Protective factors, health-risk behaviours and the impact of coexisting ADHD among adolescents with diabetes and other chronic conditions

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Abstract

Mental health problems are increasing in Swedish adolescents and mortality rates are higher in this age group than among younger. 10-20% of all adolescents suffer from a chronic medical condition (CC). Few protective factors (PF) and clustering of health-risk behaviours (HRB) are frequent among adolescents with CCs.

One of the most common CC in Swedish adolescents is type 1 diabetes mellitus (T1DM). Metabolic control often deteriorates during adolescence, especially in girls. Poor metabolic control is associated with increased risk for long-term complications, of which cognitive problems are common. However, the implication of cognitive/executive problems in patients with T1DM has not been sufficiently studied. Neither has the impact of neurodevelopmental problems (NDP), such as ADHD, on HRB in adolescents with CCs been analysed.

Methods: In paper I and II the questionnaire "Life and Health in Youth" was distributed to all students in year nine and year two of the upper secondary school in the county of Sörmland, 2008 (n=5771) and 2011 (n=5550). Adolescents with CCs were compared to healthy peers with regard to PFs and HRBs. In paper III, the "Five to Fifteen" questionnaire was used in 175 paediatric patients with T1DM. Patients with indications of NDPs were compared with patients without such problems with regard to metabolic control. In paper IV, the BRIEF questionnaire and the ADHD Rating Scale as well as data from the Swedish Childhood Diabetes Registry was used in 241 adolescents with T1DM. Patients with indications of executive problems were compared with patients without such problems with regard to diabetes control.

Results: CCs were associated with few PFs and clustered HRBs. The combination of CCs and low numbers of PFs was found to be associated with an increased risk of clustered HRBs. In the presence of coexisting ADHD the pattern of few PFs and clustering of HRBs was aggravated. ADHD was more common among adolescents with other CCs.

Definite memory and learning problems as well as mild executive problems were associated with poor metabolic control, especially among adolescents. Executive problems were also associated with many outpatient visits and low physical activity. Girls with T1DM tended to self-report executive problems to a larger extent than boys, while parents more often reported these problems in boys.

Conclusion: Knowledge about factors influencing treatment adherence and life in general is essential in the work with chronically ill adolescents. Focus must be put on enhancing PFs in order to avoid HRBs. Identification of coexisting NDPs, such as ADHD, is crucial, since such problems can adversely influence treatment adherence, HRBs and school achievements.

Keywords: Adolescent development, adolescent medicine, health behaviour, protective factors, risk-taking, type 1 diabetes, HbA1c, neurodevelopmental problems and ADHD

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To all adolescents with or without a chronic medical condition and with or without poor mental health. The future is yours!
Illustrations: Jenny Hannula
List of Papers

This thesis is based on the following original articles and manuscripts, which are referred to in the text by their Roman numerals.

I The triply troubled teenager-chronic conditions associated with fewer protective factors and clustered risk behaviours.
Nylander C, Seidel C, Tindberg Y.
Acta Paediatr. 2014 Feb;103(2):194-200

II Chronic conditions and coexisting ADHD-a complicated combination in adolescents.
Nylander C, Fernell E, Tindberg Y.
Eur J Pediatr. 2015 Sep;174(9):1209-15

III Children and adolescents with type 1 diabetes and high HbA1c - a neurodevelopmental perspective.
Nylander C, Toivonen H, Nasic S, Söderström U, Tindberg Y, Fernell E.

IV Executive problems in adolescents with diabetes are associated with poor metabolic control and low physical activity.
Nylander C, Tindberg Y, Haas J, Swenne I, Torbjörndsotter T, Åkesson K, Örtqvist E, Gustafsson J, Fernell E.
Manuscript

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### Abbreviations

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<td>ADHD</td>
<td>Attention-deficit/hyperactivity disorder</td>
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<tr>
<td>ADHD-RS</td>
<td>ADHD-Rating Scale</td>
</tr>
<tr>
<td>ASD</td>
<td>Autism spectrum disorder</td>
</tr>
<tr>
<td>BREIF-SR</td>
<td>Behavior Rating Inventory of Executive Function Self-report version</td>
</tr>
<tr>
<td>CC</td>
<td>Chronic Conditions</td>
</tr>
<tr>
<td>CGM/FGM</td>
<td>Continuous Glucose Monitoring/Flash Glucose Monitoring</td>
</tr>
<tr>
<td>DCCT</td>
<td>Diabetes Control and Complications Trial</td>
</tr>
<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
</tr>
<tr>
<td>ESSENCE</td>
<td>Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations</td>
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<tr>
<td>EQUALIS</td>
<td>External Quality Assurance in Laboratory Medicine in Sweden</td>
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<tr>
<td>FTF</td>
<td>Five-To-Fifteen</td>
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<tr>
<td>GAD</td>
<td>Glutamic Acid Decarboxylase</td>
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<tr>
<td>GEC</td>
<td>Global Executive Composite</td>
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<tr>
<td>HbA1c</td>
<td>Haemoglobin A1c (glycosylated haemoglobin)</td>
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<tr>
<td>HLA</td>
<td>Human Leucocyte Antigen</td>
</tr>
<tr>
<td>HPLC</td>
<td>High-performance Liquid Chromatography</td>
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<td>HR</td>
<td>Hazard Ratio</td>
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<tr>
<td>HRB</td>
<td>Health-risk behavior</td>
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<tr>
<td>IAA</td>
<td>Insulin Autoantibodies</td>
</tr>
<tr>
<td>IA2</td>
<td>Thyrrosine phosphate-like insulinoma antigen 2</td>
</tr>
<tr>
<td>IFCC</td>
<td>International Federation of Clinical Chemistry and Laboratory Medicine</td>
</tr>
<tr>
<td>ISPAD</td>
<td>International Society for Pediatric and Adolescent Diabetes</td>
</tr>
<tr>
<td>LARCs</td>
<td>Long acting reversible contraceptives</td>
</tr>
<tr>
<td>NDP</td>
<td>Neurodevelopmental problems</td>
</tr>
<tr>
<td>NGSP</td>
<td>National Glycohemoglobin Standardization Program</td>
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<td>OCs</td>
<td>Oral contraceptives</td>
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<td>OR</td>
<td>Odds Ratio</td>
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<td>PF</td>
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<td>Q</td>
<td>Questionnaire</td>
</tr>
</tbody>
</table>
T1DM  Type 1 diabetes mellitus  
UN  United Nations  
WHO  World Health Organization  
y9  Year nine of the 9-year mandatory school system  
ZnT8  B-cell-specific zinc transporter 8 autoantibodies
Adolescents constitute the future. It is important that they develop in a safe environment and remain healthy. However, recent studies have shown that mortality rates are higher among adolescents than among younger children in Sweden as well as in the rest of the western world (1) and that mental health problems among adolescents are increasing, particularly in Sweden (2). Some adolescents also suffer from a chronic condition such as diabetes. In order to be able to live a long and happy life, without complications, the treatment of the chronic condition must be optimized. This can be hard to accomplish, especially during adolescence.

I often meet adolescents with diabetes who struggle with their treatment and have difficulties in obtaining adequate metabolic control. It is a challenge to find their motivation and to see what is behind their struggle. When finding the key to their door it is like entering into a new world, almost as fascinating as scuba diving.

Knowledge in adolescent medicine and of neurodevelopmental disorders/neuropsychiatry is crucial in order to truly meet the adolescent with or without a chronic medical condition and with or without poor mental health. Hopefully this thesis will guide you through these areas so that you will be even better prepared for meeting and treating adolescents. Together we can, and need to, improve the conditions for our adolescents so that they develop into healthy, responsible adults in the future.
Introduction

Adolescence

The World Health Organization, WHO, defines Adolescence as the period between 10-19 years of age (3, 4) and Young People as between 10-24 years of age (4). Both WHO and the United Nations, UN, define Youth as the period between 15-24 years of age (4).

Adolescence can be described as the transitional phase between childhood and adulthood (5, 6), in which the person develops from a child, who is dependent on the parents, into an independent young adult. During this transition the individual undergoes a profound bio-psycho-social development (7). Biologically, puberty occurs and the body develops from that of a child into that of an adult. Psychologically, the cognitive skills develop from concrete thinking into more abstract reasoning. Not until late adolescence (17-23 years of age) the future is comprehended. In the middle adolescence (13-17 years of age) the development of the personal identity peaks. In order to identify one’s own identity, the individual needs to experiment and take risks. To accomplish personal identity the adolescent also revolts against the parents. This revolution starts already in early adolescence (10-13 years of age) and in middle adolescence peers constitute the most important social arena. In the late adolescence, however, parents and other adults constitute important discussion partners again.

During adolescence sexuality also develops. In the early adolescence the individual explores his/her own, developing body. During mid-adolescence flirting and sexual activity is endeavoured, while in the late adolescence more solid relationships are initiated (7).
The adolescent brain

The adolescent brain is plastic and undergoes profound structural changes (5, 8-11). Starting at 10-12 years of age, maladaptive brain connections are pruned away, while frequently used connections are strengthened (5, 8, 12). This maturation is flexible (9), partly experience-driven and affected by the surrounding environment (13).

The development occurs at different times throughout the brain, starting in sensorimotor areas (sensitive to sound, vision, smell, taste and touch), limbic system (expressing emotions) and striatum (regulates reward and motivation) (5, 14, 15) and ending in the prefrontal cortex (encompassing executive functioning, such as planning, organization and inhibition) (5, 10, 11, 13-16). The latter functions are not fully mature until 20-25 years of age (5, 11). This imbalance in maturation between emotional driven centres and inhibitory centres may explain the risk-taking in adolescence (6, 10).

Moreover, during adolescence connections between central brain regions become stronger and wider, which enables the brain to specialize in everything from complex thinking to being socially adept (5). In parallel, the white matter volume is developed in a linear fashion throughout the brain (8, 13, 16, 17). This increases the speed of the nerve impulses in the brain but also the connectivity and integration of nerve circuits (16).

The initial activation of the limbic system and striatum seems to be affected by sex hormones, which are increasing during puberty (9, 18, 19). In the striatum the neurotransmitter dopamine, deeply involved in reward stimuli, is prevalent. Studies suggest that the dopaminergic system of the striatum in adolescents is strongly expressed and thus the adolescent is highly susceptible to rewards (6, 9, 13). It is shown that the sensitivity to rewards actually peaks during adolescence (6, 9, 20) and that adolescents are sensitive to positive but not to negative feedback (13, 20). Further, the activation of the amygdala in the limbic system results in stronger reactions to threats in adolescents compared to children and adults (21).

The prefrontal cortex modulates impulses from the striatum and amygdala (16, 22). Since the maturation of the prefrontal cortex is not complete until the 20s, this modulation is incomplete until then, which may explain risk-taking and novelty seeking during adolescence (16, 23, 24).

Adolescent health

Mortality rates are higher among adolescents than among younger children in Sweden as well as in the rest of the western world (1) and mental health problems among adolescents are increasing, especially in Sweden (2, 25). A recent survey among European adolescents confirms the increase in poor mental health in Swedish adolescents and reveals frequent multiple health complains and lower life satisfaction in Swedish adolescents compared to
adolescents in other Nordic countries (25). The increase in mental health problems in Swedish adolescents is suggested to be related to poor school achievements and high unemployment rates (2). It has been shown that positive school environments promote adolescent health and prevent health-risk behaviours (26).

Although experimental behaviour can be considered a normal part of adolescent development, it sometimes develops into more risky behaviour that might compromise health, quality of life, or life itself (27). Early onset of sexual activities, unsafe sexual practices, substance use or abuse and antisocial behaviours are all examples of behaviours that might put health at risk. Protective factors, on the other hand, can be defined as conditions that improve the resistance to risk factors and disorders (28) and they can be identified at multiple levels in adolescents: The individual, the family and the community (29). The concept “social determinants of health” encompasses these levels as well as the national level (30). Worldwide, the strongest determinants of adolescent health are national wealth and access to education (30). Improving access to education and employment for young people as well as reducing the risk of transport-related injury are suggested as the most effective interventions in order to improve adolescent health worldwide (30). Moreover, safe and supportive families and schools together with positive and supportive peers are crucial to help adolescents develop their full potential (30).

