From the Department of
Medical Epidemiology & Biostatistics
Karolinska Institutet, Stockholm, Sweden

EPIDEMIOLOGICAL ASPECTS OF TYPE 1 DIABETES – EARLY LIFE ORIGINS, CHILDHOOD COMORBIDITIES, AND ADULT OUTCOMES

Awad I. Smew

Karolinska Institutet

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Epidemiological Aspects of Type 1 Diabetes – Early Life Origins, Childhood Comorbidities, and Adult Outcomes

Thesis for Doctoral Degree (Ph.D.)

By

Awad I. Smew, M.D.

Principal Supervisor
Professor Catarina Almqvist Malmros
Karolinska Institutet
Department of Medical Epidemiology & Biostatistics

Co-supervisors
Dr Tong Gong
Karolinska Institutet
Department of Medical Epidemiology & Biostatistics

Professor Paul Lichtenstein
Karolinska Institutet
Department of Medical Epidemiology & Biostatistics

Professor Lars Sävendahl
Karolinska Institutet
Department of Women's & Children's Health

Opponent
Associate Professor Liesbeth Duijts
Erasmus University Medical Centre Rotterdam
Department of Pediatrics

Examination Board
Associate Professor Helena Backman
Umeå University
Department of Public Health & Clinical Sciences

Associate Professor Sofia Carlsson
Karolinska Institutet
Institute of Environmental Medicine

Professor Helena Elding Larsson
Lund University
Department of Clinical Sciences

Abstract

Type 1 diabetes is an autoimmune disease, often with onset during childhood, that requires lifelong insulin therapy due to the loss of pancreatic beta-cells. Several aspects of type 1 diabetes epidemiology remained to be explored and were the focus of this thesis. To begin, environmental risk factors in childhood play an important role in triggering the onset of disease, especially in genetically high-risk individuals but less was known of the **early life origins** related to maternal stress during pregnancy. Next, the **comorbidity** between type 1 diabetes and asthma or allergic diseases had long been debated but evidence stood inconclusive. Lastly, while many long-term **outcomes** of type 1 diabetes in adulthood had been demonstrated, the effect of glycaemic control on final adult height was not yet known.

The aim of this thesis was therefore to address these knowledge gaps regarding epidemiological aspects of type 1 diabetes by investigating maternal depression or anxiety during pregnancy as a risk factor, furthering the understanding of the comorbidity with asthma or other allergic diseases, and examining the effect of glycaemic control on adult height. To study these associations on a population-based scale, linkages of healthcare and sociodemographic data from nationwide registers in Sweden were utilised alongside genetic information from the Swedish Twin Registry and clinical measurements from the National Diabetes Register.

Paper I identified maternal depression or anxiety during pregnancy as a risk factor for offspring type 1 diabetes. The findings did not seem to be entirely explained by familial confounding from shared genes or environment.

Paper II demonstrated the co-occurrence of asthma and type 1 diabetes in individuals, the importance of the sequential appearance of the diseases with previous asthma increasing the risk of subsequent type 1 diabetes, and the familial co-aggregation among full siblings and cousins pointing to the importance of shared familial factors.

Paper III expanded on these findings by also displaying associations between type 1 diabetes and other allergic diseases (allergic rhinitis or eczema). Familial co-aggregation of allergic rhinitis and type 1 diabetes suggested a shared liability, in contrast to the lack of such associations for eczema. No signs of a large genetic overlap between type 1 diabetes and asthma or any other allergic disease were found.

Paper IV uncovered differences in final adult height depending on glycaemic control in children and adolescents with type 1 diabetes. Having poor glycaemic control with a mean haemoglobin A1c >75 mmol/mol was associated with lower adult height in both males and females and an increased risk of short stature (adult height below -2 standard deviations) in males.

List of scientific papers

I. Smew AI, Lundholm C, Gong T, Sävendahl L, Lichtenstein P, Brew BK, Almqvist C. **Maternal depression or anxiety during pregnancy and offspring type 1 diabetes: a population-based family-design cohort study.** BMJ Open Diabetes Research & Care. 2023;11(2):e003303.

II. Smew AI, Lundholm C, Sävendahl L, Lichtenstein P, Almqvist C. **Familial coaggregation of asthma and type 1 diabetes in children.** JAMA Network Open. 2020;3(3):e200834.

III. Smew AI, Gong, T, Kuja-Halkola, R, Lundholm, C, Harder, A, Lu, Y, Sävendahl, L, Lichtenstein, P, Brew, BK, & Almqvist, C. **Disentangling the comorbidity between allergic disease and type 1 diabetes using genetically informative designs.** (Manuscript)

IV. Smew AI, Lundholm, C, Gong, T, Lichtenstein, P, Sävendahl, L, Almqvist, C. **Glycaemic control and adult height: a nationwide Swedish cohort study on childhood type 1 diabetes.** (Manuscript)

Related publications

I. Vartiainen P, Jukarainen S, Rhedin S, Prinz A, Hartonen T, Vabalas A, Viippola, Rodosthenis RS, Kuitunen S, Liu A, Lundholm C, Smew AI, Osvald EC, Helle E, Perola M, Almqvist C, Heinonen S, Ganna A. **Risk factors for severe respiratory syncytial virus infection during the first year of life: development and validation of a clinical prediction model.** The Lancet Digital Health. 2023. (In press)

II. Brew BK, Osvald EC, Gong T, Hedman AM, Holmberg K, Larsson H, Ludvigsson JF, Mubanga M, Smew AI, Almqvist C. **Paediatric asthma and non-allergic comorbidities: A review of current risk and proposed mechanisms.** Clinical & Experimental Allergy. 2022;52(9):1035–47.

III. Rhedin S, Lundholm C, Horne AC, Smew AI, Osvald EC, Haddadi A, Alfvén T, Kahn R, Król P, the Swedish Pediatric MIS-C Consortium, Brew BK, Almqvist C. **Risk factors for multisystem inflammatory syndrome in children - A population-based cohort study of over 2 million children.** The Lancet Regional Health Europe. 2022;19:100443.

IV. Lundholm C, Rejnö G, Brew B, Smew AI, Saltvedt S, Almqvist C. **Associations between maternal distress, cortisol levels, and perinatal outcomes.** Psychosomatic Medicine. 2022;84(3):288–96.

V. Smew AI, Hedman AM, Chiesa F, Ullemar V, Andolf E, Pershagen G, Almqvist C. **Limited association between markers of stress during pregnancy and fetal growth in "Born into Life", a new prospective birth cohort.** Acta Paediatrica. 2018;107(6):1003–10.

