio"/>
Q27	Det kommer att finnas bra möjligheter för mig.	Stämmer inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Ganska bra <input type="radio"/>	Mycket <input type="radio"/>	Stämmer helt <input type="radio"/>
Q28	Jag känner att folk behandlar mig annorlunda.	Stämmer inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Ganska bra <input type="radio"/>	Mycket <input type="radio"/>	Stämmer helt <input type="radio"/>
Q29	Jag känner mig säker på mig själv.	Aldrig <input type="radio"/>	Sällan <input type="radio"/>	Ibland <input type="radio"/>	Ofta <input type="radio"/>	Alltid <input type="radio"/>
Q30	Jag kommer att behöva planera allting mer i framtiden.	Stämmer inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Ganska bra <input type="radio"/>	Mycket <input type="radio"/>	Stämmer helt <input type="radio"/>



Q31	Jag känner mig ledsen eller deppig.	Inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Sådär <input type="radio"/>	Mycket <input type="radio"/>	Jättemycket <input type="radio"/>
Q32	Jag blir väldigt lätt arg.	Inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Sådär <input type="radio"/>	Mycket <input type="radio"/>	Jättemycket <input type="radio"/>
Q33	Jag är på gott humör.	Aldrig <input type="radio"/>	Sällan <input type="radio"/>	Ibland <input type="radio"/>	Ofta <input type="radio"/>	Alltid <input type="radio"/>
Q34	Jag är sur eller irriterad.	Aldrig <input type="radio"/>	Sällan <input type="radio"/>	Ibland <input type="radio"/>	Ofta <input type="radio"/>	Alltid <input type="radio"/>
Q35	Jag gör saker utan att minnas att jag har gjort dem.	Stämmer inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Ganska bra <input type="radio"/>	Mycket <input type="radio"/>	Stämmer helt <input type="radio"/>
Q36	Jag glömmer viktiga saker.	Stämmer inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Ganska bra <input type="radio"/>	Mycket <input type="radio"/>	Stämmer helt <input type="radio"/>
Q37	Jag håller mig vaken på bussen eller i spårvagnen.	Stämmer inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Ganska bra <input type="radio"/>	Mycket <input type="radio"/>	Stämmer helt <input type="radio"/>
Q38	Jag får hemska mardrömmar.	Inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Sådär <input type="radio"/>	Mycket <input type="radio"/>	Jättemycket <input type="radio"/>
Q39	Jag hålla mig vaken när jag tittar på tv/bio.	Stämmer inte alls <input type="radio"/>	Lite grann <input type="radio"/>	Ganska bra <input type="radio"/>	Mycket <input type="radio"/>	Stämmer helt <input type="radio"/>
Q40	Jag sover dåligt på natten.	Aldrig <input type="radio"/>	Sällan <input type="radio"/>	Ibland <input type="radio"/>	Ofta <input type="radio"/>	Alltid <input type="radio"/>

# PAPERS