**Chronic conditions in adolescents**

It has been reported that approximately 10% of Swedish children and adolescents suffer from a chronic illness, defined as a disability interfering with normal life and/or demanding treatment for at least three months during a year (31). Asthma, type 1 diabetes (T1DM), epilepsy and inflammatory bowel disease are all examples of chronic illnesses prevalent in paediatric patients. Neurodevelopmental conditions are also common in children and adolescents. The worldwide prevalence of attention-deficit/hyperactivity disorder (ADHD) among school children has been estimated to about 5% (32) and
about 1% of Swedish school children are diagnosed with autism spectrum disorders (ASD) (33) and Tourette syndrome (34) respectively. However, neurodevelopmental problems commonly co-exist in children and adolescents and when this overlap is taken into account, it has been reported that approximately 7-10% of young people suffer from a neurodevelopmental problem (33). The overall prevalence of chronic conditions in childhood and adolescents should thus be estimated to 15-20% rather than the earlier suggested 10% (31), when neurodevelopmental disorders also are taken into account.

Some of these conditions require daily and lifelong medical treatment. Other conditions entail social problems, resulting in difficulties exploring life, while other adolescents with chronic conditions participate in risk-taking behaviour (35). In fact, increasing data indicates that adolescents with chronic conditions are engaged to same extent or even more in health-risk behaviours compared with their healthy counterparts (36-42) and there is evidence that health-risk behaviours tend to cluster together (43-46). Due to this, young people with chronic conditions are doubly disadvantaged during their adolescence (41, 47).

Moreover, adolescents with disabilities are less exposed to protective factors (36, 48) and children with chronic conditions are more exposed to bullying (49), have fewer contacts with peers and more emotional problems than healthy counterparts (50). Furthermore, studies on socioeconomic factors and vulnerability in Swedish adolescents report a correlation between chronic conditions and social strain, with physical abuse as the uttermost consequence (51, 52). Earlier studies also indicate an association between chronic conditions in children and lower family socioeconomic status, compared to healthy peers (53).

Type 1 diabetes

The incidence of T1DM in Sweden is the highest in the world, after Finland and Sardinia (54) and T1DM is one of the most common chronic condition among paediatric patients in Sweden (55). The incidence of T1DM increased during 1999-2004, while incidence levels remained stationary 2005-2007 (56). In 2014 the incidence among 0-17 year olds was 38.4 per 100 000 person years (57). However, updated figures show a somewhat higher incidence.

T1DM is an autoimmune disorder that affects the insulin producing β-cells
of the pancreas (58, 59). Antibodies against glutamic acid decarboxylase 65 (GAD), insulin (IAA), tyrosine phosphate-like insulinaoma antigen 2 (IA2) and β-cell-specific zinc transporter 8 autoantibodies (ZnT8) as well as HLA risk types (typically DR3/DR4) are associated with the condition (60).

The symptoms of T1DM include polyuria, polydipsia and weight loss. The diagnosis is confirmed by these symptoms in combination with random plasma glucose ≥11.1 mmol/L, by two fasting plasma glucose ≥7.0 mmol/L or by HbA1c >48 mmol/mol at two separate occasions (60).

Self-management of T1DM includes frequent blood glucose monitoring, carbohydrate estimation, insulin dose calculation, insulin administration and partaking in regular exercise (61). Blood glucose between 4-8 mmol/L and HbA1c <57 mmol/mol are recommended according to current Swedish national guidelines for diabetes in children and adolescents (62).

**Type 1 diabetes in adolescents**

Getting T1DM during adolescence is complicated and related to poorer long-term metabolic control, compared to patients getting diabetes <10 years of age (63). Also, metabolic control often deteriorates during adolescence (35, 64). However, two distinct trajectories of metabolic control across adolescence have been identified: moderate control with slight deterioration (representing a majority of adolescent patients) and poor control with rapid deterioration (<10% of patients). Adolescents with poor and rapidly deteriorating metabolic control reported lower paternal monitoring and frequency of help with diabetes management, lower functional autonomy, and lower self-control than others. Patients in this group were also more likely to report diabetes-related emergency room visits and diabetes-related hospitalizations (64).

The metabolic deterioration during adolescence is especially prevalent in girls (65). However, there is a gender difference in HbA1c already at diagnosis (55, 66) and at follow up where girls present higher values than boys (55). One reason for this phenomenon in adolescent girls can be increased GH-secretion, which induces insulin resistance (67). Other reasons for poor metabolic control in adolescents has been speculated to be irregular meal (68) and exercise patterns (69), poor adherence to treatment regimens (70) as well as risk-taking behaviours (41).

Risk-taking behaviours are baneful in patients with T1DM. Tobacco smoking in patients with T1DM is associated with an increased risk for premature death by cardiovascular disease (71). Alcohol inhibits gluconeogenesis in the liver (35), which may result in severe hypoglycaemia. Ingestion of carbohydrates and measuring of blood glucose before sleep can prevent this (35). Further, cannabis smoking can first lead to excess snacking and then to loss of appetite (35). Drug use, in general, also alters brain functions, increasing the risk for mistakes with diabetes management (35). Ado-
lescents with T1DM should be encouraged to refrain from smoking, binge drinking and use of other drugs (35).

Sexual activity in adolescents with T1DM must be specially acknowledged. Focus should be put on avoiding hypoglycaemia after intercourse (35) as well as optimizing metabolic control in case of pregnancy (35). Poor metabolic control during pregnancy increases the risk for congenital malformations and foetal death (72, 73). Contraceptives should be advocated in the group of sexually active adolescents with T1DM (35). Condoms, newer oral contraceptives (OCs) with lower oestrogen doses and newer progesterones as well as long acting reversible contraceptives (LARCs, including intrauterine devices and implantable rods) are recommended (35).

**Long-term complications from T1DM**

Patients with T1DM and good metabolic control have a double risk for death from any cause or from cardiovascular disease, compared to controls without T1DM (74). In patients with poorer metabolic control this risk is even higher. With HbA1c ≥83 mmol/mol the adjusted Hazard Ratio is 8.51 for death from any cause and 10.46 for death by cardiovascular disease as compared to controls without T1DM (74). Recently it has been shown that young adults with mean HbA1c >78 mmol/mol had a significantly higher proportion of retinopathy, microalbuminuria and/or macroalbuminuria compared to the group with HbA1c below 57 mmol/mol (75). Other studies show that HbA1c exceeding 70 mmol/mol is associated with long-term complications, such as cardiovascular disease and nephropathy (76) while these complications are not seen when long-term mean HbA1c is kept below 60 mmol/mol (77).

The main complications of T1DM are micro- and macrovascular diseases, manifested as retinopathy, nephropathy, neuropathy, and cardiovascular disease (78). These may result in visual impairments and blindness, renal failure and hypertension, pain, muscle weakness, autonomic dysfunction, cardiac disease, peripheral vascular disease and stroke (78). Recently cognitive dysfunctions, based on neuropsychological testing, were reported to be five times more common in adults with T1DM, compared to adults without diabetes (79). Cognitive problems are thus discussed as one of the major complications to T1DM as well.

**Executive functioning problems and ADHD**

Executive functions serve to organize and control thought and behaviour (80) and are often defined as the "conductor" of the brain. Key elements of executive functions include planning and organization abilities, anticipation, initiation of activity, different aspects of attention, impulse control and self-regulation, utilization of feedback, selection of efficient problem-solving strategies, mental flexibility and working memory (81). Functional magnetic resonance imaging and positron emission tomography have related brain
networks involved in executive functioning to the prefrontal cortex of the brain (80).

Impaired executive functioning is one of the characteristics of ADHD (82). Executive functioning problems are also commonly occurring in individuals with impaired intellectual abilities (83), in ASD (84) as well as in patients with anxiety and depression (85). These neurodevelopmental disorders commonly co-exist in children and adolescents, which is why the acronym ESSENCE (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations) has been developed (33). The concept of ESSENCE advocates a holistic and multidisciplinary approach to patients presenting with early neurodevelopmental symptoms.

Executive functioning problems are presented on a spectrum, ranging from mild problems to more severe, compatible with the diagnosis of ADHD (86). There are 18 symptom criteria of ADHD, according to the DSM-IV (87) and DSM-5 (88). The three subtypes/presentations of ADHD are: The combined, the inattentive and the hyperactive/impulsive type/presentation. At least 6 out of 9 symptoms in each domain have to be present in order to fulfil the diagnostic criteria for ADHD (87, 88). The new DSM-5 states that in young people from the age of 17 and older at least five symptoms are required (88). The symptoms should be present before 12 years of age, be clinically significant in at least two different environments and cause functional disabilities during at least 6 months (88).

To emphasize that ADHD is a dimensional syndrome, the term sub-threshold ADHD has been used. The term was defined by 4-5 of the ADHD-criteria according to the DSM-IV manual, by the American Academy of Pediatrics.

The heritability of ADHD is around 76%, suggesting a strong genetic role in ADHD aetiology (89). Thus parents of patients with ADHD are likely to carry the same condition. Moreover, boys are more frequently diagnosed with ADHD during childhood (90) and it is discussed that girls’ executive problems frequently are unnoticed and undiagnosed (91).

In adolescents with ADHD, time perception is often affected (86). Moreover, adolescents and adults with ADHD are at heightened risk of drug abuse (92) and antisocial behaviour (93).
Clinical guidelines for the treatment of children and adolescents with ADHD recommend the use of multimodal treatment consisting of behavioural interventions, such as parent management training and teacher consultations as well as pharmacological treatment (94). Behavioural interventions include increased support from adults in many daily life situations; reminders, help to organise tasks, get started, follow and complete tasks as well as help to find alternative solutions when required (95). This support is required both in schools and during leisure time (96, 97). The most common pharmacological–treatment is stimulant-medication (96, 97). The latter has been shown to prevent risk-behaviour such as criminality (98).

The brain and ADHD

The brain development is suggested to be altered in patients with ADHD and anatomical imaging studies of ADHD consistently point to involvement of the frontal lobes with a developmental delay of cortical thickness trajectories (8). The development of parietal lobes, basal ganglia, corpus callosum and cerebellum are also altered (8). Functional magnetic resonance imaging studies reveal a hypoactivation of frontoparietal networks, involving executive functions, and hypoactivation of ventral networks, involving attention, in children with ADHD (99). However, there were also indications of hyperactivation of regions in the ventral network, which might support the symptom of distractibility in ADHD (99).

Moreover, children with ADHD have been found to have a delayed striatal development (100). In youths and adults with ADHD striatal activation is also low (101), yielding a suppressed reward system. However, the striatal activity is increased with stimulant-medication (101), which also improves cortical development in adolescents with ADHD (102).
Diabetes and neurodevelopmental/neuropsychiatric conditions

Mild cognitive problems are reported in both children (103-109) and adults (79, 110, 111) with T1DM. Working memory (107) and other executive functions are particularly affected (111). These cognitive dysfunctions have been related to an early onset of the disease (107, 108, 110-113) and to a history of hypoglycaemic seizures (107, 108) but not to long-term metabolic control (108). However, there are studies in adults reporting an association between chronic hyperglycaemia and cognitive dysfunctions (114, 115), while another study reveals a lack of correlation between severe hypoglycaemia or ketoacidosis and cognitive problems in children with T1DM (116). The diathesis theory suggests that the young brain may be harmed by hyperglycaemia early in life, which confers a vulnerability to insults, such as hypoglycaemia, later in life (117). Testing with brief cognitive tests several times a day during four to six weeks in school children with T1DM have revealed decreased mental efficacy during spontaneously occurring acute hypo- and hyperglycaemic episodes (118).

Magnetic resonance imaging studies have shown that patients with T1DM have morphological changes in the grey and white matter of the brain. However, the CNS changes in adolescents are subtle and their functional significance uncertain (119). In this context it is noteworthy that ketoacidosis at onset of T1DM has been found to result in morphologic and functional brain changes, associated with adverse moderate neurocognitive outcomes (120).

A number of studies report an increased risk of psychiatric disorders (121-124), including ADHD (125), in adolescents with T1DM. This is found
particularly six months after disease onset but also later in life (125). However, the association between ADHD and diabetes is debated and it has been demonstrated that ADHD is associated with type 2 but not with type 1 diabetes (126). Although conflicting results in the relationship between ADHD and T1DM, executive problems will yield specific difficulties for patients with T1DM. The treatment of T1DM requires regular insulin injections and dose adjustments in relation to carbohydrate content of the meal as well as planned or accomplished physical activity. This is demanding and requires good cognitive skills. Earlier studies of children with T1DM demonstrate an association between good executive functions, treatment adherence and consequent good metabolic control (127). Good metabolic control has also been associated with lower impulsiveness when compared to patients with poor metabolic control (128).
The overall aim of the present studies was to increase the knowledge about factors influencing the treatment and the life situation of adolescents with chronic conditions.