Contents

List of abbreviations

ATC	Anatomical Therapeutical Classification
BMI	Body mass index
CATSS	Child and Adolescent Twin Study of Sweden
CI	Confidence interval
DAG	Directed acyclic graph
GH	Growth hormone
GWAS	Genome-wide association study
HbA1c	Hemoglobin A1c
HLA	Human leukocyte antigen
HR	Hazard ratio
ICD	International Classification of Diseases
IGF-1	Insulin-like growth factor-1
LD	Linkage disequilibrium
LISA	Longitudinal integrated database for health insurance and labour market studies
MBR	Medical Birth Register
MGR	Multi-generation Register
NDR	National Diabetes Register
NPR	National Patient Register
OR	Odds ratio
PDR	Prescribed Drug Register
PPV	Positive predictive value
PRS	Polygenic risk score
SD	Standard deviation
SNP	Single nucleotide polymorphism
STAGE	Study of Twin Adults: Genes and Environment
STR	Swedish Twin Registry
TPR	Total Population Register
YATSS	Young Adult Twins in Sweden Study

1 Introduction

1.1 Overview of type 1 diabetes

Type 1 diabetes, also known as type 1 diabetes mellitus, was described already in ancient Egypt and later in ancient Greece, with the name originating from the ancient Greek word *diabeinein*, or "to pass through", related to the first description of the symptoms of excessive urine amounts, and the Latin word *mellitus*, meaning "sweet as honey" (1). In 1898, Langerhans described the insulin-producing beta cells of the pancreas giving name to the islets of Langerhans, in 1922 Banting demonstrated that insulin derived from those cells could lower blood sugar levels, thereby being able to treat the first children, and in 1923 Banting and colleague Macleod were awarded the Nobel Prize in Medicine or Physiology for their discovery (2). Since then, over the past 100 years, considerable research efforts have focused on understanding disease mechanisms, and optimising treatment (3).

Several aspects regarding the early life origins, childhood comorbidities, and adult outcomes of type 1 diabetes remain to be explored, and were the theme of this thesis.

1.1.1 Clinical presentation and treatment

1.1.1.1 Symptoms

Type 1 diabetes arises from a dysregulation of blood glucose levels owing to the irreversible destruction of pancreatic beta-cells and subsequent insulin deficiency. Symptoms present themselves when roughly 90% of the beta cells are destroyed. The presentation varies depending on age of the child, with younger children experiencing a quicker disease progression from the debut of symptoms (4). Symptoms are related to hyperglycaemia and typically include increased thirst and diuresis, often nocturnal, weight loss, and fatigue. In older children, symptoms progress more slowly, and it is not uncommon for a child's first hospital admission to be due to ketoacidosis with symptoms including abdominal pain, nausea and vomiting, dehydration and breathing difficulties. Untreated, ketoacidosis leads to loss of consciousness, coma due to cerebral oedema and ultimately, death (4).

1.1.1.2 Insulin treatment and glycaemic control

Treatment of type 1 diabetes is essential; replacement therapy with exogenous insulin is life-saving and lifelong. The goal of treatment is to stabilise glucose levels in order to prevent acute complications such as hyperglycaemia or ketoacidosis, as well as late complications related to micro- and macroangiopathy including retinopathy, nephropathy and neuropathy (5,6). Adequate treatment plans comprising of blood glucose monitoring, insulin use, physical activity and a healthy diet can ensure good

glycaemic control, i.e., the dynamics of blood glucose levels over time (7). Adequate glycaemic control also includes lack of symptoms as well as normal development and growth throughout childhood and adolescence (7).

1.1.2 Epidemiology

Type 1 diabetes represents 90% of all forms of childhood-onset diabetes and is one of the commoner endocrine diseases of childhood with a prevalence in western societies of roughly 0.5% (8).

Incidence of type 1 diabetes has gradually increased over the past decades and is continuing to increase around 3% annually (8). There are, however, large geographical variations in global incidence with incidence rates among children ranging from 0.1 cases in 100 000 individuals per year in low incidence countries to up to 60 cases in 100 000 per year in high incidence countries like Finland (9). Incidence of type 1 diabetes in Sweden is among the highest in the world with 47 cases in 100 000 per year in children aged 5-10 years (10). Recent data indicates a larger increase in cases in younger children aged 0-5 years, as well as a higher rate of incidence increase in general in certain low prevalence European countries, compared to incidence increase levelling off in other higher prevalence countries like Sweden (11).

1.1.3 Pathogenesis

The insulin deficiency in type 1 diabetes arises from an autoimmune-mediated destruction of the insulin-producing pancreatic beta-cells via antibodies against islet cell antigens (12). The appearance of circulating antibodies precedes the clinical development of type 1 diabetes and it is therefore postulated that islet autoimmunity is the first stage of disease development (13). The antibodies against glutamate decarboxylase, insulinoma-associated protein 2, zinc transporter 8, and insulin, can arise early in childhood with peak incidence during the second year of life (14). It is sufficient to have one or more of these antibodies to confirm a type 1 diabetes diagnosis. This islet autoimmunity can have a remitting-relapsing course before actual disease onset (15). During the second stage, two or more islet autoantibodies develop, which may induce dysglycaemia but without presentation of diabetes symptoms (13). Within 10 years, 70% of these children develop type 1 diabetes (16). In the third stage, the functional beta cell mass decreases enough to cause symptoms of diabetes (13).

Autoimmunity itself and progression from islet immunity to overt type 1 diabetes is thought to be triggered by an interplay between environmental (17) and genetic (18,19) factors. However, these factors mainly seem to have their effect in genetically predisposed individuals (18,20).

1.1.4 Genetic background

The primary risk factors for beta cell autoimmunity are genetic, and type 1 diabetes is strongly associated with the presence of certain high-risk major histocompatibility genotypes accounting for around 45–50% of the disease's genetic susceptibility (12). As an example, approximately 90% of children diagnosed with type 1 diabetes in Scandinavia share one or both of the human leukocyte antigen (HLA)-DR3-DQ2 or HLA-DR4-DQ8 haplotypes (19), compared to around 45-50% in the general population. Other HLA haplotypes and non-HLA single nucleotide polymorphisms (SNPs) are associated with type 1 diabetes, both by affecting the appearance of antibodies and the progression of disease (19). Currently, evidence from genome-wide association studies (GWAS) have identified around 60 genomic regions and 50 potential causal genes (21–23).

Within families, there is evidence for aggregation of type 1 diabetes (24). The risk of developing disease varies greatly depending on genetics and family history, with a 5% risk of disease among those with a high-risk genotype or first-degree relative with type 1 diabetes, a 25% risk of disease among those with both and a 50% risk of disease among those with a high-risk genotype and multiple first-degree relatives (25). The concordance rate is approximately 50% among monozygotic twins and 15% among dizygotic twins (26,27). Given these relatively low concordance rates, it is obvious that environmental risk factors must play an important role in type 1 diabetes aetiology.

1.1.5 Environmental risk factors

The recent and ongoing increases in the incidence can only be explained by changes in lifestyle and environment, emphasising the importance of environmental triggers. Multiple factors have been the focus of research initiatives, including early life infections such as enterovirus, breastfeeding, gluten introduction, vitamin D exposure, early microbial exposure, and perinatal characteristics (17,28). The accelerator hypothesis suggests that rapid weight gain during infancy and childhood may lead to increased insulin resistance whereas the beta cell stress hypothesis identifies factors leading to an increased insulin demand as potential risk triggers - this could include trauma, glucose overload, puberty and stress (17). In contrast to other childhood diseases, not as much focus has been made on research studying the effect of exposures during pregnancy. However, there is an increasing body of literature investigating the early life origins of type 1 diabetes (29–35).

