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COMORBIDITY BETWEEN NEURODEVELOPMENTAL DISORDERS AND CHILDHOOD-ONSET TYPE 1 DIABETES

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Comorbidity between Neurodevelopmental Disorders and Childhood-onset Type 1 Diabetes

Thesis for Doctoral Degree (Ph.D.)

By

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"It always protects, always trusts, always hopes, always perseveres.

Love never fails."

Popular science summary of the thesis

Imagine you're holding two jigsaw puzzles, one that maps out childhood-onset type 1 diabetes, and another that represents neurodevelopmental disorders like attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder, and intellectual disability. This thesis delves into the intricate spaces where these two puzzles might intertwine, examining their interconnectedness and its impacts on people's health and educational outcomes.

The first piece we put down sought to investigate the direct link from childhood-onset type 1 diabetes and the risk of subsequent neurodevelopmental disorders. We discovered that those with childhood-onset type 1 diabetes faced a heightened risk of developing neurodevelopmental disorders, , a risk that escalated when glycemic control wasn't optimal. The second piece of the puzzle focused on shared familial liability between childhood-onset type 1 diabetes and neurodevelopmental disorders. We noticed a pattern: not only were those with childhood-onset type 1 diabetes more likely to be diagnosed with neurodevelopmental disorders, but so were their full siblings. Moving on to the third piece, we examined how a neurodevelopmental disorder might affect an individual's diabetes management in the long run, and observed that neurodevelopmental disorders, notably ADHD and intellectual disabilities, associated with increased risk of poor glycemic control and diabetes-related complications like nephropathy and retinopathy. Finally, the fourth piece focused on how having both type 1 diabetes and ADHD might impact one's educational achievements. The data suggested that children and adolescents with both conditions seem to face more challenges in achieving the expected educational milestones.

While our puzzle isn't yet complete, every piece of evidence we uncover draws us nearer to understanding the intricate relationship between childhood-onset type 1 diabetes and neurodevelopmental disorders. More importantly, it paves the way for enriching the lives of those affected, from health outcomes to academic achievements.

Abstract

Childhood-onset type 1 diabetes and neurodevelopmental disorders, including attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder, and intellectual disability, globally represent substantial health challenges. Each condition places a substantial challenge on the individuals, their families, and healthcare systems. The comorbidity between these two types of disorders has been a research focus, with findings suggesting a higher prevalence of neurodevelopmental disorders among individuals with childhood-onset type 1 diabetes. However, the underlying mechanism of this comorbidity remains largely unknown, and the potential alteration in the health and socio-economic outcomes due to this comorbidity remains unexplored. This thesis aimed to elucidate the potential mechanisms behind the comorbidity between childhood-onset type 1 diabetes and neurodevelopmental disorders and explore its impact on health and education outcomes, with the goal of improving early detection, prevention, and management strategies to enhance the quality of life for the affected children and adolescents.

In Study I, we examined the impact of childhood-onset type 1 diabetes and the role of glycemic control on the risk of subsequent neurodevelopmental disorders. We found that individuals with childhood-onset type 1 diabetes had a higher risk of developing neurodevelopmental disorders than the general population. Notably, this risk was highest among those with less optimal glycemic control. These findings provided insight into the role of glycemic control, a crucial diabetes-related factor, in the occurrence of comorbidity between childhood-onset type 1 diabetes and neurodevelopmental disorders.

In Study II, we investigated the potential contribution from shared familial liability to the comorbidity between childhood-onset type 1 diabetes and neurodevelopmental disorders. We found that the elevated risk of neurodevelopmental disorders did not only appear in individuals with childhood-onset type 1 diabetes but also in their full-siblings. The general family co-aggregation pattern and the results of the quantitative genetic modeling, however, did not conclusively show that familial liability contributes to the comorbidity. This ambiguity underscores the need for subsequent research to further elucidate the underlying causes of this comorbidity.

In Study III, we explored the impacts of neurodevelopmental disorders on long-term glycemic control and the risk of diabetic complications in individuals with childhood-onset type 1 diabetes. We found that neurodevelopmental disorders, particularly ADHD and intellectual disability, were associated with increased risk of poor glycemic control and diabetic complications such as nephropathy and retinopathy. These observations highlight that taking neurodevelopmental aspects into account can be crucial when

designing interventions and follow-ups for individuals with childhood-onset type 1 diabetes.

In Study IV, evaluated the interplay between childhood-onset type 1 diabetes, ADHD, and academic outcomes, spanning from compulsory education to university levels. We found that children and adolescents with both type 1 diabetes and ADHD were significantly less likely to achieve educational milestones, crossing different education levels, and had less favorable compulsory school performances compared to their peers without these conditions. These results underline the importance of providing targeted support to minimize the educational gap between the affected children and adolescents and their peers.

List of scientific papers

I. **Liu S**, Kuja-Halkola R, Larsson H, Lichtenstein P, Ludvigsson JF, Svensson AM, Gudbjörnsdottir S, Tideman M, Serlachius E, Butwicka A. Poor glycaemic control is associated with increased risk of neurodevelopmental disorders in childhood-onset type 1 diabetes: a population-based cohort study. Diabetologia. 2021 Apr;64:767-77.

II. **Liu S**, Kuja-Halkola R, Larsson H, Lichtenstein P, Ludvigsson JF, Gudbjörnsdottir S, ... & Butwicka A. Childhood-onset type 1 diabetes and neurodevelopmental disorders: a genetically informative register-based cohort study. (*manuscript*)

III. **Liu S**, Kuja-Halkola R, Larsson H, Lichtenstein P, Ludvigsson JF, Svensson AM, Gudbjörnsdottir S, Tideman M, Serlachius E, Butwicka A. Neurodevelopmental disorders, glycemic control, and diabetic complications in type 1 diabetes: a nationwide cohort study. The Journal of Clinical Endocrinology & Metabolism. 2021 Nov 1;106(11):e4459-70.

IV. **Liu S**, Larsson H, Lichtenstein P, Ludvigsson JF, Gudbjörnsdottir S, Serlachius E, Kuja - Halkola R, Butwicka A. Childhood - onset type 1 diabetes and attention - deficit/hyperactivity disorder with educational attainment: A population - based sibling - comparison study. Acta Paediatrica. 2022 Nov;111(11):2131-41.

Related scientific papers not included in the thesis

I. **Liu S**, Ludvigsson JF, Lichtenstein P, et al. Educational Outcomes in Children and Adolescents with Type 1 Diabetes and Psychiatric Disorders. JAMA Netw Open. 2023;6(4): e238135. Published 2023 Apr 3. doi:10.1001/jamanetworkopen.2023.8135

II. **Liu S,** Leone M, Ludvigsson JF, Lichtenstein P, Gudbjörnsdottir S, Landén M, Bergen SE, Taylor MJ, Larsson H, Kuja-Halkola R, Butwicka A. Early-Onset Type 2 Diabetes and Mood, Anxiety, and Stress-Related Disorders: A Genetically Informative Register-Based Cohort Study. *Diabetes Care*. 2022 Dec;45(12):2950-6.

III. **Liu S,** Leone M, Ludvigsson JF, Lichtenstein P, D'Onofrio B, Svensson AM, Gudbjörnsdottir S, Bergen SE, Larsson H, Kuja-Halkola R, Butwicka A. Association and Familial Co-aggregation of Childhood-Onset Type 1 Diabetes With Depression, Anxiety, and Stress-Related Disorders: A Population-Based Cohort Study. *Diabetes Care*. 2022 Sep;45(9):1987-93

IV. Tate AE, **Liu S**, Zhang R, Yilmaz Z, Larsen JT, Petersen LV, Bulik CM, Svensson AM, Gudbjörnsdottir S, Larsson H, Butwicka A. Association and familial co-aggregation of type 1 diabetes and eating disorders: a register-based cohort study in Denmark and Sweden. *Diabetes Care*. 2021 May 1;44(5):1143-50.

Contents

List of abbreviations

A	Additive genetic factors
ADA	American Diabetes Association
ADHD	Attention-deficit/hyperactivity disorder
ASD	Autism spectrum disorder
C	Shared environmental factors
CI	Confidence interval
DKA	Diabetic ketoacidosis
E	Non-shared environmental factors
GAD65	Glutamic acid decarboxylase 65-kilodalton isoform
GPA	Grade point average
HAB	Habilitation Register
HBA1c	Glycated Hemoglobin
HR	Hazard Ratio
HURPID	Halmstad University Register on Pupils with Intellectual Disability
ICD	International Classification of Diseases
LISA	Longitudinal Integrated Database for Health Insurance and Labor Market Studies
MGR	Multi-Generation Register
NDR	National Diabetes Register
NPR	National Patient Register
NSR	National School Register
OR	Odds ratio
PASTILL	Clinical Databases for Child and Adolescent Mental Health Services in Stockholm
PDR	Prescribed Drug Register
TPR	Total Population Register
β	Regression coefficient

1 Introduction

Type 1 diabetes and neurodevelopmental disorders represent two highly challenging health conditions affecting children and adolescents globally.

Type 1 diabetes, a chronic autoimmune disease that often onset during childhood, results from the destruction of insulin-producing beta cells, leading to a lifetime dependency on exogenous insulin administration and stringent blood glucose management to mitigate the risk of serious complications [1]. Neurodevelopmental disorders, in contrast, are a heterogeneous group of conditions that impair cognitive, social, and motor functioning, with attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and intellectual disability being the most common manifestations [2]. Both type 1 diabetes and neurodevelopmental disorders place significant strain on the affected children and adolescents, their families, and healthcare systems [2,3], underscoring the necessity of understanding their potential interconnections and joint effects.

The complex relationship between childhood-onset type 1 diabetes and neurodevelopmental disorders has gotten extensive attention in recent years, with epidemiological and clinical studies showing an increased prevalence of neurodevelopmental disorders in type 1 diabetes [4-6]. Despite substantial progress in understanding the individual pathogenesis of type 1 diabetes and neurodevelopmental disorders, the etiological underpinnings of their comorbidity remain elusive.

Moreover, neurodevelopmental disorders can introduce difficulties in many parts of life for children and adolescents with type 1 diabetes. Not only can the presence of neurodevelopmental disorders negatively impact diabetes management and self-care tasks, such as blood glucose monitoring and insulin administration [7], but also, the comorbidity may have intersecting impacts on the school experiences of affected individuals, potentially compromising their academic performance and results [8,9]. However, there is a paucity of data on the health and educational results of children and adolescents with this comorbidity.