Specific aims were:
- To explore to what extent Swedish adolescents with chronic conditions report protective factors and health-risk behaviours compared with their healthy peers, taking gender into account.
- To investigate the impact of protective factors on health-risk behaviour in adolescents with chronic conditions.
- To outline the impact of different chronic conditions on protective factors and health-risk behaviours.
- To explore to what extent ADHD coincides with other chronic conditions.
- To outline how coexisting ADHD influences the presence of protective factors and health-risk behaviours.
- To investigate the prevalence of neurodevelopmental problems in paediatric patients with T1DM compared with a historic norm group.
- To examine the association between neurodevelopmental problems and high HbA1c.
- To investigate the association between executive functioning problems, reported as ensuing difficulties in daily life, and diabetes control in adolescents with T1DM.
Subjects and methods

<table>
<thead>
<tr>
<th>Paper</th>
<th>Number of participants (response rate)</th>
<th>Age</th>
<th>Design</th>
<th>Sources of measure</th>
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<tr>
<td>I: The triply troubled teenager – chronic conditions associated with fewer protective factors and clustered risk behaviours</td>
<td>5771 (82%)</td>
<td>15-18 years</td>
<td>Cross sectional</td>
<td>Q: Life and health in Youth, Sörmland 2008</td>
</tr>
<tr>
<td>II: Chronic conditions and coexisting ADHD – a complicated combination in adolescents</td>
<td>5550 (80%)</td>
<td>15-18 years</td>
<td>Cross sectional</td>
<td>Q: Life and health in Youth, Sörmland 2011</td>
</tr>
<tr>
<td>III: Children and adolescents with type 1 diabetes and high HbA1c – a neurodevelopmental perspective</td>
<td>175 (75%)</td>
<td>5-16 years</td>
<td>Cross sectional</td>
<td>Q: Five to Fifteen, Medical records, HbA1c SWEDIABKIDS</td>
</tr>
<tr>
<td>IV: Executive problems in adolescents with diabetes are associated with poor metabolic control and low physical activity</td>
<td>241 (51%)</td>
<td>12-18 years</td>
<td>Cross sectional</td>
<td>Q: BRIEF-SR, ADHD-RS, socio-demographic factors SWEDIABKIDS including HbA1c</td>
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Q = Questionnaire

Subject selection and data collection

Paper I and II
The first two studies were based on the cross-sectional and school-based survey “Life and Health in Youth, Sörmland” (129). A questionnaire was
distributed to all adolescents attending school year nine (y9) of the nine-year mandatory school system (corresponding to 15 years of age) and year two (post2) of post mandatory school (corresponding to 17-18 years of age) in all nine municipalities in the county of Sörmland during February 2008 and March 2011, respectively. Post2 is attended by 90% of Swedish adolescents. No special schools for children with intellectual disabilities were included in these studies.

The questionnaire was distributed by school employees and completed in the classroom during a lesson at ordinary school hours. A second chance was given for those not attending school on the first day of the survey. To ensure confidentiality, questionnaires were returned anonymously in closed envelopes. Answers were managed and scanned by the Centre for Clinical Research Sörmland.

In total, 5771 valid questionnaires were completed in 2008 (response rate 82%) and 5550 questionnaires in 2011 (response rate 80%).

Paper III

The third study was performed as a population based, multicentre study in children and adolescents with T1DM in Sörmland and Skaraborg, June 2009- June 2011. All patients (5-16 years, n=233) with diabetes were invited to a neurodevelopmental screening through the validated Five-To-Fifteen (FTF) questionnaire. To be eligible for the study, the parents had to have knowledge in the Swedish language, without the use of an interpreter. Parents completed the questionnaire at home and returned it to the clinic in sealed envelopes. Health care personal without knowledge of the outcome in the FTF questionnaire, collected HbA1c levels from the medical records. Information about age of onset and diabetes duration was collected from the Swedish Childhood Diabetes Registry, SWEDIABKIDS.

In total, 190 (82%) parents returned the questionnaire. Three questionnaires were discarded due to incomplete data. Another 12 patients were diagnosed the previous year. Since they were considered to be in the partial remission phase, when HbA1c naturally is lower, they were also omitted from analyses. Thus 175 questionnaires (75%) were included in the analyses.

Paper IV

The fourth study was performed as a multicentre study at the paediatric clinics in Stockholm, Uppsala and Jönköping, during March 2013- February 2015. The study focused on executive problems among adolescents (12-18 years old, n=477). To be eligible for participation, the patients had to understand and speak Swedish without requiring an interpreter. They also needed to have cognitive skills enabling them to complete the questionnaires. Finally, to avoid patients in the partial remission phase, during which HbA1c
normally is lower, the participants should have a duration of diabetes of >2 years. Consequently, no new cases of T1DM were included during the time period of data collection.

The adolescents completed the BRIEF-SR questionnaire (Behavior Rating Inventory of Executive Function Self-report Version) that screens for executive problems. Parents completed the ADHD-RS (ADHD Rating Scale) based on DSM-IV criteria for ADHD. Patients and parents completed the questionnaires independently at the clinic after regular meetings and returned to the diabetes team in sealed envelopes.

Data on ethnic background and parental working status were collected from the questionnaire while data on gender, age, HbA1c at all outpatient visits, number of outpatient visits, present smoking, level of physical activity, occurrence of ketoacidosis and severe hypoglycaemic events were collected from SWEDIABKIDS.

In total 241 adolescents and/or parents participated, yielding an overall response rate of 51% (241/477). The response rate ranged from 43-64% in the different centres. Questionnaires were completed by 238/241 patients (99%) and 183 parents (76%). Parent reports were missing in 58 (24%) of the 238 cases in which patient questionnaires were completed and three parents responded without their child participating.

**Measures**

**The Life and Health in Youth- questionnaire**

The questionnaire included 96 questions for y9 and 98 questions for post2 in 2008 and 87 and 89 questions, respectively, in 2011 regarding gender, socio-demographic background, lifestyle, health, school results, influence in school and society, social network, physical abuse and experimental behaviour. Corresponding questions were identical in the two questionnaires (129). The questions had been used in other school-based, published, studies (130, 131). However, they were also tested on adolescent focus groups to ensure that they were clearly formulated and understood by the target group.

**Socio-demographic factors**

In paper I and II information on gender and school year was obtained from the questionnaire. Ethnic background was categorized as non-Swedish when the adolescent and/or both parents were born outside Sweden according to the current Official Statistics of Sweden (112). Since family income was not assessed, the variable “parental working status” was used as a proxy for socioeconomic status. The reference category for “parental working status” referred to both parents being employed or studying as compared to one or both parents being unemployed or on sick-leave. These questions and defini-
tions of ethnic background and parental working status were also used in paper IV.

**Chronic conditions**

Presence and severity of CCs were reported and assessed by the adolescents themselves in the following questions: “Do you have any of the following diseases or impairments: Asthma, allergy, diabetes, epilepsy, inflammatory bowel disease, impaired hearing, vision, motor function or reading/writing difficulties. No, yes mild or yes severe.”

In paper I, two categorical groups were created regarding chronic illness. The chronic condition group included adolescents answering “yes, severe” to one or more of the questions on impaired hearing and/or vision, impaired motor function, asthma or allergy plus students answering “yes, mild/moderate” or “yes, severe” to one or more of the questions on diabetes, epilepsy and inflammatory bowel disease. Those who answered “no” to all of the above questions were considered the comparison group.

In paper II, four categorical groups of adolescents with chronic conditions were created, regardless of the presence of coexisting ADHD. The groups were;
1. Reference group including adolescents reporting none of the below conditions.
2. Chronic non-neurological conditions including adolescents answering “yes, severe” to one or more of the questions on asthma or allergy plus “yes, mild/moderate” or “yes, severe” to one or more of the questions on diabetes and inflammatory bowel disease,
3. Chronic neurological conditions including adolescents answering “yes, severe” to one or more of the questions on impaired hearing, vision, and/or motor function and/or reading/writing difficulties, as well as “yes, mild/moderate” or “yes, severe” epilepsy,
4. Combined chronic non-neurological and neurological conditions, including students reporting both non-neurological and neurological conditions, as defined above.

Five categorical groups were then created regarding CCs with or without the presence of coexisting ADHD. A student was regarded as having ADHD if he/she had reported being diagnosed as having ADHD by a physician/psychologist and/or being on medication for ADHD. The five groups created were as follows;
1. Healthy comparison group, reporting neither ADHD nor other CCs,
2. Chronic non-neurological conditions, as defined above without reported coexistent ADHD,
3. Chronic neurological conditions, as defined above without reported coexistent ADHD,
4. ADHD but no other reported chronic condition,
5. ADHD in combination with non-neurological and/or neurological conditions.

Youths reporting only mild/moderate impairments of hearing, vision, motor function, reading/writing, asthma or allergy were not considered to meet the criteria for either the CCs group or the healthy comparison group. This group was omitted from further analyses after having checked that it did not differ from the study groups regarding background variables, but consisted of intermediate results when it came to the studied outcomes.

**Protective factors**

In paper I and II, seven protective factors on the personal, family and community level were identified and corresponding variables created from the questionnaire. The answers were dichotomized as follows:

1. Having a bright/optimistic view of the future (very bright or somewhat bright *versus* neutral, somewhat dark or very dark),
2. Finding it easy to talk to one or both parents about difficult matters (yes *versus* neutral or no),
3. Living in one household (yes or no),
4. Enjoying school (very much or much *versus* neutral, hardly or not at all),
5. Having passed all school subjects (yes or no),
6. Ever having been bullied (never *versus* once or more) and
7. Physical exercise at least 30 minutes ≥ 2 times per week (seven alternatives categorized into yes or no).

An equally weighted combined index of the seven protective factors was created. The summative risks were categorized as 6-7 (reference category), 4-5 or 0-3 protective factors. Few protective factors were then defined as 0-3 protective factors. The combined index was coded as missing if all of the underlying questions had been unanswered.

**Health-risk behaviours**

Similarly, seven health-risk behaviours were identified and created from the questionnaire. The answers were dichotomized into:

1. Smoking at present (daily or sometimes *versus* not at present),
2. Getting drunk (once or more per month *versus* more seldom or not at all),
3. Ever having used drugs (once or several times *versus* never),
4. Violent behaviour (having threatened others more than once and/or hit others on purpose so that victims were injured once or more *versus* not at all),
5. Having engaged in criminal acts (shoplifting > 5 times, ever selling stolen goods and/or ever breaking in *versus* not at all),
6. Early sexual debut (having had first sexual intercourse before 15 years of age according to an open question) and
7. Self-harm behaviour the last year (having tried to cut or otherwise harm themselves at any time versus not at all).

Further, an equally weighted combined index of the seven health-risk behaviours was created. The summative risks were categorized as none (reference category), 1, 2-3, or ≥4 risk behaviours. Clustered health-risk behaviours were then defined as ≥4 health-risk behaviours. If all of the included questions on health risk behaviours were missing the combined index was also regarded as missing.

The Five to Fifteen questionnaire

The FTF questionnaire is a Nordic validated questionnaire that targets neurodevelopmental and behavioural problems (132, 133). The original FTF normative sample was based on 854 Swedish children (132). The FTF has good inter-rater and test-retest reliability (132).

The questionnaire contains 181 items, divided into eight different domains: Memory, learning, language, executive functions, motor skills, perception, social skills, and emotional/behavioural regulation. Scores above the 75th percentile in each domain are considered an indication of mild problems (expected 25% of the population) while scores above the 90th percentile (expected 10% of the population) constitute indications of definitive problems. Scores above the 90th percentile are commonly, as well as in paper III, used as cut off for screening purposes. However, in the executive domain, an area including abilities such as planning, organizing and following instructions, which all are essential for diabetes management, scores above the 75th percentile were taken into account.

BRIEF-SR

The BRIEF-SR is an 86-item patient report measure of youth executive functioning, validated for subjects between 11 and 18 years of age (81). The BRIEF-SR has well-established internal consistency, reliability and validity for both community and clinical samples (81, 134). BRIEF-SR items are scored on a three-point Likert scale and the participants indicate whether the item applies "never", "sometimes" or "often" at present or within the past 6 months. Lower raw scores indicate better executive functioning. The total score comprises the global executive composite (GEC).