1.2 Early life origins

1.2.1 The Developmental Origins of Health and Disease

The Developmental Origins of Health and Disease framework and field of research has over the past decades emphasised the importance of intrauterine environment and

maternal risk factors during pregnancy for subsequent perinatal, child and adult health (36). This was first demonstrated by Barker et al., showing a link between low birth weight and mortality from coronary heart disease. Since then the DOHaD line of research has expanded from studying foetal growth as a proxy for critical in utero insults, to studying a range of prenatal exposures conducive with an adverse foetal environment that via a range of mechanisms may be associated with later disease including cardiovascular, metabolic and endocrine.

1.2.1.1 Early life stress and mechanisms

In particular, the role of maternal stress during pregnancy as an adverse foetal environment has been a key area of interest. Associations have been found between maternal stress during pregnancy and adverse pregnancy and perinatal outcomes including low birth weight (37,38), as well as a range of childhood health outcomes (39). These include pre-school wheezing (40) or asthma (41), coeliac disease (42), atopic or allergic disease (43,44), infections (45), and obesity (46), to name a few.

Stress is commonly viewed as a concept where an event or situation is perceived subjectively and differently among individuals. The two components of stress are the stressor and its response (47). Adequate response to stress can be necessary, and is an innate reaction intended on maintaining homeostasis and protecting the individual from the stressor (48). It is the perception of stress, rather than its objective nature, that can influence health outcomes by modifying the stress response. Negative stress (distress) results from an imbalance between stressors and coping abilities (49). This leads to a heightened perception of stress with an increased risk of maladaptive emotional responses such as depression, anxiety, or other behavioural changes (50).

The main physiological pathway of the stress response is the hypothalamic-pituitary-adrenal (HPA) axis that, when activated, leads to the release of cortisol from the cortex of the adrenal gland. Normally, the axis is regulated by negative feedback, whereby cortisol inhibits the continued release of corticotropin-releasing hormone and adrenocorticotropic hormone (51), but chronic activation of this pathway can also lead to a dysregulation (52). This excess exposure to glucocorticoids in foetal life is what is thought to program pathologies later in life (53–55). This could potentially apply to type 1 diabetes as well.

1.2.2 Stress as a risk factor for type 1 diabetes

According to the beta cell stress hypothesis, any factor that increases the demand of insulin could play a role in type 1 diabetes disease development (17). As an example of this, psychological stress during childhood has been shown to reduce insulin sensitivity and may even, via increased cortisol levels, directly affect the immune response (17). Added

evidence for the biological plausibility may come from findings of an increased risk of autoimmune disease in those with a stress-related disorder (56).

There seems to be an increasing amount of evidence regarding the role of various forms of childhood stressors or adversities on diabetes development (57–62). Less is, however, known on the possible programming effects of early life stress, i.e., maternal stress during pregnancy or in the perinatal period. Certain proxies for early life stress, during either pregnancy or the first year of life, such as maternal bereavement and self-reported serious life events have been examined in relation to islet-cell autoimmunity and offspring type 1 diabetes (63–66). Other forms of maternal stress, such as psychological distress arising from psychiatric illness during pregnancy, have, on the other hand, not yet been investigated as risk factors.

1.2.2.1 Maternal depression or anxiety during pregnancy

Studying psychiatric illness during pregnancy may be a suitable proxy for stress, and of clinical relevance given psychological distress associated with these conditions in an already vulnerable part of life. For instance, conditions such as depression or anxiety are common in women of child-bearing age and affect around 15-20% in the perinatal period (67). Depression or anxiety during pregnancy as well as treatment for those conditions, has also been associated with preterm birth (68,69) and childhood asthma (70). Given the increasing rise in awareness around depression and anxiety in society today, it is important to further understand transgenerational impacts and risks for the child's future health.

At the time of the start of the doctoral project, no studies investigating associations between maternal psychiatric illness and type 1 diabetes existed. Since then, three recent register-based Swedish studies have been published. They have demonstrated an increased risk of type 1 diabetes in offspring of mothers with a history of any psychiatric disorder (71) or depression (72), as well as an increased risk of depression, anxiety or a stress-related disorder in parents of children with type 1 diabetes. None of them studied the pregnancy-period.

In summary, while stressors during childhood seem to be associated with type 1 diabetes, less is known on the role of early life stress. Previous studies have not systematically addressed the timing of the stressor in relation to pregnancy. Specifically, maternal depression or anxiety as a proxy during pregnancy has not been studied as a risk factor for offspring type 1 diabetes. Moreover, the role of familial confounding has not been explored in studies of stress and type 1 diabetes.

1.3 Childhood comorbidities

Comorbidities of chronic childhood diseases represent an increased burden to the individual and the healthcare system, through increased healthcare use, decreased quality of life and poorer disease control (73). Exploring the existence and nature of comorbidities is important for the understanding of the diseases and may improve clinical management of the children as well as identify targets for preventative measures such as screening and treatment strategies.

Clustering of autoimmune disorders is common, given their partially shared mechanisms of disease development (74). The co-aggregation of a range of organ-specific autoimmune diseases, including type 1 diabetes, thyroiditis, coeliac disease, vitiligo and Addison's disease, has been demonstrated among twins, with stronger associations among monozygotic twins, indicating the importance of genetic factors to the disease overlap (75) - as well as between other familial relations (76). Susceptibility genes identified from GWAS seem to show pleiotropy among a range of autoimmune diseases including type 1 diabetes, further indicating a genetic overlap (77). In contrast, the evidence regarding the comorbidity between type 1 diabetes and asthma, or other allergic diseases, is not as conclusive.

1.3.1 Comorbidity of type 1 diabetes with asthma and other allergic diseases

1.3.1.1 Asthma and other allergic diseases

Asthma is the most common chronic disease of childhood with a prevalence of around 6–10% in school-aged children worldwide and in Sweden (78,79). It is in general characterised by airway inflammation, hyper-responsiveness and re-modelling with smooth-muscle constriction, leading to airway wall obstruction and thickening (80). Despite the complex nature of asthma pathophysiology, in children, asthma is generally described as allergic or immunoglobulin E-mediated with certain allergens eliciting an allergic sensitisation that leads to airway inflammation (80).

Other allergic diseases, such as allergic rhinitis and eczema, are highly comorbid with asthma. This has been demonstrated both in cohort studies (81,82) and GWAS (83). Non-allergic comorbidities also exist, including autoimmune ones, both in children and adults (84,85).