To address these knowledge gaps, we utilized Swedish data to elucidate potential mechanisms underlying the comorbidity between childhood-onset type 1 diabetes and neurodevelopmental disorders, as well as to investigate potential ramifications of this comorbidity on the health and educational outcomes of children and adolescents, with the goal of paving the way for more targeted prevention, early detection, and optimized management strategies, ultimately improving the quality of life for those affected.

2 Literature review

2.1 Type 1 Diabetes

Type 1 diabetes is a chronic autoimmune disease characterized by the body's immune system attacking the beta cells in the pancreatic islets, leading to minimal or absent endogenous insulin production. Insulin deficiency disrupts glucose uptake and metabolism at the cellular level, causing glucose accumulation in the bloodstream, which, over time, causes injury to various organs in the body [1].

2.1.1 Etiology of type 1 diabetes

Although type 1 diabetes can develop at any age, it typically manifests during childhood (<18 years). It remains one of the most common chronic health conditions among children and adolescents. The number of children with type 1 diabetes has exceeded one million, with a prevalence of 9.5/10,000 globally and 8.6/1,000 in Sweden [10,11], and with an estimated global annual rise of around 3% [12]. The exact cause of type 1 diabetes is not yet fully comprehended; however, it is acknowledged as a multifaceted interaction between genetic predisposition and environmental risk factors [13,14].

Empirical evidence derived from family- and twin-based studies suggest that approximately 50% of the susceptibility to type 1 diabetes is attributable to genetic factors, thereby signifying a noteworthy influence of genetic predisposition [15]. Thus far, genetic investigations have revealed over 60 loci linked to the susceptibility of type 1 diabetes, collectively accounting for approximately 80% of the genetic risk [16]. Various factors influence genetic susceptibility to disease, including the major histocompatibility complex region, which is located on chromosome 6p21 and contains the human leukocyte antigen (HLA) gene. While studies have shown that this region contributes to about 50% of the overall genetic risk associated with the disease [17], a portion of the risk remains unexplained; recent findings suggest the involvement of previously unidentified loci, particularly those harboring low-frequency or rare genetic variants [18].

Multiple environmental risk factors have also been linked to type 1 diabetes [19,20]. Early-life exposure to viral infections, such as enteroviruses, can substantially contribute to islet inflammation and increase the risk of developing type 1 diabetes [21]. Dietary factors during infancy, childhood and adolescence, such as vitamin D levels and its pathway components [22], and the diversity of the gastrointestinal microbiome [23], have also been identified as potential risk factors. Recent research also has linked childhood obesity to beta-cell stress as a possible contributing factor [24].

2.1.2 Management of type 1 diabetes

The optimal management of type 1 diabetes necessitates the maintenance of blood glucose levels in proximity to the norm. The recommended glycated hemoglobin

(HbA1c) target for children and adolescents with type 1 diabetes, as per the American Diabetes Association (ADA), is less than 7% (63 mmol/mol) [25]. Suboptimal glycemic control can lead to a variety of life-course outcomes for affected individuals, such as an increased risk of acute and chronic diabetic complications [8,19], underperformance in academics [26–28], limited employment opportunities in adulthood [29,30], decreased quality of life [31,32], and premature mortality [33–35].

The regulation of blood glucose levels is primarily achieved through the use of insulin, whereby the administration of exogenous insulin enables patients to mimic the secretion of insulin in the body [14]. The procedure requires the administration of several insulin doses throughout the day, encompassing nocturnal basal insulin, inter-meal insulin to compensate for carbohydrate consumption, physical exertion, and supplementary doses for hyperglycemia. Since insulin is a peptide hormone, it must be administered via subcutaneous injection to ensure proper absorption into the bloodstream. Two prevalent insulin delivery methods in pediatric diabetes management are multiple daily injection therapy using insulin pens and continuous subcutaneous insulin infusion system therapy, also known as insulin pumps [36]. In addition to the administration of insulin, it is imperative to consider other variables such as dietary adjustments (monitoring carbohydrate intake) and consistent physical activity to attain optimal diabetes management and sustain appropriate glycemic control [37,38].

The complex nature of diabetes management demands significant cognitive and executive function engagement, rendering the task of managing type 1 diabetes that begins in childhood a constantly evolving process. During the initial phases, the caregiver bears the main responsibility for management. Over a period of time, the management process experiences a shift towards a collaborative dynamic between the caregiver and child, ultimately resulting in the child taking up self-management responsibilities. The advancement in the management of diabetes in children requires the continuous acquisition and improvement of skills and implementation of psychological adjustments to effectively control their diabetes throughout their lifespan [39]. The dynamic nature of diabetes management necessitates that affected individuals develop adequate proficiency and psychological adaptation over time [40].

2.1.3 Complications of type 1 diabetes

Type 1 diabetes is often associated with two acute complications, namely diabetic ketoacidosis (DKA) and hypoglycemia. These acute complications arise due to temporary fluctuations in blood glucose levels. DKA is a pathological state that arises due to hyperglycemia, leading to lipolysis and subsequent ketone body formation [41,42]. This metabolic derangement can have fatal consequences if left untreated. DKA is frequently instigated by non-administration of insulin, ailment, or undetected type 1 diabetes. In the absence of proper medical intervention, DKA may lead to a state of

unconsciousness or mortality. Moreover, DKA may result in hospitalization and an interruption in routine activities, such as absence from school and social engagements, in the affected individuals. The occurrence of hypoglycemia, a state of low blood sugar, can be attributed to an imbalance between insulin doses, carbohydrate intake, and physical activity [43]. Hypoglycemia can lead to acute symptoms such as confusion, dizziness, and blurred vision, potentially compromising daily activities and safety. If left untreated, severe hypoglycemia can result in loss of consciousness, seizures, and in extreme cases, can be life-threatening.

Type 1 diabetes is also associated with increased risks of chronic microvascular and macrovascular complications [44,45]. Microvascular complications are complications that affect small blood vessels. For example, diabetic retinopathy, which refers to damage to the blood vessels in the retina resulting in vision impairment or even blindness; diabetic nephropathy, which involves damage to the kidneys, leading to impaired kidney function and potential kidney failure; and diabetic neuropathy, which is characterized by nerve damage, often causing symptoms like tingling, numbness, and pain. Macrovascular complications affect the body's large blood vessels, such as cardiovascular disease and peripheral arterial disease. Several risk factors contribute to the complications mentioned above, including but not limited to hypertension, dyslipidemia, tobacco use, and physical activity.

Primary factors driving the development of these chronic complications in type 1 diabetes include the cumulative effects of persistently elevated blood glucose levels (hyperglycemia) [46]. The pervasive nature of hyperglycemia can cause harm and functional disruptions to a myriad of cells, tissues, and organs. Beyond hyperglycemia, the length of time a person has lived with diabetes significantly influences the progression of such complications. This is partially due to the prolonged exposure to hyperglycemia, coupled with other metabolic alterations such as lipid irregularities and elevated oxidative stress. To address these concerns, standard diabetes management guidelines advocate for individuals, especially children and adolescents, to undergo consistent health assessments starting five years post-diagnosis [25]. These evaluations are crucial in identifying and managing potential risks like hypertensive inclinations, albuminuria, and diabetic retinopathy.

2.2 Neurodevelopmental Disorders

Neurodevelopmental disorders, as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, are a heterogeneous group of conditions that manifest early in the developmental period and cause differing developmental and functioning deficits in the nervous system [47]. ADHD, ASD, and intellectual disability are common neurodevelopmental disorders causing significant impairments. Each of these conditions presents unique challenges and can have a significant impact across

personal, social, educational, and/or occupational domains among the affected individuals.

2.2.1 Attention-deficit/hyperactivity disorder

ADHD is typified by the clinical manifestations of inattention, hyperactivity, and impulsivity [48]. The precise cause of ADHD is yet to be fully understood, although it is widely accepted to be a complex condition with genetic components and multiple contributing environmental factors. The heritability of ADHD was estimated to be 70-80% based on twin studies, suggesting that if one twin has ADHD, there's a 70-80% chance the other twin will also have the condition if they are identical [49]. Environmental factors, crossing prenatal, perinatal, or postnatal factors, were also identified to contribute to the development of ADHD, such as premature delivery, low birth weight, and early childhood exposure to lead or other toxins, traumatic brain injury, or social adversity, such as childhood maltreatment [50].

2.2.2 Autism spectrum disorder

ASD is characterized by difficulties with social interaction and communication and restricted and repetitive behaviors, interests, or activities. As a spectrum disorder, the symptoms and severity of ASD can vary widely from person to person [51]. Some individuals with ASD may need significant support in their daily lives, while others may need less support and, in some cases, live entirely independently. Like ADHD, the etiology of ASD is complex and multifactorial, involving a mixture of genetic and environmental factors. Empirical evidence from twin and family studies indicates a significant degree of heritability, which explains approximately 50-80% of the susceptibility to ASD [52]. The remaining variability (20-50%) is presumably attributable to environmental influences, such as advanced parental age during childbearing and prematurity [53].

2.2.3 Intellectual disability

Intellectual disability is characterized by persistent limitations in intellectual functioning and adaptive behaviors. This condition is estimated to affect approximately 1% of the global population [54]. The causes of a fraction of intellectual disability are identifiable genetic factors or chromosomal abnormalities, such as Down syndrome (trisomy 21 syndrome) and Fragile X syndrome. The present thesis investigated intellectual disability other than this cause-specific intellectual disability, for which the etiology seems complex and remains unclear. Like other neurodevelopmental disorders, studies examining the impact of environmental risk factors on intellectual disability have yielded inconsistent findings [55]. Despite the identification of over a dozen factors, such as prenatal, perinatal, and neonatal factors, that have a significant association with an

elevated risk of intellectual disability, a meta-analysis revealed that none of these factors could establish definitive causal associations [56].

While the exact causes of ADHD, ASD, and intellectual disability are not fully understood, research suggests that they result from a complex interplay of genetic, environmental, and neurological factors [57]. In addition, the early manifestation of these conditions has led to the hypothesis that adversities encountered during the early stages of life may play a role in the condition's development. Despite the suggestive nature of these findings, further research is required before definitive conclusions can be drawn.