Raw scores can be converted into T scores by using normative conversion tables, grouped by gender and age (11-14 years versus 15-18 years). The mean T score is 50 and T scores above 60 may warrant clinical interpretation (executive functioning problems) while T scores above 65 are considered clinically significant (considerable executive problems). In paper IV, T
scores above 60 were used as an indication of executive functioning problems and T scores above 65 as an indication of considerable executive functioning problems.

ADHD Rating Scale
The ADHD-RS (135) is a parent rated questionnaire that targets ADHD symptoms during the previous 6 months. The ADHD-RS is based on the DSM-IV criteria for ADHD with nine items pertaining to inattention and nine to hyperactivity/impulsivity. The items are scored as “applies not at all”, “applies somewhat”, “applies rather well” or “applies very well”. The symptom is considered to be present when the item was scored “rather well” or “very well”. Six such positive outcomes in a domain are denoted probable ADHD/considerable executive problems. Four to five positive outcomes are denoted sub-threshold ADHD/executive problems. These definitions were used in paper IV.

SWEDIABKIDS
The Swedish Childhood Diabetes Registry was established in 2000 (55). Outpatient attendance data from all Swedish paediatric diabetes centres are registered in SWEDIABKIDS, which thus contains data on almost all (99%) paediatric diabetes patients in Sweden (55). The registry comprises information on gender, age at diabetes onset, diabetes duration, HbA1c at all outpatient visits, number of outpatient visits, insulin administration, insulin dose, smoking, level of physical activity, occurrence of ketoacidosis, severe hypoglycaemic events as well as presence of complications such as retinopathy and nephropathy. The information on complications is, however, poorly completed (57).

In paper III and IV, information about age of onset and diabetes duration was collected from SWEDIABKIDS. Diabetes onset before 6 years of age was regarded as early onset and diabetes duration of more than 5 years as long when being a child or an adolescent.

In paper IV data on gender, age, HbA1c at all outpatient visits, number of outpatient visits, present smoking, level of physical activity, occurrence of ketoacidosis and severe hypoglycaemic events during the time of data collection were summarized.

According to the Swedish guidelines for management of diabetes in children and adolescents (62) each patient is recommended four outpatient visits per year. Since data was collected over two years (March 2013-February 2015), more than 8 outpatient visits per patient were considered as more than recommended and used as an indication of complicated diabetes care.
Physical activity was registered as never, <1 time/week, 1-2 times/week, 3-5 times/week or daily. Collected data was dichotomized into low (≤2 times/week) vs. high (≥3 times per week) level of physical activity. Presence of ketoacidosis (pH <7.3) (62) was registered as well as presence of severe hypoglycaemia (defined as in need of help from other person, unconsciousness or seizures).

HbA1c
Glucose exposure mediates glycosylation of haemoglobin. Since the erythrocyte usually has a lifespan of up to 120 days, glycosylated haemoglobin (HbA1c) is a measure of metabolic control over the previous approximate three months (136).

All HbA1c calibrations in Sweden are standardized through EQUALIS (External Quality Assurance in Laboratory Medicine in Sweden). Until 2010 HbA1c was measured in percentages with HPLC, calibrated to the Swedish Mono S method (137). Swedish HbA1c-values have traditionally been approximately 1% lower than the worldwide Diabetes Control and Complications Trial (DCCT)/National Glycohemoglobin Standardization Program (NGSP) standard. In 2010, a new worldwide standard, the IFCC method, was introduced (136). The IFCC method reports HbA1c in mmol/mol.

In paper III HbA1c >8.0% (73 mmol/mol) was used as a proxy for poor metabolic control. In paper IV, information about HbA1c during the two years of data collection, was received from SWEDIABKIDS. A mean HbA1c for the two years was calculated. Mean HbA1c >70 mmol/mol was considered high and used as an indication for poor metabolic control. Moreover, the presence of single HbA1c above 100 mmol/mol, 80 mmol/mol, 70 mmol/mol and 60 mmol/mol, respectively were also registered.

Statistical analyses

Paper I and II
Univariate tests (Chi-square) were used to test the associations between socio-demographic factors and chronic conditions as well as the association between protective factors and health-risk behaviours. Adolescents reporting only mild/moderate impairments of hearing, vision and motor function, asthma or allergies were not considered to meet the criteria for either the chronic conditions group or the control group. This group was omitted from further analyses after control that it did not differ from the study groups re-
garding background variables and that it obtained intermediate results as far as the studied outcomes were concerned.

In paper I, associations between chronic conditions and protective factors as well as health-risk behaviours were tested with multivariate logistic regressions, adjusted for school year, ethnic background and parental working status and stratified by gender to avoid confounding. Summative indexes for clustering of protective factors and health-risk behaviours were tested in univariate tests, stratified by gender. Finally, combinations of chronic conditions and number of protective factors were tested for their impact on clustering of health-risk behaviours in adolescents in multivariate logistic regression models, adjusted for gender, school year, ethnic background and parental working status.

In paper II, univariate tests were used to test the associations between socio-demographic factors and chronic conditions as well as frequency of ADHD in different groups of chronic conditions. Further, the combined indexes for protective factors and health-risk behaviours were tested for associations with chronic conditions and/or ADHD in univariate tests. Thereafter, associations between the different groups of chronic conditions and/or ADHD and few protective factors and clustered health-risk behaviours, respectively, were tested in multivariate logistic regressions, adjusted for gender, school year, ethnic background and parental working status.

Associations were expressed as crude odds ratios (OR) and adjusted odds ratios (adjOR) with 95% confidence intervals (CI). The results were considered to be significant when the p-value was <0.05 in two-tailed analyses.

Paper III

The presence of high HbA1c (>73 mmol/mol, 8%) was compared between patients with signs of neurodevelopmental problems and patients without such problems in the FTF questionnaire.

The statistical analyses were based upon the hypothesis that neurodevelopmental problems, as measured by the prevalence of FTF scores above the 90th percentile in the different domains, and above the 75th percentile in the executive domain, may correlate to higher HbA1c. The logistic regression models were restricted to adolescents 12-16 years of age, since in this age group the adolescents are likely to manage their diabetes treatment more or less independently. The regressions were made with HbA1c-level as dependent variable and FTF-scores as explanatory adjusting for gender in a first step, adding age of diabetes onset and disease duration into our final model.

Chi-square test, or Fisher’s test when small numbers, were used to test for associations and a p-value <0.05 was considered statistically significant. Associations were given as crude Odds Ratio (OR) and adjusted Odds Ratio (adjOR) with 95% Confidence Interval (95% CI).
Paper IV

First, the representativeness of respondents was tested against non-respondents using solid registry data from SWEDIABKIDS. The mean age of the patients, mean age at diabetes onset, mean diabetes duration, mean HbA1c, mean number of outpatient visits and gender were compared between the groups.

Second, the gender distribution of executive functioning problems was analysed among all adolescents with self-rated executive functioning (based on BRIEF-SR), adolescents with both self-rated and parent-rated adolescent executive functioning (based on BRIEF-SR) and the latter adolescents’ corresponding parent-rated executive functioning (based on ADHD-RS).

Third, statistical analyses were performed based on the hypothesis that executive functioning problems, as measured by the presence of GEC T-scores above 60 and 65 or the presence of ≥ 4 and ≥ 6 criteria met in either or both domains of the ADHD-RS, respectively, may correlate to high HbA1c or other signs of poor diabetes control. Chi-square test, or Fisher’s test when small numbers, were used to test for associations. *P*-values <0.05 were considered statistically significant.

Fourth, logistic regression analyses were made with mean HbA1c >70 mmol/mol, >8 outpatient visits and low physical activity as dependent variables, respectively, and executive problems rated by patients (GEC T-scores ≥60) as explanatory adjusting for gender and age in a first step, for gender, age, diabetes centre, long diabetes duration and early onset of diabetes in a second step. The same analyses were made for parent-rated executive functioning problems (≥4 scores in either or both domains of the ADHD-RS). Results were given as crude Odds Ratio (OR) and adjusted Odds Ratio (adjOR) with 95% Confidence Interval (95% CI).

All data was analysed in SPSS (19.0 and 22.0) for Windows (SPSS Inc., Chicago, IL).

Ethical considerations

In paper I and II some questions could be potentially distressful for the respondents, such as the questions pertaining to bullying and self-harm behaviours. The questionnaire included information on where to receive counseling if participation had caused distress. The studies were approved by the Regional Ethical Review Board in Stockholm D-nr. 2008/1855-31/5.

In paper III and IV all patients and parents were informed about the studies by their diabetes doctor or nurse. Written consent was obtained by patients over 12 years of age and by patients and parents when patients were
below 15 years of age. All questionnaires were anonymously answered and returned to the diabetes team in sealed envelopes. Patients with indications of neurodevelopmental/executive dysfunctions were offered a consultation and further assessment by a child neurologist or psychiatrist. The studies were approved by the Regional Ethical Review Board in Gothenburg (paper III) 2009/641-08 and Uppsala (paper IV) Uppsala D-nr. 2012-332.
Results

Paper I

Of the total sample of 5771 adolescents (15-18 years of age), 459 (8%) reported that they had a chronic condition and 3327 (58%) reported that they did not. Together these 3786 adolescents constituted the study population, whereof 1934 (51%) were boys and 1987 (53%) attended year 9 of mandatory school (corresponding to 15 years of age). Further, 488 (13%) had two parents born in a country other than Sweden and 582 (16%) reported that one or both parents were unemployed or on sick-leave.

More girls than boys reported chronic conditions \((p<0.001)\). Chronic conditions were also more common among adolescents with a Swedish background as compared to those with foreign background \((p<0.05)\) and among those with at least one parent out of work compared to two working parents \((p<0.01)\). No difference was seen in reported chronic conditions according to school year.

Girls with CCs encompassed less individual protective factors compared to their healthy peers and compared to boys (Table 1). They were less likely to have a bright/optimistic view of the future, to live in one place, to enjoy school, to pass in all subjects and to never have been exposed to bullying, as compared to the comparison group. Boys with a CC were significantly less likely to enjoy school, to pass in all subjects and to never have been exposed to bullying as compared to healthy peers. They also tended to be less physically active as compared to healthy counterparts (Table 1).

All individual health-risk behaviours tended to be overrepresented among boys who reported having a CC as compared to their healthy peers (Table 1). However, present smoking, having tried drugs other than alcohol, violent behaviour, criminal acts and self-harm behaviour were all overrepresented in boys with a CC at a statistically significant level. Girls with a CC reported having tried drugs other than alcohol, violent behaviour, early sexual debut and self-harm-behaviour significantly more frequently than their healthy peers. Also, criminal acts tended to be overrepresented in girls with CCs (Table 1).
Table 1. Associations between chronic health conditions in adolescents and protective factors as well as health-risk behaviours, by gender.