Similarly to type 1 diabetes, incidence of asthma and allergic disease has been increasing over the past decades (86), often attributed to the "hygiene hypothesis" (87). Environmental risk factors for asthma and allergic diseases have been described as an explanation for the increase in incidence. These include early life factors such as maternal stress during pregnancy, early life exposure to antibiotics, infections, environmental pollutants and socioeconomic status . Interestingly, several of these are also risk factors

for type 1 diabetes. Given these epidemiological similarities it does not seem unreasonable that asthma or other allergic diseases and type 1 diabetes may co-occur.

1.3.1.2 Th1/Th2-paradigm

Asthma and allergic diseases are T-helper cell-2 (Th2) mediated, whereas autoimmune conditions, such as type 1 diabetes are characterised by stronger T-helper cell-1 (Th1) immune responses. Th1- and Th2 immune responses have previously been described as mutually inhibitory, contributing to the so called Th1/Th2 paradigm, stating that Th1 inflammation may counteract the development of atopic disease while Th2 inflammation may suppress the severity and onset of autoimmune disease (88). However, the picture is probably more complex with regulatory T-cells also at play. Furthermore, the results of epidemiological studies assessing the relationship between asthma or other allergic diseases and type 1 diabetes have been conflicting.

1.3.1.3 Epidemiological findings

A meta-analysis from 2003 that pooled conflicting results from 25 studies reported an inverse relationship between asthma and type 1 diabetes (OR 0.82, 95% CI 0.68-0.99) (89). In contrast, other studies, including more recent ones, have shown positive associations between the occurrence of asthma and type 1 diabetes (90–96). Literature on the relationship between type 1 diabetes and allergic rhinitis or eczema is heterogeneous, conflicting and inconclusive, potentially due to methodological issues in some of them, with small sample sizes and retrospective studies suffering from recall bias (97–103).

When studying the relationship between type 1 diabetes and allergic disease, previous research has mainly focused on assessing the subsequent risk of one disease upon development of the other, posing a causal question. Given similarities in the epidemiology of type 1 diabetes and allergic disease, an alternative question to ask is instead if there are shared factors, either genetic, environmental, or both, possibly clustered within families, that could contribute to the possible comorbidity. For example, Stene et al. (90) demonstrated the co-occurrence of both asthma and type 1 diabetes at a population-level within countries, concluding that although the Th1/Th2-balance may play a role in the development of disease at the individual-level, susceptibility to asthma and type 1 diabetes seems to cluster in countries, perhaps due to shared genes or environment. The existence of a shared familial liability has yet to be demonstrated.

In summary, the evidence regarding the co-occurrence between type 1 diabetes and allergic disease (asthma, allergic rhinitis, and eczema) is inconclusive and the comorbidity therefore warrants further investigation. The existence of shared familial factors contributing to both diseases is unknown.

1.4 Adult outcomes

Achieving and maintaining optimal glycaemic is an important goal for type 1 diabetes management, mainly in order to avoid negative outcomes. Certain long-term outcomes such as macro- and microvascular complications are well described in the literature (9). Other less-studied outcomes include growth, specifically height in adulthood, which was a focus of this thesis.

1.4.1 Normal growth – reaching final adult height

Growth is important from a physical, psychological and social perspective and adequate growth throughout childhood and adolescence is generally recognised as an indicator of good health (104).

Several important factors influence longitudinal bone growth, ultimately leading to the final adult height of an individual. These include genetic determinants of growth potential, as well as environmental factors such as medical conditions including chronic diseases, inflammation and malnutrition, alongside psychologic well-being, and socioeconomic factors. The mechanisms behind growth are complex, consist of an interplay between hormones and growth factors, can be affected by inflammatory cytokines, and vary over the lifespan (105). The rate of normal growth changes from *in utero* and during the first years of life, when the rate is the highest, to slowing down in childhood, before increasing again during puberty, and reaching final adult height (105).

The so-called "infancy, childhood and puberty" (ICP)-model was presented by Karlberg et al. in 1989 and is a mathematical modelling of growth from birth to adulthood (106). The model consists of different phases that each reflect different hormonal elements of the growth process. In infancy, growth velocity is high during the first year of life, with height increasing by approximately 25 cm, and is significantly influenced by nutritional status. During childhood and adolescence, in contrast, nutrition has less influence, with hormonal regulators being more important. The main anabolic hormones in childhood are growth hormone (GH), insulin-like growth factor-1 (IGF-1) and thyroid hormone. Sex steroids stimulate growth throughout puberty with the closure of the growth plate marking the end of linear growth and that final height has been reached (105).

Growth impairment can lead to short stature. Apart from primary diseases affecting the regulation of growth, such as deficiencies of important hormones like GH, chronic inflammation may also affect longitudinal growth. Growth impairment is for instance commonly seen in children with chronic inflammatory diseases such as asthma, inflammatory bowel disease, chronic renal failure, cystic fibrosis, juvenile idiopathic arthritis or diabetes (107–109). This could possibly be due to malnutrition, increased levels of pro-inflammatory cytokines, or intake of glucocorticoids – affecting growth at a systemic (hormonal) or local (growth plate) level.

1.4.2 Type 1 diabetes and final adult height

The effects of type 1 diabetes on growth are debated in the literature. Before the introduction of physiological insulin replacement therapy and continuous glucose monitoring, poorly controlled type 1 diabetes was more common, which led to stunted growth (110). However, given better clinical management of patients with type 1 diabetes, the effect of type 1 diabetes on growth in general and final adult height in particular is not as clear (111).

Growth impairment in children with type 1 diabetes is thought to be related to changes in the GH/IGF-1 axis, a major regulator of normal growth. The GH/IGF-1 axis is affected by type 1 diabetes, with studies showing decreased IGF-1 levels, leading to hypersecretion and increased levels of GH in children with type 1 diabetes (112). In turn, high serum GH levels are an important factor contributing to typical insulin resistance during puberty. Children with the lowest IGF-1 levels also seem to have poorer metabolic control and higher HbA1c levels (113). This is in line with several studies reporting a reduction in growth velocity during puberty among those with type 1 diabetes (114). Despite this demonstrated growth dysregulation on the hormonal level that occurs in patients with type 1 diabetes, a recent review of studies showed that children with type 1 diabetes may reach normal or only slightly lower final adult height, despite reduced growth spurt during puberty (111).

1.4.2.1 Glycaemic control and final adult height

Poor glycaemic control does seem to have a negative effect on growth during childhood and adolescence (115–117). However, less is known about how that impacts reaching final adult height with a scarcity of large-scale population-based cohort studies. A German-Austrian study reported a negative correlation between adult height mean haemoglobin A1c (HbA1c) (118). Others have shown that more intensive insulin therapy strategies aimed at preventing poor glycaemic control seem to be able to normalise pubertal growth and final height (119).

In summary, the association between glycaemic control and adult height among individuals with type 1 diabetes is unclear and has not yet been studied in a Swedish material. Furthermore, data is lacking in terms of understanding the impact of sex, age at onset, and puberty.

2 Research aims

The overarching aim of this thesis was to expand the knowledge of type 1 diabetes epidemiology, focusing on origins, comorbidities and outcomes, while utilising a range of epidemiological approaches including family-based design in a Swedish register-based research setting spanning the entire population.