2.3 Comorbidity between Type 1 Diabetes and Neurodevelopmental Disorders

2.3.1 Etiology of the comorbidity

Although the exact etiology of type 1 diabetes and neurodevelopmental disorders remains elusive, the etiology of each condition appears to be multifactorial, with an intricate interplay between genetic predisposition and diverse environmental risk factors.

A unique biological mechanism appears to be involved in the susceptibility to neurodevelopmental disorders among those with type 1 diabetes. The previous research conducted by our team showed a heightened susceptibility to neurodevelopmental disorders in individuals with childhood-onset type 1 diabetes, even after accounting for various environmental risk factors [4]. Additionally, a statistically significant increase in the risk of neurodevelopmental disorders was observed in individuals with type 1 diabetes, which was not persisted in their healthy siblings. The discovery mentioned above implies that the unique environmental factors, specifically those related to diabetes, play a significant role in the development of neurodevelopmental disorders in individuals with type 1 diabetes, in addition to the influences from genetic and environmental factors that are shared between siblings.

Maintaining glycemic control, which involves regulating blood glucose levels, is a critical aspect of managing diabetes that significantly impacts an individual's physical and psychological health. The significant biological evidence supports the hypothesis that glycemic control plays a causal role in the development of neurodevelopmental disorders in children and adolescents diagnosed with type 1 diabetes [58,59]. Research has been focused on the impact of disrupted glucose metabolism in type 1 diabetes on brain development and function for numerous decades due to its adverse effects. According to Cameron et al.'s synthesis of various studies, it has been established that preserving glucose homeostasis is of utmost importance for the proper development of the brain and the adequate functioning of the central nervous system in children and adolescents with type 1 diabetes. Imbalances during crucial stages of brain development

can result in adverse consequences [59]. The available evidence indicates that dysglycemia has a detrimental effect on brain development, particularly in pediatric populations. Several studies have suggested that suboptimal glycemic control has a negative impact on cognitive functions [60-62]. In particular, deficits have been found in attention (the ability to focus on specific stimuli from the environment), working memory (the ability to temporarily collect certain information to execute cognitive tasks), as well as intellectual abilities. The results of a population-based study conducted in Denmark revealed a correlation between hyperglycemia occurring within the first two years following the onset of diabetes and heightened susceptibility to psychiatric disorders [6]. However, it should be noted that in this thesis, neurodevelopmental disorders were aggregated and classified under the broad and general term of "any psychiatric disorders".

In summary, although a correlation has been established between inadequate glycemic control and potential brain dysfunctions, it remains uncertain whether these neurocognitive impairments are linked to a heightened risk of clinically diagnosed neurodevelopmental disorders or if they are simply subclinical challenges.

2.3.2 Consequences of the comorbidity

The presence of comorbid neurodevelopmental disorders and type 1 diabetes can pose additional difficulties for affected individuals, given the symptoms associated with neurodevelopmental disorders, especially deficits in cognitive ability, learning, attention, and memory, which may result in the affected individuals experiencing reduced capacity to perform intricate diabetes management tasks. This, in turn, may negatively impact their ability to maintain optimal glycemic control. Elevated levels of blood glucose and consequent fluctuations may not only augment the likelihood of complications associated with diabetes, but also have the potential to adversely impact the development and functioning of the brain. However, there exists a dearth of knowledge regarding the impact of comorbid neurodevelopmental disorders on individuals with childhood-onset type 1 diabetes.

2.3.2.1 Health consequences

Several cross-sectional studies have investigated the management of blood glucose levels in individuals with type 1 diabetes and neurodevelopmental disorders. Overall, individuals with comorbid ADHD were found to have more inadequate glycemic control than those with type 1 diabetes alone, while no such association was observed in individuals with ASD [63-66]. However, prior studies have encountered limitations due to variations in the definition of ADHD and ASD, which have predominantly relied on self- or parent-reported questionnaire data or medical charts that lack specific diagnostic criteria [63-67]. Additionally, glycemic control in these studies was generally assessed by a point value of HbA1c. Although Macek et al. conducted a study examining comorbid

ADHD in type 1 diabetes, with HbA1c measured every three months for 12 months (4-time points for measurement) [64]. The authors defined the study as a case-control and cross-sectional study with no longitudinal analysis of glycemic control. Furthermore, there is a lack of research investigating the management of glycemic control in individuals with type 1 diabetes who also have comorbid intellectual disabilities.

The presence of other psychiatric disorders, including but not limited to depression, anxiety, and eating disorders, has been linked to a heightened susceptibility to diabetic complications in individuals with type 1 diabetes [68,69]. Contemporary diabetes guidelines emphasize that pediatric patients who experience psychological challenges are at a heightened risk of developing diabetic complications [70]. Nonetheless, there is a significant research gap exists concerning the long-term diabetic complications in individuals with comorbid childhood-onset type 1 diabetes and neurodevelopmental disorders.

2.3.2.2 Educational consequences

The negative impact of childhood-onset chronic health conditions on educational achievements and academic performance has been acknowledged for a considerable period of time. It can be anticipated that children and adolescents who have comorbid type 1 diabetes and neurodevelopmental disorders may encounter additional obstacles in their academic pursuits within the school setting.

Due to the unique characteristics of intellectual disability and ASD, which include cognitive impairments and significant social detachment, those diagnosed with either intellectual disability or ASD are frequently provided with specialized educational services [71]. Whereas children and adolescents with ADHD, providing no comorbid intellectual disability, are typically given the option to attend mainstream schools. However, type 1 diabetes and ADHD can substantially impair an individual's daily functioning, generating research interest in the educational outcomes of affected children and adolescents over the long term [3,72]. Despite this, the potential correlation between childhood-onset type 1 diabetes and ADHD has not been thoroughly examined in research on academic achievement and educational outcomes.

3 Research Aims

The overarching aim of this thesis was to investigate the causes and consequences of comorbidity between childhood-onset type 1 diabetes and neurodevelopmental disorders by addressing the following study-specific objectives:

Study I: To investigate the effect of childhood-onset type 1 diabetes on the risk of subsequent neurodevelopmental disorders and the role of glycemic control in this association.

Study II: To explore the familial co-aggregation between childhood-onset type 1 diabetes and neurodevelopmental disorders and estimate the contribution of genetic and environmental factors to their co-occurrence.

Study III: To investigate whether comorbid neurodevelopmental disorders in childhood-onset type 1 diabetes are associated with long-term glycemic control and risk of diabetic complications.

Study IV: To examine the association of childhood-onset type 1 diabetes and attention-deficit/hyperactivity disorder with educational outcomes from primary to tertiary level.

4 Materials and Methods

All studies included in this thesis utilized data from several Swedish national and quality registers (Figure 1), which provide longitudinally collected administrative data on the population level.

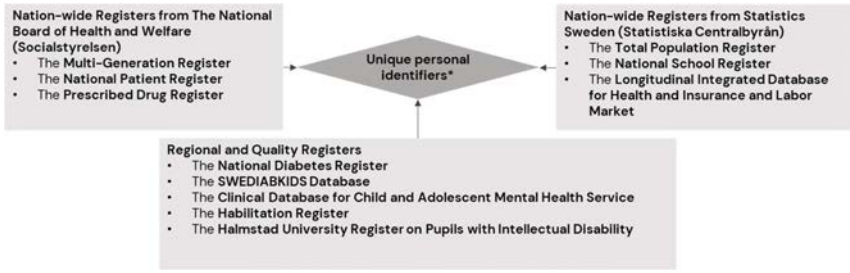

Figure 1 Swedish registers used in this thesis.
**Each individual residing in Sweden is assigned a unique personal identity number. It is a 10-digit number consisting of the individual's birth date and a four-digit code, which is crucial for accessing various services in Sweden, such as healthcare and education. The 'unique personal identifier' referred to here is a replacement, i.e., a serial number of the unique personal identity number (personnummer in Swedish).*

4.1 Data Sources – Swedish National Registers

4.1.1.1 The Total Population Register

Managed by Statistic Sweden, the Total Population Register (TPR) is an extensive database that holds demographic and vital data on all individuals living in Sweden since 1964 [73]. Each individual registered in TPR is assigned a unique personal identity number ('personnummer' in Swedish).

4.1.1.2 The SWEDIABKIDS Database

The SWEDIABKIDS database, established in 2000, is a comprehensive, nationwide registry [74]. SWEDIABKIDS contains data collected from pediatric diabetes care centers across Sweden, and includes details such as age at diagnosis, sex, type of diabetes, blood glucose levels, HbA1c measurements, and treatment regimens, as well as diabetes-related complications, hospitalizations, and comorbidities.

4.1.1.3 The National Diabetes Register

The National Diabetes Register (NDR), established in 1996, is a nationwide database in Sweden [75]. NDR gathers data from various sources, including primary care clinics, specialized outpatient clinics, and hospital-based diabetes care units, and covers information such as the type of diabetes, age at diagnosis, sex, blood glucose control, HbA1c levels, lipid profiles, blood pressure, and prescribed treatments, diabetes-related complications, comorbidities, and mortality.

4.1.1.4 The National Patient Register

The National Patient Register (NPR) is managed by the Swedish National Board of Health and Welfare (Socialstyrelsen) [76]. NPR has been operated since 1964, documenting all visits to inpatient care in Sweden since 1987 and outpatient specialists' care since 2001. Diagnoses are coded using the International Classification of Diseases (ICD) system: the ICD 8th version (ICD-8) was used during 1969–1986, the ICD 9th version (ICD-9) was used during 1987–1996, and the ICD 10th version (ICD-10) has been in use since 1997.

4.1.1.5 The Clinical Databases for Child and Adolescent Mental Health Services in Stockholm

The Clinical Databases for Child and Adolescent Mental Health Services in Stockholm (PASTILL, by its Swedish acronym) is a regional quality register, which collects data from child and adolescent psychiatric inpatient and outpatient care within Stockholm County since 2001 [77].

4.1.1.6 The Habilitation Register

The Habilitation Register (HAB) is a regional quality register launched in 1997 and collects data on using of Stockholm Country Habilitation Services due to disabilities, including neurodevelopmental disorders, such as intellectual disability and ASD [77].