<table>
<thead>
<tr>
<th>Protective factor</th>
<th>Chronic Conditions Group, n (%)</th>
<th>Comparison Group, n (%)</th>
<th>adjOR (95% CI)*</th>
<th>Chronic Conditions Group, n (%)</th>
<th>Comparison Group, n (%)</th>
<th>adjOR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>1.0</td>
<td></td>
<td></td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimistic future</td>
<td>157 (83)</td>
<td>1429 (84)</td>
<td>0.9 (0.6-1.3)</td>
<td>189 (73)</td>
<td>1292 (82)</td>
<td>0.6 (0.4-0.8)</td>
</tr>
<tr>
<td>Easy to talk to a parent</td>
<td>99 (51)</td>
<td>929 (54)</td>
<td>0.8 (0.6-1.1)</td>
<td>148 (57)</td>
<td>819 (52)</td>
<td>1.3 (1.0-1.6)</td>
</tr>
<tr>
<td>Living in one place</td>
<td>146 (75)</td>
<td>1308 (75)</td>
<td>1.1 (0.7-1.5)</td>
<td>169 (66)</td>
<td>1189 (75)</td>
<td>0.7 (0.5-0.9)</td>
</tr>
<tr>
<td>Enjoy school</td>
<td>147 (76)</td>
<td>1435 (84)</td>
<td>0.6 (0.4-0.9)</td>
<td>187 (73)</td>
<td>1301 (82)</td>
<td>0.6 (0.5-0.9)</td>
</tr>
<tr>
<td>Pass in all subjects</td>
<td>108 (56)</td>
<td>1192 (69)</td>
<td>0.6 (0.4-0.8)</td>
<td>172 (67)</td>
<td>1239 (78)</td>
<td>0.5 (0.4-0.7)</td>
</tr>
<tr>
<td>Never been bullied</td>
<td>165 (85)</td>
<td>1594 (92)</td>
<td>0.5 (0.3-0.8)</td>
<td>222 (85)</td>
<td>1460 (92)</td>
<td>0.5 (0.4-0.8)</td>
</tr>
<tr>
<td>Phys. exercise ≥2 times/week</td>
<td>126 (66)</td>
<td>1209 (71)</td>
<td>0.8 (0.6-1.1)</td>
<td>165 (65)</td>
<td>955 (61)</td>
<td>1.3 (1.0-1.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Health-risk behaviour</th>
<th>Boys</th>
<th>Girls</th>
<th>adjOR (95% CI)*</th>
<th>Boys</th>
<th>Girls</th>
<th>adjOR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Present smoking</td>
<td>55 (29)</td>
<td>333 (19)</td>
<td>1.7 (1.2-2.4)</td>
<td>64 (25)</td>
<td>318 (20)</td>
<td>1.2 (0.9-1.7)</td>
</tr>
<tr>
<td>Getting drunk monthly</td>
<td>67 (35)</td>
<td>497 (29)</td>
<td>1.4 (1.0-2.0)</td>
<td>73 (28)</td>
<td>353 (23)</td>
<td>1.3 (0.9-1.8)</td>
</tr>
<tr>
<td>Ever using drugs</td>
<td>39 (20)</td>
<td>183 (11)</td>
<td>2.2 (1.4-3.3)</td>
<td>28 (11)</td>
<td>96 (6)</td>
<td>1.7 (1.1-2.8)</td>
</tr>
<tr>
<td>Violent acts</td>
<td>60 (32)</td>
<td>339 (20)</td>
<td>1.9 (1.3-2.7)</td>
<td>33 (13)</td>
<td>82 (5)</td>
<td>2.4 (1.5-3.8)</td>
</tr>
<tr>
<td>Criminal acts</td>
<td>77 (40)</td>
<td>482 (28)</td>
<td>1.8 (1.3-2.5)</td>
<td>51 (20)</td>
<td>210 (13)</td>
<td>1.4 (1.0-2.1)</td>
</tr>
<tr>
<td>Sexual debut &lt;15 years</td>
<td>42 (24)</td>
<td>306 (19)</td>
<td>1.5 (1.0-2.1)</td>
<td>75 (30)</td>
<td>294 (19)</td>
<td>1.7 (1.2-2.3)</td>
</tr>
<tr>
<td>Self-harm behaviour</td>
<td>18 (10)</td>
<td>81 (5)</td>
<td>1.8 (1.0-3.2)</td>
<td>65 (26)</td>
<td>184 (12)</td>
<td>2.4 (1.7-3.3)</td>
</tr>
</tbody>
</table>

adjOR = adjusted Odds Ratio  
CI = Confidence Interval  
* adjusted for school year, ethnic background and parental working status

Both boys and girls with CCs reported fewer protective factors than the comparison groups ($p<0.001$). Correspondingly, both genders were also more likely to report clustering of 2-3 and ≥4 health-risk behaviours as compared to their healthy peers ($p<0.001$).

Further analyses were conducted to test the possible effects of concurrent chronic conditions and number of protective factors on the risk for reporting clustered health-risk behaviours, with adjustments for gender, school year, ethnic background and parental working status. As shown in Figure 1, the adjOR for clustered health-risk behaviours was 1.6 in youths with a CC and ≥4 protective factors as compared to healthy peers with corresponding level of protection. The highest risk for clustered health-risk behaviours was found among adolescents with a CC in combination with few protective factors (<4) as compared to healthy peers with more protection (≥4 factors) (adjOR 6.3). Moreover, the risk for clustered health-risk behaviours among adolescents with a CC was increased threefold for those with low protection as compared to those with high protection (adjOR 3.4 [1.7-6.6]).
Figure 1. Combined effect of chronic conditions and number of protective factors on the risk for clustering of health-risk behaviours in adolescents when compared with healthy peers with high protection expressed as adjusted odds ratios with 95% CI.

High protection ≥ 4 protective factors, low protection < 4 protective factors, clustered health-risk behaviours ≥ 4 risk behaviours
Adjusted for gender, school year, ethnic background and parental working status

Paper II

Of the total sample of 4987 adolescents (15-18 years of age), 555 (11%) reported that they had a chronic condition and 2758 (55%) reported that they were healthy. Together these 3313 adolescents constituted the study population.

In the study population, 1693 (51%) were boys and 1705 (51%) attended year 9 of mandatory school (corresponding to 15 years of age). Of the 3313 individuals, 603 (18%) had non-Swedish background and 848 (26%) reported that one or both parents were unemployed or on sick leave.

Significantly more girls than boys suffered from non-neurological conditions, while boys reported ADHD more frequently than girls. Among students with a chronic condition, the parents were more often on sick leave or unemployed compared to healthy peers. This was especially apparent among adolescents with neurological conditions, ADHD and among students reporting a combination of CCs.
In the entire study population, ADHD was reported among 118 (2.4%) of the adolescents. ADHD was more common among adolescents reporting another neurological chronic condition (OR 7.3) or a combination of conditions including a neurological condition (OR 12.7) compared to healthy peers (Table 2).

Table 2. Odds ratios for diagnosed ADHD among groups of adolescents with or without other Chronic Conditions

<table>
<thead>
<tr>
<th></th>
<th>Non-ADHD n (%)</th>
<th>ADHD n (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference group*</td>
<td>2758 (98.3)</td>
<td>49 (1.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>Non-neurological conditions</td>
<td>285 (97.9)</td>
<td>6 (2.1)</td>
<td>1.2 (0.5-2.8)</td>
</tr>
<tr>
<td>Neurological conditions</td>
<td>46 (88.5)</td>
<td>6 (11.5)</td>
<td>7.3 (3.0-18.0)</td>
</tr>
<tr>
<td>Non-neurological and neurological conditions</td>
<td>106 (81.5)</td>
<td>24 (18.5)</td>
<td>12.7 (7.5-21.6)</td>
</tr>
</tbody>
</table>

* Students reporting neither non-neurological nor neurological conditions.

The presence of few protective factors and clustered health-risk behaviours were more common among adolescents reporting CCs than among healthy comparisons (p=0.000). This was more frequently reported among all groups of students reporting CCs but especially if reporting ADHD and if ADHD was reported in combination with other CCs (Figure 2).
Students reporting a chronic condition, but no ADHD, had twice the risk of fewer protective factors as compared to their healthy peers after adjustments for gender, school year, ethnic background and parental working status. Among adolescents reporting ADHD alone, the corresponding adjOR was 5.1. When ADHD was reported in combination with other CCs the adjOR for fewer protective factors increased to 9.3 as compared to the healthy comparison group (Table 3).

With regard to clustering of health-risk behaviours, students reporting a chronic condition had a two-fold increased risk as compared to their healthy counterparts. Correspondingly, adolescents reporting only ADHD had an adjOR for clustered health-risk behaviours of 5.0 and an adjOR of 7.8 when ADHD was combined with other CCs (Table 3).
Table 3. Odds ratios for <4 protective factors and ≥4 health-risk behaviours among the chronic condition groups (as compared to the healthy comparison group)

<table>
<thead>
<tr>
<th>Interaction tested</th>
<th>&lt;4 protective factors, n (%)</th>
<th>Crude OR (95% CI)</th>
<th>AdjOR (95% CI)*</th>
<th>≥4 health-risk behaviours, n (%)</th>
<th>Crude OR (95% CI)</th>
<th>AdjOR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy comparison group</td>
<td>219 (9)</td>
<td>1.0</td>
<td>1.0</td>
<td>176 (18)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Non-neurological conditions</td>
<td>39 (15)</td>
<td>1.9 (1.3-2.7)</td>
<td>1.8 (1.2-2.7)</td>
<td>34 (27)</td>
<td>1.7 (1.1-2.6)</td>
<td>1.7 (1.0-2.7)</td>
</tr>
<tr>
<td>Neurological conditions</td>
<td>31 (24)</td>
<td>3.4 (2.2-5.2)</td>
<td>2.8 (1.7-4.5)</td>
<td>28 (44)</td>
<td>3.5 (2.1-5.8)</td>
<td>3.0 (1.7-5.3)</td>
</tr>
<tr>
<td>ADHD</td>
<td>28 (36)</td>
<td>5.9 (3.6-9.5)</td>
<td>5.1 (3.0-8.8)</td>
<td>26 (54)</td>
<td>5.3 (2.9-9.5)</td>
<td>5.0 (2.7-9.4)</td>
</tr>
<tr>
<td>ADHD and other conditions**</td>
<td>16 (52)</td>
<td>11.2 (5.5-22.9)</td>
<td>9.3 (4.1-20.9)</td>
<td>12 (67)</td>
<td>8.9 (3.3-24.0)</td>
<td>7.8 (2.5-24.1)</td>
</tr>
</tbody>
</table>

*Adjusted for gender, school year, ethnic background and parental working status

**Non-neurological and/or neurological conditions

Paper III

In the study sample of 175 paediatric patients with T1DM age ranged from 5-16 years (mean 11.8 ± 2.7 years) and HbA1c ranged from 43-102 mmol/mol (5.1-10.8%) (mean 65 ± 12 mmol/mol [7.2 ± 1.1%]). The mean HbA1c did not differ significantly between the three participating clinics: 63 mmol/mol (7.0%), 64 mmol/mol (7.1%) and 67 mmol/mol (7.4%), respectively.

Age was significantly associated with HbA1c with mean HbA1c of 63 ± 10 mmol/mol (7.0% ± 0.9%) among 5-11-year-olds and 66 ± 13 mmol/mol (7.3% ± 1.2%) among 12-16-year-olds (p=0.04). Having HbA1c >73 mmol/mol was significantly more common in the older age group and among children having had their diabetes disease for more than 5 years. More girls than boys tended to have a high HbA1c. Among the 12-16-year-olds, the distribution of HbA1c >73 mmol/mol was 30% among girls and 17% among boys (ns.).

In the total group of patients with T1DM, the prevalence of domain scores above the 90th percentile, and above the 75th percentile in the executive domain (23%), were in accordance with the historic normative group (132). The same pattern was seen for the different age groups. When stratifying for age, 21% of the 5-11 years old patients and 24% of the 12-16-year-olds presented mild problems in the executive domain (ns.).

Definite memory and learning problems were associated with high HbA1c, particularly in the older age group (12-16-year-olds).

In the final model, restricted to the 12-16 year old patients, associations between outcome in the FTF-domains and HbA1c were analysed taking gender, age at diabetes onset and duration of the disease into account. Significant associations were found between definitive learning problems, memory and mild executive dysfunction and high HbA1c when gender was included.
in the model. The associations were, however, strengthened when age at onset and disease duration were taken into account (Table 4). The stronger associations between FTF scores and high HbA1c-level in the fully adjusted analyses could be explained by the fact that younger age at diabetes onset (<6 years of age) and a longer disease duration (≥5 years) tended to be related to a higher prevalence of HbA1c>73 mmol/mol but a lower prevalence of definite problems in learning and memory among 12-16-year-olds (data not shown).

Table 4. Associations between domain scores in the Five to Fifteen questionnaire and HbA1c-levels in 104 12-16 years old patients with type 1 diabetes

<table>
<thead>
<tr>
<th>Domain</th>
<th>HbA1c &gt;73 mmol/mol n (%)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR* (95% CI)</th>
<th>Adjusted OR** (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive dysfunction #</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>15 (62.5)</td>
<td>1.0</td>
<td>2.4 (0.9-6.5)</td>
<td>2.7 (1.0-7.6)</td>
</tr>
<tr>
<td>Yes</td>
<td>9 (37.5)</td>
<td></td>
<td></td>
<td>3.1 (1.1-9.1)</td>
</tr>
<tr>
<td>Memory problems ##</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>19 (79.2)</td>
<td>1.0</td>
<td>3.3 (0.9-11.8)</td>
<td>3.8 (1.0-14.7)</td>
</tr>
<tr>
<td>Yes</td>
<td>5 (20.8)</td>
<td></td>
<td></td>
<td>5.0 (1.2-20.1)</td>
</tr>
<tr>
<td>Learning problems ##</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>17 (70.8)</td>
<td>1.0</td>
<td>3.7 (1.2-11.6)</td>
<td>3.9 (1.2-12.7)</td>
</tr>
<tr>
<td>Yes</td>
<td>7 (29.2)</td>
<td></td>
<td></td>
<td>5.0 (1.5-17.2)</td>
</tr>
</tbody>
</table>

# Scores above the 75th percentile, ## Scores above the 90th percentile
*Adjusted for gender, **Adjusted for gender, debut <6 years of age, duration >5 years

Paper IV

In total, the study recruited 241 (51 %) adolescent patients (12-18 years old) with type 1 diabetes mellitus (T1DM) from four diabetes centres. The mean age, age of diabetes onset, diabetes duration, HbA1c, number of outpatient visits and gender distribution did not differ between respondents and non-respondents.