The specific aims of the thesis were:

- To investigate maternal depression or anxiety as a risk factor for offspring type 1 diabetes and the role of familial confounding (*Paper I)*.

- To further the understanding of the comorbidity between type 1 diabetes and asthma, or other allergic diseases by investigating co-occurrence, shared familial factors, and the genetic overlap (*Papers II & III*).

- To examine the effect of glycaemic control during childhood and adolscence on adult height in individuals with type 1 diabetes as well as the impact of sex, age at disease onset, and puberty (*Paper IV)*.

3 Methodological considerations

3.1 Overview of *Papers I–IV*

All four papers of this thesis are population-based register cohort studies. Table 1 presents a summary of the most important elements of the materials and methods used for each paper. Study populations were chosen to maximise the number of included study participants within the restrictions of register coverage and data availability.

Table 1 Overview of specific methodology for *Papers I-IV*

	Paper I	***Paper II***	***Paper III***	***Paper IV***
Design	Cohort study with sibling-comparison and paternal negative control	Cohort study within individuals and familial co-aggregation among relatives	*Part I:* Cohort study within individuals and familial co-aggregation among relatives *Part II:* Cross-sectional molecular genetic designs	Cohort study
Population	Children born in Sweden 2002–2019 identified from the Medical Birth Register (**N=1,807,809**)	Children born in Sweden 2001–2013 identified from the Medical Birth Register (**N=1,284,748**)	*Part I:* Individuals born in Sweden 1987–2017 identified from the Total Population Register (**N=3,272,014**) *Part II:* Cohort of genotyped individuals from the Swedish Twin Registry (**N=30,880**) and summary statistics from published genome-wide association studies	Individuals with type 1 diabetes, born in Sweden 1982–2002 and registered before and after 18 (males) or 20 (females) years of age in the National Diabetes Register (**N=12,095**)
Follow-up	From birth until outcome event, emigration, death, or 31st December 2013 (children <4.5 years of age) or 31st December 2015 (children ≥4.5 years of age)	From 1 year of age until outcome event, emigration, death, or 31st December 2020	*Part I:* From birth until 31st December 2021 *Part II:* From birth until 31st December 2016	From first registration in the National Diabetes Register in childhood/ adolescence until first registration of adult age, data available through 2020

Table 1 (continued)

	Paper I	*Paper II*	*Paper III*	*Paper IV*
Exposure	Maternal depression/ anxiety during pregnancy	Asthma or type 1 diabetes, separately	*Part I:* Allergic disease (asthma, allergic rhinitis, eczema) *Part II:* Polygenic risk scores for allergic disease or type 1 diabetes separately	Levels of haemoglobin A1c
Outcome	Type 1 diabetes	Type 1 diabetes or asthma, separately in individuals or their relatives	*Part I:* Type 1 diabetes in individuals or their relatives *Part II:* Type 1 diabetes or allergic disease, separately.	Final adult height. *Secondary:* Short stature and change in Z-score for height from diabetes onset until adult age
Covariates	Sex, birth year. *Maternal factors:* early pregnancy BMI, parity, age at delivery, type 1 diabetes, and highest level of educational attainment	Sex, birth year. Relative's asthma or type 1 diabetes (in familial co-aggregation analysis)	Sex, birth year. Relative's allergic disease (in familial co-aggregation analysis)	Age and calendar year of diabetes onset, any other autoimmune disease, asthma, maternal adult height, parental type 1 diabetes, parental country of birth, and highest parental educational attainment
Statistical analysis	Flexible parametric models and Cox regression. Likelihood ratio tests for interaction	Logistic and Cox regression	*Part I:* Logistic regression, tetrachoric correlations *Part II:* Logistic regression, linkage-disequilibrium score regression	Linear and logistic regression. Likelihood ratio tests for interaction

3.2 Registers as data sources

The data used in this thesis all originated from linkages of population-based nationwide Swedish healthcare and sociodemographic registers. Sweden, alongside other Nordic countries, is uniquely placed to conduct large-scale observational studies based on high quality register data thanks to a history of long-term data collection and conservation. Since 1947, all Swedish residents are given a unique personal identity number (120). As this number is used in all official interactions with the welfare state including the healthcare and school system, individual-level linkage is possible between various national registers enabling the possibility of following individuals over the life course and through multiple aspects of society.

This type of register-based research can be defined as utilising data on human subjects from sources including governmental agencies or other organisations that has not been collected primarily or solely for research purposes. Register-based research falls under the umbrella of "real-world data" that can in some countries, include other secondary data sources for research such as electronic health records or insurance claims databases.

Using registers as data sources has multiple benefits. The strengths include no individual-level data collection, the inclusion of entire populations with minimal selection issues compared to an enrolled study, large enough sample sizes for the study of rare exposures and outcomes, often complete and long follow-up time over the life course not contingent on responses within a cohort study, as well as mainly prospective data entered in real-time reducing the risk of recall bias.

Nevertheless, the secondary use of routinely collected healthcare data comes with certain constraints. The data are by default entirely observational and oftentimes not gathered with research in mind, thereby limiting the researcher to both the available registers as well as the available data within them. This can result in a lack of variables that otherwise would have been of interest such as self-reported measures and subjective scores, clinical parameters, biomarkers, lifestyle factors or primary health care data. Furthermore, data can be unstructured, prone to random and non-random misclassification and measurement error, and depending on sampling, may not reflect the target population (121).

The national healthcare and sociodemographic registers used throughout this thesis are summarised in Figure 1 (p.17) and described in more detail in the following sections.

3.2.1 Healthcare data

National healthcare data registers are held by the National Board of Health and Welfare, a state-funded governmental body that routinely collect a range of information related to healthcare.

The **National Patient Register** (NPR) was started in 1964, initially with varying coverage across the country due to the stepwise inclusion of Swedish counties reporting to the register. Full coverage was reached for in-patient visits in 1987 and out-patient visits were added in 2001 with around 80% coverage. The register contains information from all hospital visits including the main and secondary discharge diagnostic codes according to the International Classification of Health and Diseases (ICD), date and duration of admission, codes for interventions, and identifiers for specific clinics and hospitals (122). The real-time data input by healthcare providers in hospitals is routinely transferred to the register and requires no active reporting. Missingness is therefore limited.

Healthcare visits in primary, or ambulatory are not registered, while private care is underreported which contributes to the lower coverage in out-patient care. Which diseases are reported to the register therefore depends on the severity of the disease and on which level care is given for that disease. For instance, life-threatening conditions requiring hospitalisation are all recorded, whereas less severe diseases may not require neither in- nor out-patient hospital admission. Certain diseases may in general be followed in primary care, and a registered diagnosis for such a disease in the NPR may represent a more severe or complicated phenotype.