4.1.1.7 The Halmstad University Register on Pupils with Intellectual Disability

The Halmstad University Register on Pupils with Intellectual Disability (HURPID) consolidates data from specialized upper secondary schools targeted to pupils with intellectual disability, including demographic details, diagnostic information, educational assessments, and individualized support measures [78].

4.1.1.8 The Prescribed Drug Register

The Prescribed Drug Register (PDR) is a national database in Sweden that systematically collects and maintains information on prescribed and dispensed medications for the Swedish population [79]. Launched in July 2005, PDR gathers data from all Swedish pharmacies, capturing details on prescribed medication dispensations. It records essential information such as the Anatomical Therapeutic Chemical (ATC) classification code, the dispensed quantity, dosage, and duration of the medication.

4.1.1.9 The Multi-Generation Register

The Multi-Generation Register (MGR) is a nationwide demographic database in Sweden that links information on individuals and their biological parents [80]. MGR comprises data on individuals born in Sweden since 1932 and their parents, creating a vast network of familial connections.

4.1.1.10 The National School Register

The National School Register (NSR) contains information on compulsory school education performance since 1988 [81]. It covers pupils' standardized test grades for all school subjects from all municipal and independent compulsory schools in Sweden.

4.1.1.11 The Longitudinal Integrated Database for Health and Insurance and Labor Market

The Longitudinal Integrated Database for Health Insurance and Labor Market Studies (LISA, by its Swedish acronym) is a comprehensive national database in Sweden that compiles and preserves longitudinal information related to health insurance, the labor market, education, and demographics for the Swedish population [81]. Established in 1990, LISA covers all Swedish residents aged 16 and above and consolidates demographic information; labor market information like employment status, occupation, and income; health insurance information; and education-related data such as level of education and area of study.

4.2 Main Measures

4.2.1 Childhood-onset type 1 diabetes

For Studies I to IV, childhood-onset type 1 diabetes was defined as type 1 diabetes onset and diagnosed before age 18.

In Studies I, III, and IV, childhood-onset type 1 diabetes was identified from the SWEDIABKIDS database and/or the NDR based on their recorded type of diabetes and age at diagnosis. In Study II, childhood-onset type 1 diabetes was identified from the NPR using ICD-codes (ICD-8 and ICD-9: 250; ICD-10: E10) and age at diagnosis. Although ICD-8 and -9 do not distinguish type 1 and type 2 diabetes, type 2 diabetes onset during childhood was infrequent in the Swedish population during that period.

4.2.2 Neurodevelopmental disorders

Neurodevelopmental disorders, including ADHD, ASD, and intellectual disability, were identified from the NPR, PASTILL, HAB, HURPID, and PDR following the criteria shown in Table 1.

Table 1 ICD codes used to identify neurodevelopmental disorders.

	NPR, PASTILL, HAB, HURPID			**PDR**
	ICD-8	ICD-9	ICD-10	ATC-codes
Any neurodevelopmental disorders	Any code from the following specific diagnosis			
ADHD	-	314	F90	N06BA01–02,

				N06BA04, N06BA09
ASD	-	299.0, 299.8	F84.0, F84.1, F84.5, F84.8, F84.9	
Intellectual disability	310-315	317-319	F70-F79	

4.2.3 Glycemic control

For Study I and III, information on HbA1c was obtained from the SWEDIABKIDS database and the NDR, which was reported according to the International Federation of Clinical Chemistry standard with a standard unit of millimoles per mole (mmol/mol). The values have been converted into percentages (%) according to the criteria in the Diabetes Control and Complication Trial [82]. The accuracy of HbA1c measured in the participating clinic units covered by the data sources was ensured by an external quality assessment scheme.

In Study I, glycemic control was reflected by 1) mean HbA1c, which was estimated as the area under the curve divided by the time interval between the first HbA1c value and the last HbA1c value using the trapezoidal methods [83], and 2) point value of HbA1c, which was modeled as a time-varying variable. In Study III, glycemic control was reflected by mean HbA1c, calculated as mentioned above.

4.2.4 Diabetes complications

For Study III, chronic diabetic complications, including diabetic nephropathy and retinopathy, were examined. They were defined based on relevant ICD codes in the NPR and stated diagnosis criteria in the SWEDIABKIDS and the NDR. Details are listed in Table 2.

Table 2 ICD codes and diagnostic criteria used to identify diabetic complications.

	NPR			SWEDIABKIDS and/or NDR
	ICD-8	ICD-9	ICD-10	
Nephropathy				
Any nephropathy	250.04	250D	E10.2	Defined microalbuminuria or macroalbuminuria
Microalbuminuria	-	-	E10.2A	Two positive test results from three samples taken within one year, with albumin: creatinine ratio of 3-30 mg/mmol or urinary albumin of 20-200 µg/min (20-300 mg/L)
Macroalbuminuria	-	-	E10.2B	Two positive test results from three samples taken within one year, with albumin: creatinine ratio >30

				mg/mmol or urinary albumin >200 µg/min (>300 mg/L)
Retinopathy				
Any retinopathy	250.02	250E, 362A	H36	Simplex, preproliferative or proliferative retinopathy or macular pathology
None-proliferative diabetic retinopathy	-	-	H36.A	Simplex and preproliferative retinopathy
Proliferative diabetic retinopathy	-	-	H36.B	Proliferations or earlier laser photocoagulation

4.2.5 Education outcomes

For Study IV, the examined education outcomes comprised compulsory education outcomes and post-compulsory education outcomes. Throughout the timeframe covered by this thesis, every child living in Sweden had an obligation to begin compulsory education at approximately six years old. Compulsory education typically spans nine years, encompassing both primary and lower secondary levels of education. Upon completing the ninth year of compulsory school, students undergo an evaluation to determine their qualifications for a three-year upper secondary school. Following upper secondary school, individuals have the option to pursue higher education at the university level. The examined education outcomes and their criteria, if applicable, are presented in Table 3.

Table 3 Examined education outcomes and their detailed information.

Outcomes	**Detailed criteria/information**
Compulsory education outcomes	*Information obtained from NSR*
Completing compulsory school	Have such a record in the register
Compulsory school performance	*Assessed for individuals who graduated between 1998 and 2012*
Eligibility to upper secondary school	Pass three core subjects (i.e., Swedish, English, and Math)
Grade upon graduation (GPA)	Calculated for the three core subjects and 13 additional subjects. Alphabetical grades were transformed into points: 'Inte Godkänd' (0-points), 'Godkänd' (10-points), 'Väl Godkänd' (15-points), and 'Mycket Väl Godkänd' (20-points)
Post-compulsory education outcomes	*Information obtained from LISA*
Finishing upper secondary school at age 19 Starting university at age 21 Finishing university at age 25	Recorded with such education level in LISA by the expected age*

** The expected age of achieving each of these outcomes was set according to the Statistic Sweden [84].*

4.2.6 Covariates

For Studies I, III, and IV, a range of covariates has been adjusted, with details in Table 4.

Table 4 Covariates and their detailed information.

	Diagnosis codes | Information			**Study**
	Individual level covariates			
Psychiatric diagnoses	ICD-8	ICD-9	ICD-10	I, III, IV
Anxiety disorders	300.00-300.30, 300.50-300.99, 307	300, 300A-300D, 300F-300X, 308-309	F40-F45, F48	
Conduct disorder	-	312	F91	
Eating disorders	-	307B, 307F	F50	
Learning disability	-	315	F81	
Psychotic disorders	295, 297-299	295, 297, 298	F20-F29	
Mood disorders	296, 300.40	296, 300E, 311	F30-F39	
Substance misuse	291, 303, 304	291, 303, 304, 305A, 305X	F10-F19	
Somatic diagnoses				IV
Autoimmune disease	269.00,269.99, 245.03, 243.99, 244.00-244.09, 696.00-696.19,696.98, 712.00-712.50, 242.00-242.20	579A, 245C, 243, 244D, 244W, 244X, 696A-B, 696W, 714A-X, 242A-X	K90.0, E06.3, E03, L40, M05, M06, M08, E05	
Asthma	493.00-493.09	493A-X	J45, J46	
Inflammatory bowel disease	563.10, 563.99, 569.02	555, 556	K51, K50, K52.3	
Epilepsy	345	345	G40, G41	
Chromosomal abnormality	759.30-759.50,759.83,310.5, 311.50,312.50,313.50,314.50,315.50	758	Q90-Q99	I, II, III, IV
Organic brain disorder	-	-	F00-F09	IV
Smoking status	Current or former or never			III
Body mass index	Kg/m^2			
Blood pressure	systolic and diastolic blood pressure (mmHg)			

Blood lipids	High-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides (mmol/L)	
	Parental level covariates	
Parental highest education level	Primary and lower secondary, upper secondary, and post-secondary education	I, III, IV
Parental psychiatric comorbidity	Any diagnosis of psychiatric disorders listed above	I, IV
Parental age at birth	Maternal and paternal age at the child's birth	IV
Parental parity at birth	Maternal and paternal parity at the child's birth	IV

4.3 Study Designs

All studies included in this thesis employed observational study designs. Observational study designs are a category of research methodologies used to investigate patterns, relationships, or phenomena in a real-world setting. By enabling data collection from naturally occurring events, observational study designs serve as a crucial tool for speculating and understanding the complex interplay between exposures and outcomes [85].

4.3.1 Cohort study

A cohort study is a type of observational research design that follows a group of individuals, referred to as a cohort, over a specified period. This study design aims to analyze the relationship between certain independent variables (i.e., exposures, characteristics, or risk factors) and subsequent dependent variables (i.e., outcomes or events) [85]. The primary advantage of cohort study design lies in its ability to establish temporal relationships, estimate the incidence or risk of an outcome in the exposed and non-exposed groups, and examine multiple outcomes in relation to a single exposure at the same time.

4.3.2 Family-based study

4.3.2.1 Familial co-aggregation design

Familial co-aggregation design serves as a research methodology designed to investigate the potential influence of both genetic and non-genetic (i.e., environmental) factors on the co-occurrence between two conditions (e.g., traits) [86].

The interpretation of familial co-aggregation contains two parts [87]. First, suppose the prevalence/incidence of condition/trait B is higher in relatives of individuals with condition/trait A than in relatives of individuals without condition/trait A. This may indicate that familial factors shared among relatives could be involved in the etiology that underlies the occurrence of conditions/traits A and B. Second, if the magnitudes of estimated associations between conditions/traits A and B differ across different types

of relatives, it may suggest the comparative importance of genetic and environmental factors that contribute to the co-occurrence of conditions/traits A and B.