Age of the participating patients ranged from 12-18 years (mean 15.2 ± 2.0 years) and HbA1c ranged from 30-130 mmol/mol (mean 65.9 ± 14.0 mmol/mol). The mean HbA1c in the four centres (62.0, 64.5, 67.4 and 68.5 mmol/mol) did not differ significantly.

The adolescents’ and parents’ rating of the T1DM patients executive problems did not differ at a significant level between participating centres (data not shown). Self-rated executive problems were, however, more often reported among participating girls than boys in both the full sample of adolescents (n=238) and after the restriction to adolescents having a parent rating their executive functioning (n=167). The reported prevalence of self-
rated executive problems was 27% in girls versus 15% in boys \( (p=0.032) \) in the full sample and 23% versus 7% \( (p=0.005) \) in the restricted sample. The same pattern was seen for considerable self-rated executive problems reported by 22% of the girls and 8% of the boys \( (p=0.005) \) in the full sample and correspondingly by 17% versus 5% \( (p=0.014) \) after the restriction to adolescents with parent response. An opposite pattern in gender distribution was noted when the 167 parents, with a child completing BRIEF-SR, rated their child’s executive functions. Executive problems were indicated in 25% of the boys and 12% of the girls \( (p=0.028) \) and considerable executive problems were reported for 19% of the boys and 9% of the girls \( (p=0.045) \). Diagnosed ADHD before participating in the study was affirmed by six patients and seven parents (one girl, six boys), corresponding to 1% of the girls and 6% of the boys \( (p=0.118) \).

In Table 5, the distribution of gender, age and diabetes related variables in participants with and without reported executive problems is shown. Patient- and parent-rated executive problems were associated with mean HbA1c >70 mmol/mol and any HbA1c >80 mmol/mol, while patient-rated executive problems also were associated with any HbA1c >70 mmol/mol. Both patient- and parent-rated executive problems were related to low physical activity. Further, parent-rated executive problems were associated with >8 outpatient visits as well as with episodes of hypoglycaemia (Table 5). However, no significant associations were found between socio-demographic factors and executive problems (data not shown).
Table 5. Distribution of diabetes related variables among adolescent diabetes patients with and without executive problems as rated by the patient and the parent, respectively.

<table>
<thead>
<tr>
<th>Executive problems</th>
<th>Patient rating (^a) (BRIEF-SR GEC T-score ≥60)</th>
<th>Parent rating (^b) (≥4 scores in either or both domains of the ADHD-RS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No problems N=172 %</td>
<td>Executive problems N=45 %</td>
</tr>
<tr>
<td>Gender, girl</td>
<td>47 64 0.032</td>
<td>55 33 0.028</td>
</tr>
<tr>
<td>Age, ≥15 years</td>
<td>50 64 0.114</td>
<td>46 39 0.511</td>
</tr>
<tr>
<td>Mean HbA1c &gt;70 mmol/mol</td>
<td>30 58 0.000</td>
<td>30 52 0.017</td>
</tr>
<tr>
<td>Any HbA1c &gt;100 mmol/mol</td>
<td>7 7 1.000</td>
<td>6 15 0.085</td>
</tr>
<tr>
<td>Any HbA1c &gt;80 mmol/mol</td>
<td>29 47 0.025</td>
<td>28 46 0.045</td>
</tr>
<tr>
<td>Any HbA1c &gt;70 mmol/mol</td>
<td>47 78 0.000</td>
<td>47 64 0.083</td>
</tr>
<tr>
<td>Any HbA1c &gt;60 mmol/mol</td>
<td>76 84 0.182</td>
<td>72 82 0.265</td>
</tr>
<tr>
<td>&gt;8 outpatient visits</td>
<td>17 27 0.135</td>
<td>17 36 0.015</td>
</tr>
<tr>
<td>Smoker</td>
<td>2 5 0.277</td>
<td>2 0 1.000</td>
</tr>
<tr>
<td>Physical activity ≤2 times/week</td>
<td>46 78 0.000</td>
<td>47 69 0.025</td>
</tr>
<tr>
<td>Ketoacidosis</td>
<td>2 0 1.000</td>
<td>2 3 0.563</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>18 11 0.267</td>
<td>15 30 0.041</td>
</tr>
<tr>
<td>Diabetes onset &lt;6 years of age</td>
<td>30 29 0.861</td>
<td>27 24 0.755</td>
</tr>
<tr>
<td>Diabetes duration ≥5 years</td>
<td>65 69 0.635</td>
<td>63 58 0.580</td>
</tr>
</tbody>
</table>

\(a\) = all BRIEF-SR questionnaires completed by patients  
\(b\) = all ADHD-RS completed by parents

As shown in Table 6, adolescents with T1DM and reported executive functioning problems had an almost three times higher risk for adverse outcomes such as high mean HbA1c, many outpatient visits and low level of physical activity when compared to patients without such problems after full adjustments in the logistic regressions. With full adjustments for gender, age, diabetes centre, diabetes onset < 6 years of age and diabetes duration ≥ 5 years the adjOR for a high mean HbA1c was 2.9 in adolescents with self-rated executive problems as compared to those without. The corresponding adjOR for a high mean HbA1c was 3.2 in adolescents with parent-rated executive problems. Self-rated executive problems were significantly associated with >8 outpatient visits with an adjOR of 2.8 and parent-reported executive problems resulted in a corresponding adjOR of 3.0. Similarly a strong association was seen between self-rated executive functioning and low physical
activity, adjOR 3.7, and also in adolescents whose parents rated executive problems, adjOR 3.2 (Table 6).

Table 6. Crude and adjusted odds ratios between self- and parent-rated executive problems in adolescents with T1DM and high mean HbA1c (>70 mmol/mol), >8 outpatient visits and low physical activity.

<table>
<thead>
<tr>
<th></th>
<th>Patient-rated executive problems a (BRIEF-SR GEC T-scores ≥60)</th>
<th>Parent-rated executive problems b (≥4 scores in either or both domains of the ADHD-RS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean HbA1c &gt;70 mmol/mol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>3.3 (1.7-6.4)</td>
<td>2.5 (1.2-5.4)</td>
</tr>
<tr>
<td>adjOR* (95%CI)</td>
<td>3.0 (1.5-6.1)</td>
<td>3.1 (1.4-7.1)</td>
</tr>
<tr>
<td>adjOR** (95%CI)</td>
<td>2.9 (1.4-5.9)</td>
<td>3.2 (1.4-7.2)</td>
</tr>
<tr>
<td>&gt;8 outpatient visits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.8 (0.8-3.9)</td>
<td>2.7 (1.2-6.3)</td>
</tr>
<tr>
<td>adjOR* (95%CI)</td>
<td>2.4 (1.0-5.4)</td>
<td>2.5 (1.1-6.0)</td>
</tr>
<tr>
<td>adjOR** (95%CI)</td>
<td>2.8 (1.1-6.6)</td>
<td>3.0 (1.2-7.3)</td>
</tr>
<tr>
<td>Physical activity ≤2 times/week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>4.2 (1.9-9.4)</td>
<td>2.5 (1.1-5.7)</td>
</tr>
<tr>
<td>adjOR* (95%CI)</td>
<td>3.8 (1.7-8.7)</td>
<td>3.1 (1.3-7.3)</td>
</tr>
<tr>
<td>adjOR** (95%CI)</td>
<td>3.7 (1.6-8.5)</td>
<td>3.2 (1.3-7.6)</td>
</tr>
</tbody>
</table>

a = all BRIEF-SR questionnaires completed by patients
b = all ADHD-RS completed by parents
* Adjusted for gender and age
**Adjusted for gender, age, diabetes centre, diabetes onset < 6 years of age and diabetes duration ≥ 5 years
Discussion

Main findings

- Chronic conditions were associated with few protective factors and clustered health-risk behaviours.
- Girls with chronic conditions encompassed less individual protective factors compared to their healthy peers and compared to boys.
- All individual health-risk behaviours tended to be overrepresented among boys who reported a chronic condition.
- The combination of chronic conditions and low numbers of protective factors was found to be especially hazardous and associated with an increased risk of clustered health-risk behaviours.
- ADHD was more common among adolescents with other chronic conditions, especially among adolescents with neurological conditions.
- The pattern of few protective factors and clustering of health-risk behaviours among adolescents with chronic conditions was aggravated in the presence of ADHD.
- Definite memory and learning problems as well as mild executive problems were associated with HbA1c >8.0% (73 mmol/mol), among adolescents with T1DM.
- Executive functioning problems in adolescents with T1DM were associated with HbA1c >70 mmol/mol, many outpatient visits and low physical activity.
- Girls with T1DM tended to self-report executive functioning problems to a larger extent than boys, while parents rather reported these problems in boys.

Protective factors and health-risk behaviours among adolescents with chronic conditions

This thesis concludes that adolescents with chronic conditions are encompassed by fewer protective factors and engage in more health-risk behaviours than their healthy peers. The combination of chronic conditions and low numbers of protective factors was found to be especially hazardous and was associated with an increased risk of reporting clustered health-risk behaviours. As a group, adolescents with chronic conditions are thus triply
disadvantaged by their chronic condition, low numbers of protective factors and exposure to health-risk behaviours.

The present findings are in accordance with earlier studies stating that adolescents with disabilities are less exposed to protective factors (36, 48) and that adolescents with chronic illnesses are at risk for clustering of health-risk behaviours (43-46). Still, the combined effect of chronic conditions and low numbers of protective factors on clustered health-risk behaviours has not been reported before.

Protective factors

Due to the increased risk of clustering of health-risk behaviours, it is alarming to simultaneously note that adolescents with chronic conditions also are encompassed by fewer protective factors. One reason for the reported low numbers of protective factors in these adolescents could be the presence of the chronic condition itself, which might impair the adolescents’ opinion about the future, reduce self-esteem and lead to bullying. Furthermore, the presence of the chronic condition might impede participation in school activities (138), resulting in less enjoyment of school and difficulties in passing all subjects.

Another reason that adolescents with chronic conditions show fewer protective factors might be that the chronic condition itself puts strain on family relations (139, 140), sometimes resulting in separation of parents, as was registered among the girls in paper I. However, earlier studies on children
with cancer (141) and other chronic conditions (142) did not demonstrate a higher divorce rate among the involved parents.

Health-risk behaviours
Several explanations have been put forth as to why health-risk behaviours often co-occur in adolescents with chronic conditions (43-46). It is argued that young people with chronic conditions may have a greater need to gain peer acceptance, which could lead to participation in health-risk behaviours. These activities have also been described as a way to establish autonomy from parents, feel mature, cope with stress and to feel “normal” (42). Further, it is suggested that some young people whose chronic condition might shorten their life span choose to live their life “to the fullest”, which could include engaging in risky behaviour (46).

Gender differences
One reason for the noted gender difference in reported protective factors might be the different timing of puberty. Girls’ earlier puberty and personal development including emancipation from the family (143) in combination with a chronic condition and its emotional stress on family relationships thereby, might be reflected by a higher rate of separated parents among girls aged 15-17 years.

The 15- and 17-year-old girls with chronic conditions in paper I and II also reported less optimistic thinking about the future but greater ease in talking to parents as compared to the boys. In parallel to the reasoning above, this might be explained by girls’ earlier entrance into the late adolescence phase, characterised by realizing that the future becomes reality, which may engender pessimistic feelings regarding their own possibilities but also more stable relations to other persons within and outside the family (143).