The **Medical Birth Register** (MBR) contains data on births from 1973 onwards (123,124). Roughly 96–99% of all live births are covered. Details are registered regarding the mother's pregnancy and delivery as well as the offspring's perinatal period from antenatal clinics by midwifes, upon admission to obstetric units for interventions or delivery and postnatal care, respectively. Antenatal care registrations include maternal self-reported medication use in early pregnancy according to the Anatomical Therapeutic Chemical (ATC) classification system (from 1996 onward) or tobacco use as well as measurements of weight and height (from 1982 onward). Measurements and diagnoses of the new-born are registered upon delivery. We used this register as the study base for identification of our study populations in *Papers I & II* as well as for inclusion of maternal and offspring covariates in *Papers I, II, & IV*.

The **Prescribed Drug Register** (PDR) provides information on all dispensed medication prescriptions since 2005 including details regarding, among others, substance type according to ATC, and dates of prescription and dispensation (125). Since the register contains information on all dispensed prescription, irrespective of from which level of care it originated (i.e., also from primary care), it is possible to use this medication information to identify diseases, such as asthma, that otherwise would have been difficult to correctly identify solely based on hospital diagnoses. In contrast, medications administered in hospital, prescribed but not dispensed, sold over the counter, or illegally acquired are not identifiable from the register.

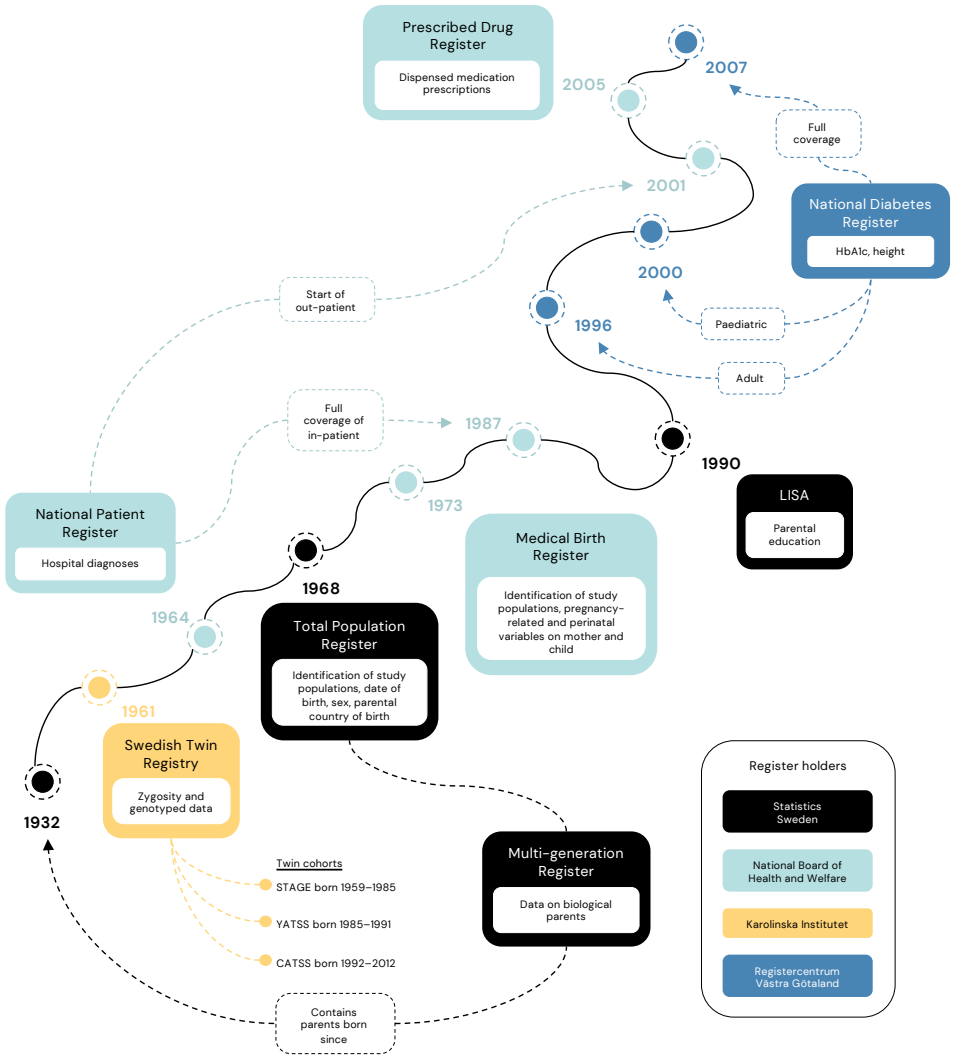

Figure 1 Overview of the Swedish population-based healthcare and sociodemographic registers used as data sources in this thesis including with what information they contributed

3.2.2 Sociodemographic data

Statistics Sweden is the governmental agency responsible for collection and maintenance of sociodemographic information on the Swedish population (126).

The **Total Population Register** (TPR) was started in 1968 and contains a wide range of sociodemographic information on each individual including the following used in this thesis; sex, birth date, country of birth, migration (immigration, emigration or moving within the country), and date of death (126).

The **Multi-generation Register** (MGR) includes individuals born 1932 who were still alive in 1961 and is a link between individuals and their biological (or adoptive) parents (127). Based on this linkage it is subsequently possible to identify other types of relatives including siblings and cousins as was done in *Papers I–III*.

The **Longitudinal integrated database for health insurance and labour markets studies** (Swedish acronym LISA, "Longitudinell integrationsdatabas för sjukförsäkrings- och arbetsmarknadsstudier") covers the Swedish population aged 16 years or above since 1990 with annual registrations regarding education, income, occupation, and sick leave among others (128). For this thesis, we extracted data on the highest level of parental education attainment, reported to be available for >98% citizens 25–64 years of age with high validity, especially in individuals born in Sweden.

3.2.3 Genetic data from the Swedish Twin Registry

The **Swedish Twin Registry** (STR) is one of the world's largest databases of twins born after 1886 (129). Twins who have taken part in specific twin cohort studies are included in the registry. For *Paper III*, we used data from the STR to establish zygosity of twins based on DNA-testing or on validated questionnaires regarding physical similarities (130). We also utilised the registry as a source of genetic data and constructed a cohort of genotyped individuals on which to develop and test polygenic risk scores (see *Paper III*, Figure 1B). For that, we used data from three twin cohorts: "Study of Twin Adults: Genes and Environment" (STAGE), "Young Adult Twins in Sweden Study" (YATSS), and "Child and Adolescent Twin Study of Sweden" (CATSS).

3.2.4 Clinical data on type 1 diabetes from a quality register

Alongside the aforementioned national healthcare and sociodemographic registers, there are several quality registers in Sweden, designed to develop and support the quality of healthcare as well as contribute with statistics for research. These registers are routinely used in the healthcare setting in order to monitor, contrast and compare data nationally and regionally (131). In this thesis, we relied on individual-level data from aforementioned national healthcare and sociodemographic registers that were also linked to the quality register for diabetes: The **National Diabetes Register** (NDR).