4.3.2.2 Quantitative genetic modeling

Quantitative genetic modeling is used to quantify the relative contribution of genetic and non-genetic factors [88].

One of the common approaches utilizes the different degrees of familial relatedness between full- and maternal half-siblings. Full-siblings share, on average, 50% of their segregating alleles. Maternal half-siblings share, on average, 25% of the segregating alleles. In addition, full- and maternal half-siblings can be assumed to share common environmental factors, given their similar prenatal environment and often shared upbringing environment [89]. In this way, by comparing the concordance rates of the co-occurred conditions between full- and maternal half-sibling pairs, we can determine if genetic influence plays a significant role in the co-occurrence of traits A and B. For instance, if the correlation between condition/trait A in sibling-1 and condition/trait B in sibling-2 is stronger in full-sibling pairs than in maternal half-sibling pairs implies that the covariation between condition/trait A and B is affected by shared genetic factors.

4.3.3 Sibling-comparison study

The sibling-comparison study, which analyzes the exposure-outcome relationship among siblings, is one type of within-cluster comparison design [90]. Within-cluster comparison design is an approach to address confounding issues in observational studies, which ensures that, within the cluster, individuals are conditionally exchangeable for cluster-constant confounding. As illustrated in Figure 2, X and Y represent exposure and outcome in two individuals from the same cluster, i.e., siblings 1 and 2; C denotes cluster-varying confounders, i.e., confounders that are different between siblings 1 and 2, for example, sex and birth year; and U indicates (unmeasured) confounders that are constant for the same cluster, i.e., factors that shared among siblings, such as genetic, environmental and socio-economic status.

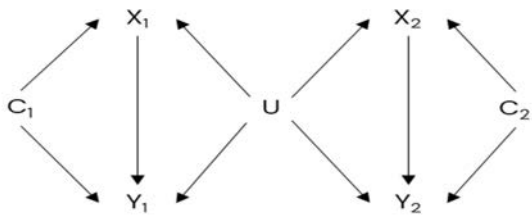

Figure 2 Directed acyclic graph representation of within-cluster comparison design.

The goal of sibling-comparison study is to control for the (unmeasured) familial confounders shared between siblings (U) and provide a more accurate estimate of the exposure-outcome association.

4.4 Statistical Methods

4.4.1 Regression models

4.4.1.1 Cox regression models

Cox regression models analyze the connection between predictors and time-to-event data. They calculate hazard ratios (HR) to reveal how exposure impacts event risk, considering censoring and time-varying variables [91]. Cox model results are often presented as HRs with a 95% confidence interval (95% CI).

4.4.1.2 Logistic regression models

Logistic regression models model the relationship between the binary outcome's exposure and log-odds using a logistic function, which constrains the predicted probabilities between 0 and 1. Logistic model results are often presented as odds ratios (OR) with 95% CI [92].

4.4.1.3 Linear regression models

Linear regression models are a class of statistical techniques that estimate the coefficients, often denoted as β, representing the linear relationship between the exposure and outcome [93].

4.4.2 Generalized estimating equation

Generalized estimating equations are a statistical method for analyzing correlated data, such as longitudinal or clustered observations [94]. Cluster robust variance estimation, or sandwich variance estimation, is a technique that adjusts standard errors to account for intra-group correlation, leading to more accurate hypothesis testing and confidence intervals in the presence of clustered or dependent data.

4.4.3 Structural equation modeling

Structural equation modeling represents a statistical method that integrates both factor and regression analyses to delineate the influence of latent constructs, which are typically unmeasured, on the collected data [95].

In the field of quantitative genetics, structural equation modeling may be utilized to contrast correlations between full-sibling pairs and maternal half-sibling pairs [96]. This comparison assists in segregating the variations noticed in a particular trait or phenotype into fractions credited to additive genetic influences (A), common

environmental factors (C), and distinct environmental elements (E), inclusive of any measurement inaccuracies. Under the presumption that these latent components remain independent, the variance of a phenotype is comprised of the individual variances of A, C, and E, which can be represented as: Variance (Phenotype) = Variance (A) + Variance (C) + Variance (E). As a result, the variance proportion of each latent component is reflective of the degree of impact of genetic and environmental factors on the variation of a phenotype.

The comparison of correlations between full-sibling pairs and maternal half-sibling pairs is predicated on a few specific assumptions: the correlation of A stands at 50% among full-siblings and 25% among maternal half-siblings; C exhibits a correlation of 1 across all siblings, while E shows no correlation among any siblings.

Bivariate models serve to calculate the relative contribution of factors A, C, and E to the total variance of two phenotypes and the covariance between them [97]. In other words, it quantifies the degree to which the same genetic components contribute to two different conditions/traits (termed as the 'genetic correlation') and provides estimates for the relative influence of genetic factors, shared environmental factors, and distinct environmental factors.

4.5 Study-Specific Designs

An overview of the methodology aspects of each study included in the present thesis is presented in Table 5.

Table 5 Overview of the methodology aspects of each study.

Study	Data sources	Study Design	Study Population	Measures	Statistical Methods
I	TPR, SWEDIABKIDS, NDR, NPR, PASTILL, HAB, HURPID, PDR	Cohort study	Individuals with childhood-onset type 1 diabetes and matched references without type 1 diabetes	Exposure: childhood-onset type 1 diabetes, glycemic control Outcome: Any and specific neurodevelopmental disorders	Cox regression models
II	TPR, MGR, NPR, PDR, HURPID	Family-based study	Individuals born in Sweden 1973-2015.	Exposure: childhood-onset type 1 diabetes Outcome: Any and specific neurodevelopmental disorders	Logistic regression models and structural equation modeling
III	TPR, SWEDIABKIDS, NDR, NPR, PASTILL, HAB, HURPID, PDR	Cohort study	Individuals with childhood-onset type 1 diabetes	Exposure: Any and specific neurodevelopmental disorders Outcome: glycemic control, diabetes complications	Logistic regression models (multinomial) and Cox regression models
IV	TPR, MGR, SWEDIABKIDS, NDR, NPR, PDR, NSR, LISA	Sibling-comparison study	Individuals born in Sweden 1981-1995	Exposure: childhood-onset type 1 diabetes and any and specific neurodevelopmental disorders Outcomes: education outcomes	Logistic regression models and generalized estimating equation

4.6 Ethical Considerations

For this thesis, several Swedish Registers were utilized to gather clinical and socio-economic data about the study participants. Ethical considerations in register-based observational studies entail a cost-benefit analysis.

The urgency of behavioral health issues such as neurodevelopmental disorders poses significant societal and personal burdens, especially in individuals with childhood-onset type 1 diabetes. Understanding their causes could facilitate early detection and intervention, reducing the overall disease burden. Randomized controlled trials offer quality evidence but not all research questions can be studied in clinical trials due to practical and ethical reasons, leading to the application of observational studies for etiological and social outcome research. Studies in this thesis provide significant contributions, appealing to practitioners and professionals alike, and directing future research. However, misuse of sensitive personal data could pose risks. The following ethical considerations have been considered to protect the rights, privacy, and well-being of the individuals whose information has been used.

Firstly, like many register-based studies, obtaining informed consent from all study 'participants' was not feasible; however, we have ensured that using registry data without informed consent in this thesis followed Swedish regulations and was approved by the appropriate ethical review board. Second, all data was sourced from Statistic Sweden and the National Board of Health and Welfare. Personal identity numbers have been replaced with unique identifiers that could be linked to the original number through an encrypted file. The encrypted file is stored at official departments responsible for the data linking and remains unknown to the researcher, which minimizes the risk of unauthorized access or data breaches. Thirdly, the studies involved in this thesis have been approved by the relevant ethical review board, which ensures that the proposed projects adhere to ethical guidelines and that the rights of participants are protected. Lastly, we shared the results from these studies via open-assess peer-reviewed journals, ensuring the findings were accessible to the public and other researchers, which promoted transparency, accountability, and the advancement of scientific knowledge.

By addressing these considerations, we ensured that this thesis contributes to advancing knowledge and public health while minimizing any potential risks or harms to the individuals whose data is being used.

5 Results

5.1 Study I: Association Between Glycemic Control and Risk of Neurodevelopmental Disorders in Childhood-Onset Type 1 Diabetes

In this study, we included 8,430 individuals with childhood-onset type 1 diabetes (onset age <18 years) with documented HbA1c within the 1st year after the diabetes diagnosis. For each individual, 10 sex- and birth-year reference individuals from the general population were matched, resulting in a total of 84,300 individuals in the reference group. Follow-up started at the diabetes diagnosis for each individual and his/her matched reference and ended at the first diagnosis of any neurodevelopmental disorder, emigration, death, or December 31st, 2013.

Distributions of sex and birth year were identical between individuals with and without type 1 diabetes, reflecting that the matching process worked well. They were also comparable regarding other psychiatric morbidities before the start of follow-up, parental highest education level, and psychiatric morbidity (data not shown). For those with type 1 diabetes, the median HbA1c was 7.5%, with a frequency of HbA1c measurement of every 3.2 months.

During a median follow-up of 5.6 years, the incidence rate of neurodevelopmental disorders across individuals with and without childhood-onset type 1 diabetes is shown in Table 6.

Table 6 Incidence rate * for neurodevelopmental disorders between individuals with type 1 diabetes and matched reference individuals, according to mean HbA1c levels.

	Matched reference individuals	**Overall, type 1 diabetes**	**Mean HbA1c <7.5%**	**Mean HbA1c 7.5-8.6%**	**Mean HbA1c >8.6%**
Any diagnosis	6.12	7.95	7.05	7.39	11.30
ADHD	4.61	5.93	4.56	5.80	8.99
ASD	1.30	1.68	2.31	1.31	1.50
Intellectual disability	0.61	0.80	0.59	0.82	1.15

** Incidence rate: per 1,000 person-years.*

As demonstrated in Figure 3, overall, type 1 diabetes was associated with elevated risks of any neurodevelopmental disorders, particularly ADHD and ASD. When examining different HbA1c levels, those with mean HbA1c >8.6% had the highest risks for any neurodevelopmental disorders and ADHD.