Our observed gender difference in health-risk behaviours in youths with chronic conditions are in line with earlier studies, where it is stated that boys are at higher risk for adjustment problems than girls (144). In contrast to others (138, 145), however, we noted that boys with a chronic condition were more prone to drug use than healthy boys. As in other studies, we showed that chronically ill or disabled girls are more likely to use drugs (145) and engage in violent acts (48), but also to engage in early sexual activities (48, 145) and acquire self-harm behaviour/suicidality (48), to a higher degree than healthy peers. One hypothesis may be that by interfering with development of the personal identity in adolescent girls a chronic condition results in lower self-esteem that might be linked to early sexual debut and self-harm behaviour.
Coexisting ADHD

ADHD was more prevalent among adolescents with other chronic conditions, especially among adolescents with neurological conditions, which is in line with earlier studies (33, 146-150). ADHD in children has been reported to be related to greater impairment of social and psychosocial functioning among parents (151), which may result in poorer protection of the adolescent. Since both genetic (82, 89, 152) and environmental factors have been implicated in the aetiology of ADHD (82, 97) the presence of executive functioning problems among parents may result in fewer protective factors surrounding the adolescent.

The fact that ADHD as such is associated with impaired impulse control (82) and health-risk behaviours (93, 153-155) may to a great extent explain the high reported levels of health-risk behaviours among adolescents with chronic conditions and coexisting ADHD.

The association between both few protective factors and clustered health-risk behaviours among adolescents with non-neurological conditions, neurological conditions and ADHD, respectively, remained after adjustment for socio-demographic factors. This implies that this pattern cannot solely be explained by a poor social environment but rather by factors related to the chronic conditions themselves.

Diabetes and coexisting neurodevelopmental problems

Paediatric patients with T1DM and concomitant definite learning and memory problems had high HbA1c to a significantly larger extent than the patients without neurodevelopmental problems. This association was especially seen among 12-16-year-olds who are likely to manage their diabetes treatment more or less independently. Moreover, adolescent patients having mild problems in executive functioning also demonstrated a clear association with high HbA1c, when gender, early onset and long duration were taken into account, in paper III. In paper IV executive functioning problems were associated with HbA1c >70 mmol/mol, many outpatient visits and low physical activity, after adjustments for gender, age, diabetes centre, early onset and long duration.
Diabetes control

Intact learning, memory and executive functions are of high importance for independent management of the diabetes treatment. The findings that such problems were associated with high HbA1c in adolescents with T1DM when gender, early onset and long duration were controlled for – indicate that neurodevelopmental problems per se may influence the individual’s capacity to manage the diabetes treatment.

The patients with parent-rated executive functioning problems in paper IV had a higher frequency of many outpatient visits, compared to patients without these problems. Still, these patients present with poor metabolic control, which implies that the present diabetes care should be even more adapted and tailor the treatment according to the needs of patients with executive functioning problems.

It is worrying that patients with executive functioning problems in paper IV reported low levels of physical activity. It has been shown that individuals with ADHD improve their mood and motivation for cognitive tasks after physical exercise (156). Also, regular physical activity is recommended for children and adolescents with T1DM (62). Ways to improve physical activity in this patient group needs to be expanded.

Gender differences

Self-rated executive functioning problems were more frequent in girls, while parents identified these problems to a larger extent in boys. Metabolic control has been shown to be poorer among girls than boys with T1DM (55). Moreover, girls’ executive problems, ADHD and autism spectrum disorders are frequently unnoticed and undiagnosed (91). It is thus important that girls with poor metabolic control are acknowledged and that executive problems are screened for and thoroughly investigated in this patient group.

Previously, an association between emotion regulation problems and high HbA1c has been reported for boys, but not for girls (157). However, that particular study was based on parent-reports of executive problems. Also in paper IV, parents tended to notice executive problems in boys but not as frequent in girls.

Cause of neurodevelopmental problems in patients with T1DM

The noted possible association between neurodevelopmental problems and higher age at diabetes onset/shorter diabetes duration in paper III is likely to reflect that recent diagnosis of a demanding disease, such as diabetes, during adolescence might be more challenging and difficult to cope with than having the diagnosis earlier in life. These findings are in line with earlier studies.
also revealing neurodevelopmental and psychiatric problems shortly after diabetes onset in adolescence (125). Environmental stress influences the expression of neurodevelopmental problems, such as ADHD (82, 158). To get a challenging disease like diabetes is stressful (103) and thus, it is likely that a recent diabetes diagnosis aggravates underlying neurodevelopmental problems.

Earlier, a bidirectional relationship between executive functions and glycemic control has been suggested in adolescents with T1DM: Individuals with executive problems were likely to experience difficulties in accomplishing diabetes care tasks resulting in suboptimal glycemic control. Moreover, individuals with poor glycemic control were likely to experience executive problems due to glucose depletion (61). Also, children without diabetes but with ADHD have been reported to have higher HbA1c than healthy individuals suggesting an altered glucose homeostasis in individuals with ADHD (159).

Earlier studies report mild cognitive problems both in children (103-109) and adults (79, 110, 111) with T1DM. These cognitive dysfunctions have been related to an early onset and/or long duration of the disease (106-108, 110-113, 116, 160, 161). This association was not seen in this thesis where patients with a lower age at diabetes onset seemed to be less likely to have definite problems in memory and learning, as compared to paediatric diabetes patients being older at onset. The same trend was found for mild executive problems.

Surprisingly, no association was found between executive problems and ketoacidosis in paper IV. However, hypoglycaemia was associated with parent-rated considerable executive problems. Severe hypoglycaemia has been suggested to cause executive problems (107, 108) but it should be kept in mind that executive problems may lead to difficulties in calculating insulin doses and consequent administration of too large doses in turn causing hypoglycaemia. Difficulties to notice early signs of hypoglycaemia may also contribute.

Neurodevelopmental impairments in patients with T1DM may be difficult to detect since symptoms of poor metabolic control might overlap with symptoms of various neurodevelopmental problems, i.e. inattention, externalizing behaviour and learning difficulties. This is confirmed by the fact that the majority of the adolescents with executive functioning problems in paper IV had not previously received a neurodevelopmental/neuropsychiatric assessment. Also, the overall rate of diagnosed ADHD was 3% in paper IV, which is in agreement with previous studies on patients with diabetes (162) but somewhat lower than the general worldwide prevalence of ADHD of about 5% in children and adolescents (32).
Methodological considerations

External validity

Paper I and II were cross-sectional, school-based studies, including all adolescents attending school year nine of mandatory school and year 2 of post mandatory school in the whole county of Sörmland. Since year 2 is attended by 90% of Swedish adolescents, most adolescents in the county of Sörmland were exposed to the questionnaire.

According to Statistics Sweden, the county of Sörmland had a total population of 267,500 inhabitants in 2008 and 272,500 inhabitants in 2011. The proportion of young people (0-19 years old) was the same in Sörmland as in all of Sweden (24% in 2008 and 23% in 2011) as was the proportion of people with foreign origin (17% in 2008 and 20% in 2011). In 2008 14% of the children in Sörmland lived in low-income families compared to 12% in all of Sweden. In 2011 the overall unemployment rate was 9% in Sörmland, compared to 8% in Sweden as a whole. Thus the socio-economic situation in Sörmland was slightly poorer than that in Sweden in general. ADHD is known to be associated with socio-economic deprivation (163) and thus ADHD could have been more common in the studies from Sörmland. However, the differences in socio-economy in Sörmland compared to the rest of Sweden were subtle and the prevalence of ADHD in paper II was in fact lower (2.4%) than that in international studies (5%) (32). In general, the socio-demographics of Sörmland resembles that of Sweden in fairly well and thus the results from paper I and II should be applicable to adolescents with chronic conditions in other parts of Sweden.

Further, in paper I-III good response rates (80-82%) were obtained and thus good representativeness, which allays major concerns about selection-bias in the study sample. However, the response rate in study IV was lower. Due to practical reasons such as limited patient/parent time available for questionnaire completion as well as limited personal resources in some of the diabetes teams, only 51% of eligible patients completed the questionnaire. When registry data was used, the non-respondents revealed no significant difference in mean age, age of diabetes onset, diabetes duration, HbA1c, number of outpatient visits or gender distribution compared to the respondents.

According to the 2014 annual report from SWEDIABKIDS the distribution of HbA1c and mean HbA1c of the participating centres in paper IV resembles the national variation (57). Thus, the participating centres can be considered representative for Swedish paediatric diabetes care and the results in paper IV should be applicable to other diabetes teams in Sweden.
Internal validity

All four studies have been based on previously used questionnaires, validated screening instruments and solid registry data. Paper I and II were based on the questionnaire Life and Health in Youth, containing questions that have been used in other large school-based, published, studies (130, 131). Questions were identically formulated for the different age groups and appeared both in the 2008 and the 2011 questionnaires. Further, questionnaires were checked for misleading data and such cases were omitted from further analyses.

In paper I, II and IV the adolescents themselves completed the questionnaires, anonymously, without insight of school personal or health care professionals. This should enable a more truthful picture of the adolescents’ perceived life situation than interview studies in which the participants are exposed to an unknown interviewer.

In paper III and IV the validated questionnaires, FTF, BRIEF-SR and ADHD-RS, targeting neurodevelopmental problems in the participating age groups were used. However, in paper IV different questionnaires were used to report executive problems from adolescents (BRIEF-SR) and parents (ADHD-RS), making direct comparisons between adolescent responses and parent responses difficult. Further, some patients came to the clinic alone and no parent report was obtained. Some patients also had difficulties completing the extensive BRIEF-SR questionnaire. Those could be the ones with the largest executive problems. However, analysis of the distribution of executive functioning problems revealed no significant differences, even though the response rate differed between the centres.

Some concerns regarding selection bias need to be raised also for paper I and II. No special schools for children with intellectual disabilities were included. These schools were attended by approximately 1% of the adolescents. It was not possible to study the special situation and needs of this group. It has been reported that adolescents with intellectual disabilities participate in more health-risk behaviours than healthy peers (164). Further, students lost due to truancy and students not continuing on to post mandatory school could also be more likely to engage in health-risk behaviours. The loss of these groups would have biased the results towards normality.

It has been reported that adolescent thinking is more focused on the present, compared to the adult long-term reflections. This could have affected the responses in paper IV, when patients and parents were asked to respond to questions concerning their feelings/behaviours the previous six months. Hypothetically, parents might have easier responding to such long-term questions, but the results in paper IV revealed executive problems in 20.7% of patient responses and 18.5% in parent responses. This allays concerns about information bias due to differences in long-term reflections.
Finally, bias due to confounding was controlled for in the adjusted multivariate regression analyses performed as a last step of the statistical analyses in all the papers.

Reliability

The reported level of chronic conditions and the associations between chronic conditions, few protective factors and clustering of health-risk behaviours were consistent in Life and Health in Youth 2008 and in 2011, which indicates a good reliability in paper I and II. Further, the results in paper IV are in line with the results in paper III, even though different screening instruments and different study populations were used. This also ensures good reliability of the results.

Moreover, in paper IV patients and parents were invited to complete questionnaires, yielding a broader picture of the adolescent’s everyday situation. Parents confirmed the associations between executive functioning problems and poor diabetes control, reported by the adolescents. However, the gender distribution in executive functioning problems differed in adolescent reports and parent reports. This knowledge is new and highlights the importance of listening both to parents and adolescent patients.

In order to fully assess executive functioning, it can be claimed that teacher reports also should be collected. This was not accomplished in these studies, but is part of the further assessment offered patients with indications of severe executive problems/suspected ADHD.

In the power calculation performed prior to paper IV, a response rate of 80% was estimated and required in order to reveal the requested differences. The lower response rate in paper IV probably resulted in less significant associations than expected.

Despite the low response rate in paper IV, all studies revealed similar associations between executive functioning problems/ADHD and a vulnerability to few protective factors, clustering of health-risk behaviours and poor diabetes control, respectively. However, all studies were of cross-sectional design and causality could thus not be completely outlined. Longitudinal studies are needed in order to fully establish causal associations.
Clinical implications

Regardless of the reason for the described fewer protective factors, clustered health-risk behaviours, the gender differences in protective factors and health-risk behaviours as well as neurodevelopmental problems in patients with T1DM, it is of great importance that health professionals acknowledge the vulnerability of adolescents with chronic conditions, especially if coexisting ADHD is indicated or reported. Both the family and the school constitute target for interventions aiming at ensuring resilience and thus prohibiting the development of health-risk behaviours in these patients. Health care professionals are important both in primary and secondary prevention, and have a role in disseminating knowledge among parents, school staff and significant adults in young people's leisure activities. Secondary prevention, i.e. early identification of risky behaviour through taking of a quality-assured medical history accompanied by strategies aiming at strengthening the protective factors around the patients, should be applied to ensure resilience.