The NDR was established in 1996 and initially only registered adults. Children were originally registered in the Swedish Paediatric Diabetes Quality Register ("Swediabkids"), established in 2000 with currently 98% coverage of all children with type 1 diabetes (132,133). Since 2018, adult and paediatric information have been integrated and are both registered in the NDR, but separately accessible. In Sweden, children are followed 1-2 times per 6 months in accordance with national guidelines. All hospital visits from each of the paediatric clinics that care for children with type 1 diabetes are registered alongside baseline information collected at onset of diabetes.

Available data include results of laboratory testing, anthropometric measures and treatment regimens. Informed consent is required for inclusion into the register, and children or their parents have the right to opt-out of future registrations or withdraw their data at any time (see 3.6 Ethical considerations for further discussion regarding informed consent).

3.3 Measures and misclassification

In the following sections, the main measures used as exposures and outcomes in this thesis are presented alongside a methodological discussion on potential biases arising from misclassification.

3.3.1 Relating to type 1 diabetes

3.3.1.1 Register-based definition of type 1 diabetes

In *Papers I-III,* we used an epidemiological definition of type 1 diabetes (Figure 2) based on either a diagnosis for type 1 diabetes in the NPR or dispensed insulin prescription in the PDR (see Table 2, p. 20 for a full list of ICD and ATC codes used for all disease definitions of exposures or outcomes in the thesis).

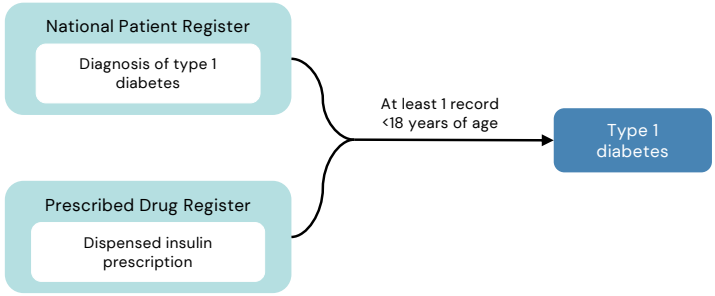

Figure 2 Definition of childhood type 1 diabetes based on diagnosis in the National Patient Register or insulin prescription in the Prescribed Drug Register before 18 years of age

While ICD-10, starting in 1995, has a specific code for type 1 diabetes, previous ICD-versions 7-9 do not differentiate between type 1 and type 2 diabetes. The unique diagnosis of type 1 diabetes has yet to be formally validated in the NPR, although older research has attempted to validate the non-specific ICD-code of type 1 or type 2 diabetes in the in-patient portion of the NPR (122). Based on a small study of 28 cases, the positive predictive value (PPV) was reported to be 0.79. Unsurprisingly, the sensitivity in an adult population was low, indicating that many cases of diabetes are diagnosed outside of hospitalised care (122). In contrast, when studying children as in this thesis, we assumed the risk of misclassification of type 1 diabetes to be low.

Table 2 List of ICD- and ATC-codes used for disease definitions

		Diagnosis		Medication*		*Paper*
		ICD-10	**Name**	**ATC**	**Name**	
Type 1 diabetes		E10	Type 1 diabetes mellitus	A10A	Insulin	*/–///*
Depression/ anxiety	Mood (affective) disorders	F30	Manic episode	N05B	Anxiolytics	/
		F31	Bipolar affective disorder			
		F32	Depressive episode			
		F33	Recurrent depressive disorder			
		F34	Persistent mood disorders			
		F38	Other mood disorders			
		F39	Unspecified mood disorder			
	Neurotic and somatoform disorders	F40	Phobic anxiety disorders	N06A	Antidepressants	
		F41	Other anxiety disorders			
		F42	Obsessive-compulsive disorder			
		F44	Dissociative disorders			
		F45	Somatoform disorders			
		F48	Other neurotic disorders			
Asthma		J45	Asthma	R03AC†	Inhaled selective beta-2-adrenoreceptor agonists	*//–///*
				R03BA	Inhaled glucocorticoids	
		J46	Status asthmaticus	R03AK	Inhaled adrenergics in combination with corticosteroids	
				R03DC	Leukotriene receptor antagonists	
Allergic rhinitis‡		J30	Vasomotor and allergic rhinitis	R01AD	Nasal corticosteroids	*///*
				R06A	Antihistamines for systemic use	
		J31.0	Chronic rhinitis	S01GX	Other ophthalmological antiallergics	
				V01A	Allergen extracts for hyposensitisation	
Eczema‡		L20	Atopic dermatitis	D07	Dermatological corticosteroids	*///*
		L30.8C	Other specified dermatitis	D11AH	Other agents for dermatitis	

Abbreviations: ATC, Anatomical Therapeutic Classification. ICD, International Classification of Diseases.
*Medication listed applies to all rows for each disease, and not for a specific diagnosis.
†Only R03AC02, R03AC03, R03AC12, R03AC13 were included.
‡Diagnoses and medication used in exclusion criteria to define allergic rhinitis and eczema can be found in the supplement of Henriksen et al.

Firstly, specificity ought to be high given that >98% of children with diabetes below 18 years of age have type 1 diabetes. Other forms of diabetes in children such as type 2 diabetes or monogenic forms are rare. Secondly, sensitivity ought to be high given that all children with type 1 diabetes require hospitalisation upon onset with subsequent out-patient follow-ups, and therefore have multiple chances of being registered with a diagnosis in the NPR. There are several examples of studies basing type 1 diabetes in children on these diagnostic records (134–136).

In *Papers I & II*, the included children were born after implementation of the unique type 1 diabetes code E10 in ICD-10, reducing the risk of misclassification. However, to further avoid this, especially in older populations such as among parents where information on diagnosis of diabetes may have been registered according to older ICD-versions, we required individuals to have received the diagnosis before 18 years of age.

Insulin prescription in the PDR as a proxy for type 1 diabetes has, on the other hand, been demonstrated to accurately capture the disease in children, and has been used in previous Swedish register studies (137,138).

In our data, we observed a great overlap between those with a diagnosis in the NPR and insulin in the PDR (Figure 3). For instance, in the exploration of our data before analysing *Paper I* (results not included in publication), we saw that out of the 8,182 children who developed type 1 diabetes during follow-up, 7,112 (86.9%) had both a type 1 diabetes diagnosis and record of insulin prescription, 766 (9.4%) only had record of insulin prescription and 304 (3.7%) only had a type 1 diabetes diagnosis.