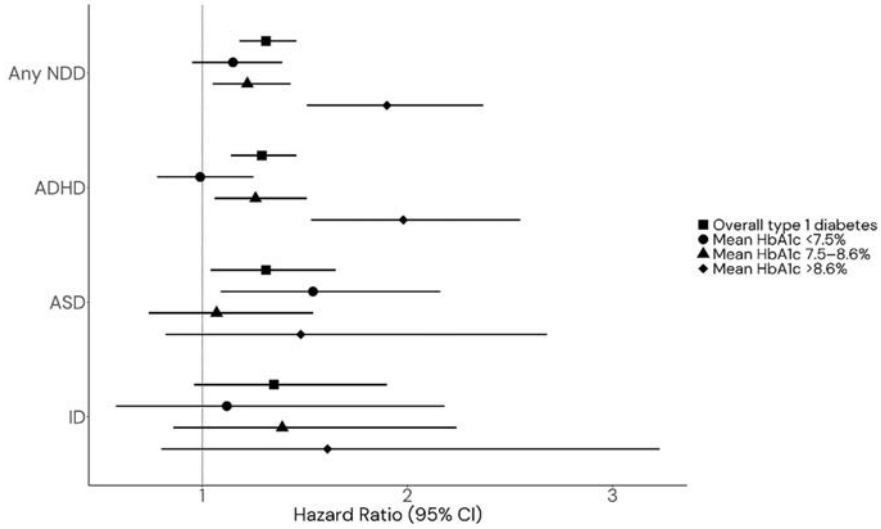

Figure 3 HRs with 95%CIs for neurodevelopmental disorders * between individuals with type 1 diabetes and matched reference individuals, according to mean HbA1c levels.
** Abbreviations: NDD, neurodevelopmental disorders; ID, intellectual disability.*

Figure 4 shows the HRs using time-varying HbA1c among individuals with type 1 diabetes. An increase of 1% in HbA1c was associated with statistically significantly increased risks of any neurodevelopmental disorders, ADHD, and intellectual disability. Compared to individuals with mean HbA1c <7.5%, the risk of neurodevelopmental disorders was much higher in those with higher HbA1c, particularly those >8.6%.

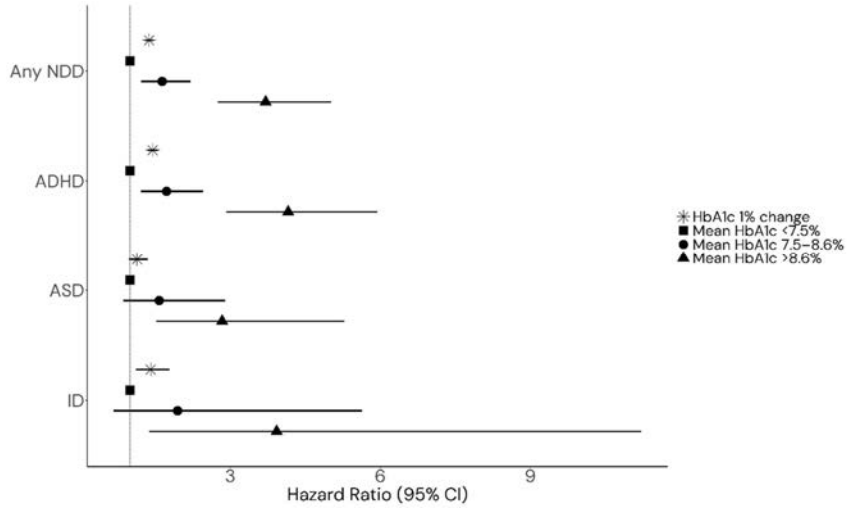

Figure 4 HRs with 95%CIs for neurodevelopmental disorders * among individuals with type 1 diabetes, according to time-varying HbA1c levels.
** Abbreviations: NDD, neurodevelopmental disorders; ID, intellectual disability.*

5.2 Study II: Familial Liability of Childhood-Onset Type 1 Diabetes and Neurodevelopmental Disorders

In this study, we included 4,066,364 individuals born in Sweden between 1973 and 2015. Among them, 23,212 (0.57%) individuals were diagnosed with childhood-onset type 1 diabetes, with a median age at diagnosis of 9.7.

Figure 5 demonstrates the patterns of associations and familial co-aggregations between childhood-onset type 1 diabetes and neurodevelopmental disorders. We observed statistically significant associations of type 1 diabetes with any and specific neurodevelopmental disorders, whereas these associations were substantially attenuated in the familial co-aggregations.

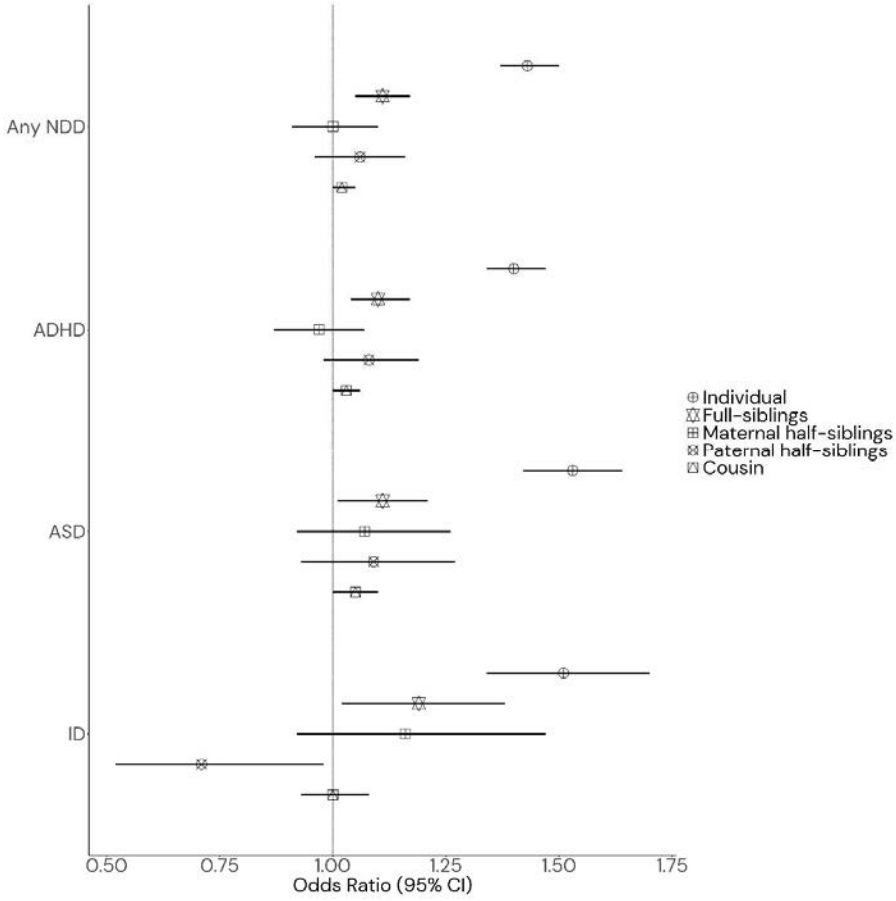

Figure 5 Association and familial co-aggregation of childhood-onset type 1 diabetes with neurodevelopmental disorders *.

** Abbreviations: NDD, neurodevelopmental disorders; ID, intellectual disability.*

The quantitative genetic modeling suggested weak, though statistically significant, phenotypic correlations between childhood-onset type 1 diabetes and neurodevelopmental disorders, with correlation coefficients ranging from 0.06 to 0.08 (Table 7). None of the estimated contributions from A, C, or E was statistically significant.

Table 7 ACE correlations between type 1 diabetes and neurodevelopmental disorders using bivariate ACE models with bootstrap *.

	Any diagnosis	ADHD	ASD	Intellectual disability
r_{ph}	0.07 (0.06, 0.09)	0.06 (0.05, 0.08)	0.07 (0.06, 0.09)	0.08 (0.05, 0.10)
r_A	0.15 (0.00, 0.28)	0.13 (-0.01, 0.27)	0.16 (-0.06, 0.38)	-0.06 (-0.38, 0.26)
r_C	-0.45 (-1.32, 0.42)	-0.55 (-1.58, 0.49)	-0.55 (-1.70, 0.59)	0.41 (-0.58, 1.40)
r_E	0.04 (-0.15, 0.23)	0.02 (-0.20, 0.23)	0.04 (-0.23, 0.31)	0.25 (-0.11, 0.60)

** Abbreviations: r_{ph}, phenotypic correlation; r_A, genetic correlation; r_C, shared environmental correlation; r_E, non-shared environmental correlation; NA, not applicable.*

5.3 Study III: Association of Comorbid Neurodevelopmental Disorders with Glycemic Control and Risk of Diabetic Complications in Childhood-Onset Type 1 Diabetes

In this study, we included 11,326 individuals with childhood-onset type 1 diabetes who were free from diabetic complications at diabetes diagnosis and had documented HbA1c values within 5 years after a diabetes diagnosis. Characteristics of these individuals are presented in Table 8, separated by their comorbid neurodevelopmental disorder status.

Table 8 Selected characteristics of type 1 diabetes with and without comorbid neurodevelopmental disorders.

	No diagnosis	Any diagnosis	ADHD	ASD	Intellectual disability
N (%)	10,562 (93.3)	764 (6.8)	415 (3.7)	89 (0.8)	71 (0.6)
Female, %	45.7	30.2	31.6	25.8	43.7
Median diabetes diagnosis Age, year	9.5	10.3	9.9	10.1	11.0
Median available follow-up year, year	7.4	8.4	8.2	8.2	9.3
Other psychiatric morbidity, %	11.6	43.2	47.5	43.8	21.1
Current or previous smoker, %	11.3	23.8	30.4	12.4	14.1

Overall, compared to those with type 1 diabetes alone, individuals with comorbid neurodevelopmental disorders were more likely to have poor glycemic control (mean HbA1c >8.6%), particularly in those with ADHD (Figure 6). They also showed increased

risks of diabetic nephropathy and retinopathy. In comparison, those with comorbid ASD and intellectual disability showed no statistically significant difference in all the outcomes, except for those with intellectual disability who had a nearly 3-fold increased risk of any diabetic nephropathy.