School

It has been suggested that the most effective worldwide interventions to enhance adolescent health are structural changes to improve access to education and employment for young people. Moreover, the increase in mental health problems in Swedish adolescents has been related to poor school achievements and high unemployment rates (2).
According to the bio-psychosocial development theory (7) the future is not comprehended until the late adolescence (17-23 years of age). However, already at the age of 15 years, adolescents need to make extensive decisions about their secondary education and thus their future, even though the brain is not mature enough for such decisions. Supposedly, this puts substantial strain on adolescents.

Paper I revealed that adolescents with chronic conditions did not enjoy school as much as their healthy peers. Earlier it has been demonstrated that children and adolescents with early onset of T1DM show poorer academic skills than healthy peers (116). Also adolescents with ADHD demonstrate academic impairments (165, 166). Thus, school must adapt to children and adolescents with chronic conditions. Adolescents with ADHD and high social acceptance show better academic skills than patients with ADHD and poor social acceptance (165). It has thus been recommended that social acceptance constitutes an important intervention target for improving academic skills among adolescents with ADHD (165).

Health care

The health care system has a crucial role in supporting and promoting adolescent health. This thesis reveals the importance of enhancing the protective factors encompassing patients with chronic conditions, in order to prevent health-risk behaviours. Physical exercise needs to be encouraged among patients with T1DM and ADHD. Nursing empowering interventions are earlier suggested to improve physical activity and prevent obesity in adolescent girls (167). These interventions should include active listening and focus on the goals of the adolescent. Special emphasis should be put on the autonomy of the young person, fun and body image and the adolescents emphasize "Don't tell me what to do" and "Don't put me down,"(167). These suggestions could be generalized into most health promoting interventions in adolescents.

Chronic conditions

During adolescence, the individual develops from a child into an independent adult. The health care system needs to encourage this transition in adolescents with chronic conditions. Parents may need special education, preferably as peer-to-peer education, targeting this transition (168).

Adolescents, compared to adults, are relatively more prone to positive feedback and less avoidant in response to negative feedback. This is consistent with recent studies of brain development, as well as epidemiological data on various types of risky behaviour, and may have important practical implications for the prevention of adolescent risk taking (20). Health care
personal are thus encouraged to focus on positive feedback to adolescent patients rather than negative feedback.

Type 1 diabetes

Adolescents with poor and rapidly deteriorating metabolic control report lower parental monitoring and frequency of help with diabetes management, lower functional autonomy, and lower self-control than others (64). It has therefore been recommended that parents remain involved in the adolescents’ diabetes treatment (169). Moreover, since friends are extremely important, especially in mid-adolescence, they are also recommended to be involved in the diabetes care (169). Friends and family should help with reminders about blood sugar measurements and insulin injections. However, these reminders must be agreed upon, in order to avoid contra-productive nagging (170).

The ISPAD (International Society for Pediatric and Adolescent Diabetes) guidelines recommend the following methods in the care of adolescent patients:

- Adolescents should be central in the communication, with discussions primarily focused on him/her;
- Adolescents should be offered time alone with the clinician and conditional confidentiality should be discussed;
- Techniques can be learnt to help the young person resolve ambivalence and change behaviour;
- A psychosocial history is a key part of the adolescent consultation, and should include resilience factors as well as risk factors (171).

Coexisting neurodevelopmental/executive problems

This thesis reveals that coexisting neurodevelopmental impairments in patients with T1DM are associated with poor metabolic control. Moreover, such impairments are important to address, since they otherwise may lead to ineffective and often inappropriate efforts to intensify diabetes therapy. This, in turn, may compound the distress and in fact worsen diabetes outcomes (172). Consequently, the diabetes care should also include neurodevelopmental/neuropsychiatric competence. Routine screening for executive problems in patients with T1DM should be considered (61, 125, 172) already at diabetes onset (173) or at least for patients with high HbA1c (174). When executive problems are suspected or identified neurodevelopmental/neuropsychiatric counselling should be easily accessible (103). Interdisciplinary diabetes teams with neurodevelopmental/neuropsychiatric competences should be created. The treatment should be simplified as much as possible and tailored according to the cognitive ability of the patient, in order to avoid unrealistic expectations and demands. The surrounding network at
home and at school should help with reminders, which preferably are agreed upon (170). Continuous glucose monitoring (CGM) or flash glucose monitoring (FGM) with rapid feedback may be beneficial.

Transition
As described in the introduction, adolescence is the transitional phase between childhood and adulthood (5, 6). The health care system has to facilitate this transition in patients with chronic conditions. Special attention needs to be put on adolescents with chronic conditions and few encompassing protective factors. As shown in this thesis adolescents with chronic conditions and few protective factors are prone to health-risk behaviours, which may have severe effects on long-term health. Thus the transition process also needs to focus on strengthening protective factors around these adolescents.

It has been established that the most important aspect in successful transition from paediatric to adult care is good coordination between paediatric and adult professionals (175). Further, in paediatrics, the transition process is initiated by providing opportunities for young people to see their doctor/nurse on their own (176) in order to encourage autonomy (177). In the adult care, adolescent development needs to be understood (176). Joint clinics between paediatric and adult health-care can improve the transfer, promote a collaborative approach, facilitate continuity of care and build confidence from both medical and patient perspectives (176). The paediatric team is asked to follow up the transition process (177). Finally, patients should be included in decision-making processes around transition services, in order to encourage youth-focused service developments (176, 178). This will help achieving optimal outcomes in young people with chronic illness (176).
Conclusion

Chronic conditions in adolescents were associated with few protective factors and clustered health-risk behaviours. The combination of chronic conditions and low numbers of protective factors was found to be especially hazardous and associated with an increased risk of clustered health-risk behaviours. In the presence of ADHD, the pattern of few protective factors and clustering of health-risk behaviours among adolescents with chronic conditions was aggravated. Further, ADHD was more common among adolescents with other chronic conditions, particularly neurological conditions.

Moreover, definite memory and learning problems as well as mild executive problems were associated with poor metabolic control, among adolescents with T1DM. Executive functioning problems were also associated with many outpatient visits and low physical activity. Finally, girls with T1DM tended to self-report executive functioning problems to a larger extent than boys, while parents rather reported these problems in boys.

Knowledge about factors influencing treatment adherence and life in general is essential in the work with chronically ill adolescents. Among these adolescents the association between risk and protective factors for development of health-risk behaviour is of special importance. Focus must be put on enhancing protective factors in order to avoid health-risk behaviours.

Detection of coexisting neurodevelopmental problems, such as ADHD, is also essential, since these problems can influence treatment adherence, health-risk behaviours and school achievements. Patients with suspected coexisting neurodevelopmental problems should be assessed with regard to cognitive functions. Consequently, both health care and school should be tailored and take the individual’s specific need of cognitive support into account. This knowledge is required by professionals working with chronically ill adolescents at all levels.
Future perspectives

This thesis stresses the importance of listening to the voice of young people with chronic conditions. The importance of taking coexisting ADHD into account when analysing health-risk behaviours in adolescents with chronic conditions, is also highlighted. Based on these aspects, patients with indications of neurodevelopmental problems in the FTF-questionnaire (paper III) were interviewed concerning problems with the diabetes treatment and suggested improvements in the diabetes care. These interviews will constitute a further study.

Patients with indications of executive functioning problems in the BRIEF-SR and/or ADHD-RS (paper IV) were assessed concerning co-existence of neurodevelopmental/neuropsychiatric disorders. The results of these assessments will constitute a future study. Further, it would also be of interest to outline how occurrence of various neurodevelopmental problems affects the diabetes care. Due to the relatively low prevalence of for instance autism spectrum disorders, larger studies, maybe register based, are required. Also, longitudinal studies are essential to fully outline the association between neurodevelopmental problems and T1DM as well as the implication of these problems in patients with T1DM.

Quality of life in patients with T1DM is shown to be similar to healthy peers, although girls with T1DM reported lower quality of life than boys (179). Poor diabetes-related quality of life is associated with depression and poor metabolic control (180). It would be of interest to assess quality of life among patients with T1DM and coexisting executive functioning problems, compared to the quality of life of patients with T1DM and no neurodevelopmental problems. Metabolic control needs to be taken into account in these analyses.

Further, intervention studies are required, in order to outline effective methods of support for patients with diabetes and coexisting neurodevelopmental/neuropsychiatric problems. These interventions should preferably be multidisciplinary involving psychologists, occupational therapists, diabetes nurses, latest diabetes appliances and school programmes.

Since the brain develops until at least the mid 20s, another intervention would be to develop transition programmes for patients T1DM in general and patients with T1DM and coexisting neurodevelopmental problems in particular. When established, their effectiveness, measured by HbA1c and quality of life before and after transition, should also be studied.
Sammanfattning på svenska


Det övergripande syftet med avhandlingen var att öka kunskapen om faktorer som påverkar behandlingen och livssituationen för ungdomar med kroniska sjukdomar. Specifika syften var att utröna i vilken grad svenska ungdomar med olika kroniska sjukdomar, inklusive ADHD, rapporterar skyddsfaktorer och riskbeteenden, jämfört med sina jämnåriga samt att utvärdera betydelsen av skyddsfaktorer för utvecklandet av riskbeteenden bland dessa ungdomar. Förekomst av utvecklingsneurologiska funktionsproblem bland ungdomar med diabetes typ 1 studerades också, liksom kopplingen mellan utvecklingsneurologiska funktionsproblem och dålig blodsockerkontroll/högt HbA1c. Slutligen studerades betydelsen av exekutiva funktionsproblem för ungdomars diabeteskontroll.
**Metod:** I delarbete I och II användes frågeformuläret ”Liv och Hälsa Ung” som delades ut till alla elever i årskurs nio och år två på gymnasiet i Sörmland 2008 (n=5771) och 2011 (n=5550). Förekomst av skyddsfaktorer och riskbeteenden jämfördes mellan ungdomar med olika kroniska sjukdomar och friska jämföringsgrupper. I delarbete III användes det på barn och ungdomar utvärderade frågeformuläret ”Fem till femton” i en multicenterstudie av 175 pediatriska patienter med diabetes typ 1. Blodsockerkontrollen bland patienter med tecken på utvecklingsneurologiska funktionsproblem jämfördes med patienter utan tecken på sådan problematik. I delarbete IV användes frågeformulären BRIEF och ADHD Rating Scale samt data från Barndiabetesregistret SWEDIABKIDS, i en multicenterstudie bland 241 ungdomar med diabetes typ 1. Diabeteskontrollen bland patienter med tecken på exekutiva funktionsproblem jämfördes med patienter utan sådan problematik.

**Resultat:** Förekomst av kronisk sjukdom var kopplat till få skyddsfaktorer och anhopning av flera riskbeteenden. Kombinationen av kronisk sjukdom och få skyddsfaktorer var extra ökad risk för anhopade riskbeteenden. Vid samsjuklighet i ADHD förvärrades också mönstret av få skyddsfaktorer och anhopning av riskbeteenden. ADHD var vanligare bland ungdomar med andra kroniska sjukdomar, speciellt bland ungdomar med sjukdomar utgående från nervsystemet. Klara minnes- och inlärningsproblem samt milda exekutiva problem var kopplade till dålig blodsockerkontroll, framförallt bland ungdomar som i större utsträckning förväntas sköta sin diabetesbehandling själva. Exekutiva funktionsproblem var också kopplade till många mottagningsbesök och låg grad av fysisk aktivitet. Slutligen rapporterades exekutiva funktionsproblem ofta av flickor än av pojkar, emedan föräldrar angav dessa problem bland pojkar i högre utsträckning.

**Slutsats:** Kunskap om faktorer som påverkar behandlingsresultat och livet i allmänhet är oerhört viktigt i arbetet med kroniskt sjuka ungdomar. Skyddsfaktorerna och riskbeteenden stärker för att kunna förebygga riskbeteende. Förekomst av samsjuklighet i utvecklingsneurologiska/neuropsykiatriska funktionsproblem, såsom ADHD, måste identifieras och belysas eftersom sådan problematik kan påverka individens behandling, riskbeteenden och skolresultat.
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