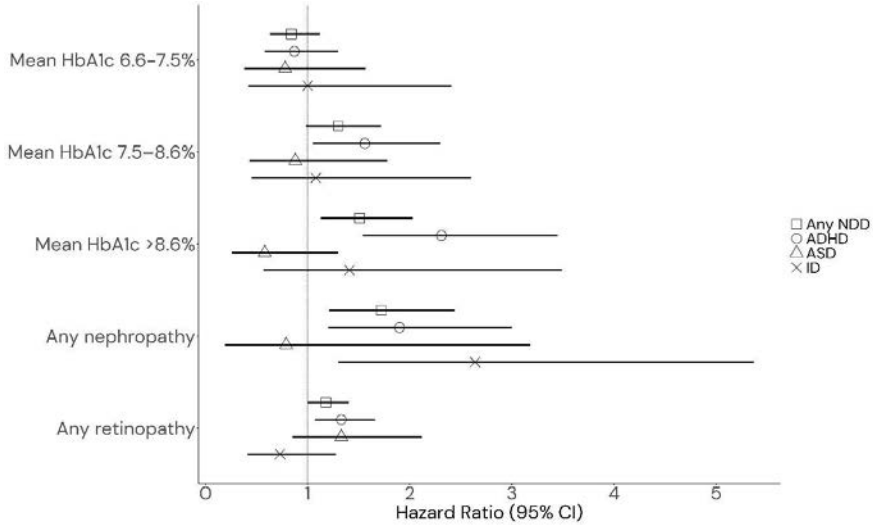

Figure 6 Comparison of glycemic control, risks of nephropathy and retinopathy between individuals with type 1 diabetes with and without comorbid neurodevelopmental disorders *.

** Abbreviations: NDD, neurodevelopmental disorders; ID, intellectual disability.*

5.4 Study IV: Education Outcomes in Individuals with Childhood-Onset Type 1 Diabetes and ADHD

In this study, we included 1,474,941 individuals born in Sweden from 1981–1995 and followed them up until December 31st, 2013. Among these individuals, 9,450 (0.6%) were diagnosed with childhood-onset type 1 diabetes, and 263 of them were also diagnosed with ADHD.

In comparison to their peers without type 1 diabetes and ADHD, individuals with comorbid type 1 diabetes and ADHD had statistically significantly lower odds of achieving education attainment from compulsory school to university or passing all 13 compulsory school subjects (data shown in the supplemental material), as well as fairly lowered GPA (Table 9). These estimates were much lower than those estimated in individuals with type 1 diabetes alone and comparable to those with ADHD alone. Overall, estimates from sibling comparison models were comparable to those from the main analyses, but with less precise estimates indicated by the wide 95% CI.

Table 9 Estimated odds ratio and linear regression coefficients with 95% CI of associations with achieving education outcomes and compulsory school performance among individuals with childhood-onset type 1 diabetes and/or ADHD.

	Adjusted model	Sibling comparison
	OR (95% CI)	
Completion of compulsory school		
No type 1 diabetes or ADHD	1 (Ref)	1 (Ref)
Type 1 diabetes	1.19 (0.97, 1.45)	1.02 (0.69, 1.52)
ADHD	0.44 (0.41, 0.48)	0.40 (0.34, 0.47)
Type 1 diabetes + ADHD	0.43 (0.26, 0.72)	1.21 (0.31, 4.77)
Eligibility to upper secondary school		
No type 1 diabetes or ADHD	1 (Ref)	1 (Ref)
Type 1 diabetes	0.86 (0.80, 0.92)	0.83 (0.72, 0.96)
ADHD	0.26 (0.25, 0.27)	0.30 (0.28, 0.33)
Type 1 diabetes + ADHD	0.26 (0.19, 0.36)	0.24 (0.12, 0.50)
Finishing upper secondary school at the age of 19		
No type 1 diabetes or ADHD	1 (Ref)	1 (Ref)
Type 1 diabetes	0.91 (0.87, 0.96)	0.80 (0.72, 0.88)
ADHD	0.19 (0.18, 0.20)	0.26 (0.24, 0.28)
Type 1 diabetes + ADHD	0.24 (0.17, 0.35)	0.19 (0.09, 0.41)
Starting a university degree at the age of 21		
No type 1 diabetes or ADHD	1 (Ref)	1 (Ref)
Type 1 diabetes	1.08 (1.01, 1.14)	1.08 (0.95, 1.22)
ADHD	0.23 (0.21, 0.26)	0.35 (0.28, 0.44)
Type 1 diabetes + ADHD	0.38 (0.17, 0.90)	0.54 (0.15, 2.01)
		β (95% CI)
GPA, all school subjects		
No type 1 diabetes or ADHD	Reference	Reference
Type 1 diabetes	-0.20 (-0.28, -0.13)	-0.22 (-0.31, -0.13)
ADHD	-3.29(-3.35, -3.23)	-2.20 (-2.29, -2.12)
Type 1 diabetes + ADHD	-3.40(-3.92, -2.89)	-2.29 (-2.99, -1.59)
GPA, core school subjects (Swedish, English, and Math)		
No type 1 diabetes or ADHD	Reference	Reference
Type 1 diabetes	-0.16 (-0.24, -0.09)	-0.10 (-0.18, -0.03)
ADHD	-2.96 (-3.01, -2.91)	-2.27 (-2.32, -2.22)
Type 1 diabetes + ADHD	-3.37 (-3.85, -2.89)	-2.53 (-3.02, -2.04)

6 Discussion

The present thesis utilized extensive population-based registries in Sweden and employed diverse epidemiological methodologies to investigate the association between childhood-onset type 1 diabetes and neurodevelopmental disorders. The comorbidity between childhood-onset type 1 diabetes and neurodevelopmental disorders seems to be primarily influenced by factors related to type 1 diabetes itself, e.g., glycemic control. On the other hand, shared familial liabilities resulting from genetic or environmental factors seem to have a relatively minor impact on this comorbidity. Moreover, this thesis revealed that individuals with childhood-onset type 1 diabetes and neurodevelopmental disorders seem to have increased risks of less optimal diabetes management diabetic complications. Furthermore, this thesis noted a concurrent risk associated with academic achievement and educational outcomes among children and adolescents with both type 1 diabetes and ADHD. Collectively, these findings underscore the intricate interplay between childhood-onset type 1 diabetes and neurodevelopmental disorders, highlighting the need for comprehensive care approaches and informing future research and policy directions in this domain.

6.1 Potential Mechanisms Underlie the Comorbidity Between Type 1 Diabetes and Neurodevelopmental Disorders

Three potential mechanisms have been identified in the investigation of the complex association between type 1 diabetes and neurodevelopmental disorders, which could provide insight into the observed co-occurrence.

Firstly, the potential comorbidity between childhood-onset type 1 diabetes and brain development may be attributed to the direct impact of the former on the latter. An increasing body of research has documented the association between type 1 diabetes and its characteristic symptoms, such as hyperglycemia, hypoglycemia, and DKA, and adverse effects on brain function and development, as observed from both neurodevelopmental and neurodegenerative viewpoints [59,98-100]. Our Study I has also contributed to supporting this hypothesis. In addition, magnetic resonance imaging investigations have demonstrated increased white matter hyperintensities and a more pronounced decline in functional connectivity, which refers to the coordinated functional associations between different brain regions, in individuals with type 1 diabetes compared to the control group [98]. Therefore, existing research indicates that type 1 diabetes and its characteristics exert negative influences on both the structure and function of the brain, potentially leading to the emergence of neurodevelopmental disorders.

Secondly, there has been a longstanding hypothesis suggesting a potential genetic link between childhood-onset type 1 diabetes and neurodevelopmental disorders. One

perspective posits that a body of evidence indicates that various susceptibility genes associated with type 1 diabetes may also play a role in increasing the likelihood of developing neurodevelopmental disorders. One illustrative instance involves the genetic marker known as HLA-DR4, which has been firmly linked to the onset of type 1 diabetes [101]. Also, evidence suggests that this marker is also associated with heightened susceptibility to a range of psychiatric disorders, including those of a neurodevelopmental nature. Meanwhile, many studies have presented contrasting findings. According to a recent meta-analysis conducted on studies examining the relationship between parental autoimmune disorders and neurodevelopmental disorders in their offspring, there is insufficient empirical support to establish a definitive link between shared genetics, and the associations observed between autoimmune diseases, such as type 1 diabetes, and neurodevelopmental disorders [102,103]. Such a lack of shared genetics was somehow consistent with findings from our Study II, where the results do not readily support shared familial liability between type 1 diabetes and neurodevelopmental disorders. Although we observed a slightly, but statistically significant, elevated risk of neurodevelopmental disorders in full-siblings of individuals with type 1 diabetes, quantitative genetic modeling yielded no statistically significant contribution from genetic components.

Thirdly, the sporadic occurrence of autoantibodies may play a role in initiating both disorders. It has been previously determined that four distinct categories of autoantibodies serve as indicators for beta cell autoimmunity in the context of type 1 diabetes. These include islet cell antibodies, antibodies targeting glutamic acid decarboxylase, such as glutamic acid decarboxylase 65-kilodalton isoform (GAD65), insulin autoantibodies, and insulinoma-associated-2 autoantibodies. The autoantibody known as GAD65 has been associated with behavioral dysfunctions [104] and has been observed to have elevated serum levels in children diagnosed with ADHD or ASD [105]. One plausible hypothesis posits that GAD65 functions as an enzyme that plays a role in the synthesis of the neurotransmitter gamma-aminobutyric acid, which is of paramount importance during the initial stages of nervous system development. Furthermore, there exists a correlation between maternal autoantibodies profiles and the likelihood of childhood-onset type 1 diabetes as well as neurodevelopmental disorders in the offspring. This suggests that these profiles may be a common biological risk factor contributing to these conditions' co-occurrence.

It is important to acknowledge that these mechanisms are currently being investigated and are subject to further refinement. Each mechanism offers a distinct viewpoint regarding the interaction between the physiological aspects of childhood-onset type 1 diabetes and the cognitive and behavioral traits associated with neurodevelopmental disorders. In the context at hand, it is imperative to recognize the comprehension of the coexistence of type 1 diabetes and neurodevelopmental disorders should not be

perceived as a segregated procedure, but rather as an intricate system of interconnections. The potential interplay between these mechanisms may lead to distinct patterns of disease initiation and advancement and could also influence the effectiveness of therapeutic interventions.

6.2 Healthcare and Socio-economic Implications of Comorbid Type 1 Diabetes and Neurodevelopmental Disorders

The comorbidity of childhood-onset type 1 diabetes and neurodevelopmental disorders entails an intricate interplay of health outcomes that significantly affects individuals across various dimensions.

At the outset, the existence of neurodevelopmental disorders can pose additional difficulties in the management of diabetes as a result of their effects on neurocognitive function, executive functioning, and behavior. The individual experiencing the comorbidity may encounter challenges in complying with the necessary protocols for managing diabetes, which comprises consistent monitoring of blood glucose levels, maintaining a well-balanced diet, and adhering to prescribed insulin therapy schedules. Non-compliance with prescribed treatment regimens may result in suboptimal glycemic control, subsequently elevating the likelihood of experiencing acute complications such as DKA and hypoglycemia. Over the course of time, individuals may encounter an increased risk of the development of long-term vascular complications. Data from our Study II provides preliminary evidence supporting this hypothesis.

Moreover, the coexistence of these conditions can have a psychological impact, leading to heightened emotional distress, which in turn can affect the management of the diseases and result in a decline in overall quality of life. The co-occurrence of these factors has the potential to exacerbate symptoms associated with depression, anxiety, or other psychiatric conditions, thereby establishing a detrimental cycle characterized by deteriorating mental well-being and suboptimal management of diabetes.

Furthermore, the potential interplay between type 1 diabetes and neurodevelopmental disorders can significantly impact various aspects of health, including sleep patterns and body weight. Disruptions in these domains can further aggravate both metabolic and psychiatric symptoms, thereby presenting additional complexities in their management.

Finally, the coexistence of both conditions may have an influence on individuals' engagement with the healthcare system, potentially leading to encounters with stigma or misconceptions from healthcare providers. This, in turn, could contribute to the complexity of the overall health outcomes experienced by these individuals.

The management of comorbid type 1 diabetes and neurodevelopmental disorders has significant socio-economic implications that extend to various aspects of an individual's life. The educational outcomes exhibit the most immediate effects. Children and adolescents who experience these comorbid conditions may frequently encounter substantial obstacles in their educational pursuits [8,106-108]. This comorbidity may contribute to both physical and cognitive impediments. Physically, there might be an increase in school absences due to necessary medical consultations or episodes related to diabetes management. Cognitively, potential manifestations may include diminished attention, challenges in information processing, and overall learning difficulties. Collectively, these factors might correlate with decreased academic performance. Longitudinally, this could potentially increase the risk of early educational discontinuation or barriers in transitioning to higher levels of education.

The management of comorbid conditions also presents a substantial burden on the families of individuals who are affected. The requirement for ongoing attentiveness in the management of diabetes, together with the necessity of addressing the demands presented by neurodevelopmental disorders, can result in significant emotional strain, financial burden, and a reduction in leisure time for families [109,110]. The aforementioned phenomenon has the potential to erode the unity within a family unit, impact the psychological well-being of parents, and ultimately diminish the overall quality of life experienced by the entire family. The likelihood of experiencing caregiver burnout is considerable, resulting in additional societal consequences as families grapple with juggling caregiving duties and other obligations. While this thesis did not delve into this specific area, there remains a compelling need for research to further elucidate these familial implications.

6.3 Strengths and limitations

6.3.1 Strengths

The key strength of this project is the use of the largest nationwide register-based samples, to our knowledge, that has been collected prospectively with medical diagnoses, disease-specific measurements, and other outcomes. This approach has effectively reduced the possibility of selection, recall, and information biases. Furthermore, the extended duration of the follow-up period facilitated a rigorous examination and monitoring of enduring patterns and impacts, augmenting the credibility and dependability of the research outcomes.

Specifically, in Study I, we utilized a matched reference cohort and implemented exact matching techniques to effectively manage potential confounding variables such as sex, birth year, and birth county. Moreover, it has been demonstrated that diabetes-related information collected through administrative means, such as glycemic control, exhibits a

high level of quality. In Study II, we employed a genetically informative design that involved four categories of siblings from the same generation. This design enabled us to explore the potential involvement of familial liability and estimate the various contributions from different sources in the comorbidity between childhood-onset type 1 diabetes and neurodevelopmental disorders. In Study III, t the robustness of clinical diagnosis reduced the potential for classification bias from other psychiatric conditions with overlapping symptoms. Moreover, the longitudinal evaluation of diabetes outcomes enhanced the study's informativeness and validity. Study IV, we were able to examine educational attainments throughout childhood and early adulthood, spanning from compulsory education to university level. We were also able to adjust for a variety of psychiatric and somatic comorbidities and, using the sibling comparison model, account for unmeasured familial, parental, and genetic confounders shared by the full-siblings.

6.3.2 Limitations

This project also has several limitations. Due to the observational nature of register-based studies, it was not feasible to determine the causal relationship between childhood-onset type 1 diabetes and its related factors and neurodevelopmental disorders, nor the relationship between the comorbidity and the health and education outcomes.

Moreover, it is imperative to acknowledge that potential residual confounding factors, such as prenatal exposures, intricate diabetes regimens encompassing insulin dosage and employment of continuous glucose monitoring devices, and parental participation in diabetes management, cannot be entirely eradicated. The circumstance above may be attributed to the restricted accessibility of comprehensive information, including metabolic biomarkers, acute diabetes complications, and intelligence assessments. Also, the intrinsic constraints of the sibling-comparison methodology, such as potential carryover effects and diverse environmental variables shared by siblings, could not be eradicated.

In addition, it is worth noting that despite the considerable sample size of this study, the projected incidence of neurodevelopmental disorders within childhood-onset type 1 diabetes is comparatively limited. One plausible rationale is that instances of neurodevelopmental disorders, specifically ADHD, were recorded through clinical diagnoses and/or medication prescriptions, which could predominantly recognize individuals who actively pursue or have been recommended for medical attention or experience more pronounced symptoms. A possible explanation is that neurodevelopmental disorders might have been underdiagnosed in the years captured by our study, as our prevalence findings are consistent with other studies conducted in Sweden during the same period.

Furthermore, the healthcare system in Sweden is financed through taxation and provides universal access to pediatric care without any associated costs. Also, the Swedish education system offers tuition-free education up until the university level, with funding provided by the state to support students. The presence of these factors may potentially constrain the extent to which our results can be applied to other contexts and compared with findings from other investigations.

7 Conclusions

This thesis underscores a significant association between childhood-onset type 1 diabetes and neurodevelopmental disorders, including ADHD, ASD, and intellectual disability. Notably, this link is amplified at higher mean HbA1c levels, reinforcing the pivotal role of glycemic control. Concurrently, the influence of shared familial liability on this relationship appears less substantial than previously suggested, indicating the need for further exploration into the underlying etiology of this comorbidity. Another key revelation of this thesis is that comorbid neurodevelopmental disorders can complicate the management of type 1 diabetes, thereby elevating the risk of chronic diabetic complications. This finding promotes the incorporation of regular neurodevelopmental assessments and tailored interventions into the clinical management of affected patients. Further, this work reveals the extent of educational challenges confronting children and adolescents with both type 1 diabetes and ADHD. It identifies ADHD as the primary contributor to these challenges, independent of other somatic, psychiatric comorbidities, or familial factors, emphasizing the importance of additional educational support to narrow this gap. Taken together, these results highlight the intricate interplay between type 1 diabetes and neurodevelopmental disorders and their joint impact on health and educational outcomes. The insights gleaned from future large-scale, longitudinal studies will be critical in clarifying the intricacies of these associations, thereby informing the development of more effective, targeted interventions and strategies.

8 Points of perspective

8.1 Clinical implications

The findings of this thesis carry clinical implications. Firstly, our findings overall support current recommendations that mental health care should be encouraged to be integrated into the broader diabetes care strategy, especially for children and adolescents who are in a crucial developmental stage.

Moreover, it is vital that healthcare practitioners anticipate the connection between diabetes management and neurocognitive and executive functions in children and adolescents with diabetes. Recognizing this relationship enables opportunities for prompt identification and intervention. Those demonstrating self-management difficultes, unexplained glycemic control issues, and academic struggles would likely benefit from a neurodevelopmental screening and assessment with targeted assistance.

Lastly, an approach that affords targeted healthcare attention, educational adjustments, and familial and social backing is necessary for children and adolescents diagnosed with both type 1 diabetes and neurodevelopmental disorders, as well as for their families. Such a comprehensive approach not only bolsters treatment adherence and aids in effective disease management, but also assists in navigating additional obstacles like academic challenges these children and adolescents may encounter.

8.2 Future research

One direction for future research involves conducting more extensive longitudinal studies. Such studies could provide valuable insights into the developmental trajectory of neurodevelopmental disorders in children and adolescents with type 1 diabetes and identity critical periods of brain development that may be particularly susceptible to hyperglycemia or other diabetes-related factors.

Though our findings do not readily suggest shared familial liability contributes to the comorbidity, a deeper dive into genetic and epigenetic factors contributing to the comorbidity could illuminate the underpinnings of the complex relationship between type 1 diabetes and neurodevelopmental disorders. This could involve genome-wide association studies and epigenetic profiling, allowing researchers to pinpoint potential genetic markers or changes in gene expression related to this comorbidity.

Moreover, subsequent research endeavors must pivot towards the systematic evaluation of the efficacy of an array of therapeutic interventions tailored for those grappling with the dual diagnoses of childhood-onset type 1 diabetes and neurodevelopmental disorders. These interventions could encompass a diverse spectrum ranging from cognitive behavioral therapies and tailored educational

programs to novel pharmacological regimens. By delineating which strategies are most efficacious, healthcare practitioners will be better equipped to optimize treatment regimens, ultimately enhancing the quality of life and outcomes for this specific patient population.

Lastly, as this intricate interplay between type 1 diabetes and neurodevelopmental disorders becomes more understood, there will be an inherent need to focus on devising comprehensive care models. Such models should holistically consider the patient's medical, educational, and psychosocial needs, ensuring an integrative approach to management. The long-term goal should remain: to ameliorate the challenges faced by affected individuals and their families, fostering improved health, academic, and overall life outcomes.

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