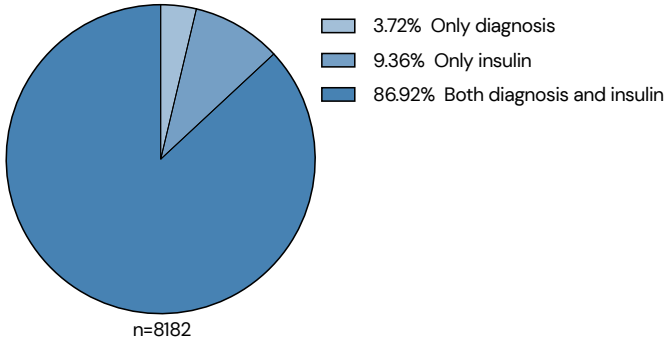

Figure 3 The overlap between diagnosis and insulin prescription among the 8182 offspring with type 1 diabetes in *Paper I*

Among the 766 children with only an insulin prescription but no type 1 diabetes diagnosis, only 1 individual received a type 2 diabetes diagnosis (ICD-10 E11), and none received diagnoses for other specified (monogenic forms, ICD-10 E13) or unspecified diabetes (ICD-10 E14). Among the 8,182 offspring with type 1 diabetes according to our definition in our cohort, only 25 (0.3%) also had a concomitant diagnosis for type 2 diabetes, 24 (0.3%) also had other specified forms including maturity onset diabetes of the young, and 63

(0.8%) also had unspecified forms of diabetes. Furthermore, other forms of diabetes than type 1 were rare overall. In the whole population for *Paper I* (n=1,807,809), only 84 children had type 2 diabetes, 51 had other specified forms, 83 had unspecified forms and one person had gestational diabetes.

Importantly, as reported in sensitivity analyses of both *Papers I & II*, basing the definition of type 1 diabetes solely on diagnosis or insulin, or requiring both, did not change the results. In summary, we believe that misclassification of type 1 diabetes throughout the thesis is minimal.

3.3.1.2 Glycaemic control

While we in *Papers I–III* studied type 1 diabetes as an exposure or outcome in itself, in *Paper IV* we had a study population of individuals with type 1 diabetes and aimed to understand how their glycaemic control might impact the risk of adult height outcomes. To that end, we were interested in defining glycaemic control. Haemoglobin A1c (HbA1c) is the glycated fraction of haemoglobin and represents average blood glucose levels during the last approximately 90–120 days (the lifespan of a red blood cell). It is therefore the gold standard for monitoring diabetes management and used extensively worldwide (139). The test is easily accessible, requires no specific handling in collection and is not altered by prandial status or time of day.

In *Paper IV*, we had access to all HbA1c measurements of our study population from the NDR. Data are derived from blood sampling taken during healthcare visits to diabetes clinics. In Sweden, laboratory methods for analysing HbA1c are standardized through an external quality assessment provider "Equalis" (External Quality Assurance in Laboratory Medicine in Sweden) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) reference method is used with values reported in mmol/mol (140). In line with recommendations (139), we also reported HbA1c values in *Paper IV* according to the National Glycohemoglobin Standardization Program in percentage units (141).

For the analyses in the study, we used all the available HbA1c values in childhood and adolescence for each individual to calculate a time-weighted mean HbA1c as the average of all yearly means (Table 3, p. 23). We did this to place less emphasis on short-term fluctuations in HbA1c. Mean HbA1c was primarily treated as a categorical variable based on target values for glycaemic control from the International Society for Paediatric & Adolescent Diabetes guidelines (142): optimal control <53 mmol/mol (<7.0%), suboptimal control 53–75 mmol/mol (7.0–9.0%) and poor control >75 mmol/mol (>9.0%).

Additionally, we analysed mean HbA1c a) continuously (both assuming a linear dose-response as well as exploring non-linearity using restricted cubic splines), b) in relation to

the number of years spent during the study period with poor glycaemic control, and c) looked at mean HbA1c separately before, during, or after expected puberty.

Puberty is an important period for longitudinal growth in children and adolescents, and our hypothesis, based on previous literature (143), was that the impact of poor glycaemic control may differ depending on when in relation to puberty high HbA1c levels occur. Unfortunately, information on pubertal stage is not recorded in the quality register and we therefore defined the ages of expected puberty as 11–16 years of age for males and 10–15 years of age for females. These pubertal ranges correspond to data from growth models for a Swedish population (144). Sensitivity analyses were also conducted to see if changing these ranges would affect the results.

Table 3 Definitions of the measures of glycaemic control used in *Paper IV* with haemoglobin A1c (HbA1c) values from the National Diabetes Register

Measures of glycaemic control	Definition
Category of mean HbA1c	Mean HbA1c (time-weighted by averaging yearly means) over the entire follow-up categorised as: ▪ Optimal control <53 mmol/mol (<7.0%) ▪ Suboptimal control 53–75 mmol/mol (7.0–9.0%) ▪ Poor control >75 mmol/mol (>9.0%)
Mean HbA1c	Mean HbA1c (of annual means) over the entire follow-up, in mmol/mol (%)
Time with poor glycaemic control	Number of years during entire follow-up poor glycaemic control calculated as the sum of time between visits with HbA1c >75 mmol/mol (>9.0%) until a visit with HbA1c <75 mmol/mol (<9.0%)
Category of mean HbA1c in relation to puberty	Mean HbA1c (of annual means) during three age intervals: ▪ Before puberty <11 years (males), <10 years (females) ▪ During puberty 11–16 years (males), 10–15 years (females) ▪ After puberty >16 years (males), >15 years (females)

3.3.2 Early life stress

Finding suitable measures of the complex psychological and physical processes that stress, or rather psychological distress, entails is a challenge. In general, three main types of approaches have been used in older literature (145). First, the environmental approach assesses the stressor itself, for instance through questionnaires regarding serious life events. Second, the psychological approach assesses the coping ability to the stressor, for example using measurements of perceived stress like the Perceived Stress Scale (146). Third, the biological approach assesses the actual physiological activation of stress systems, where one of the most commonly used biomarkers is cortisol (147,148).

However, using these aforementioned approaches requires collection of questionnaires or biological samples from clinical cohorts. When conducting population-based register studies, as in this thesis, other approaches to ascertain proxies and indicators of stress have been increasingly employed. Examples include studying the experience of severe negative health outcomes or stressful life events such as being in between jobs, severe illness or death of a family member, divorce, natural disasters, pandemics, war or financial crises (61,149,150).

Having a psychiatric condition such as depression, anxiety or stress-related disorder has also been utilised as a proxy for psychological distress, and examined in relation to a range of health outcomes in Swedish register-based material (56,151). Being affected by a psychiatric condition such as a mood- or anxiety-related disorder has impact on the daily functioning of the individual, can affect choices made in regard to lifestyle and health and can entail a great deal of psychological stress on the individual. Furthermore, the onset of this type of condition can often be related to triggering from a stressful life event or situation. For this thesis, we used maternal depression or anxiety during pregnancy as a proxy for early life stress, similarly to previous research from our group (68,70,152,153).

3.3.2.1 Maternal depression or anxiety as a proxy

In *Paper I*, we used a register-based definition (Figure 4) of depression or anxiety (maternal or paternal) based on a diagnosis of a mood- or anxiety-related disorder registered in the NPR or dispensed prescription of medication used to treat those conditions registered in the PDR or MBR (Table 2, p. 20). The main exposure period was during pregnancy (defined as 90 days before conception to delivery date).

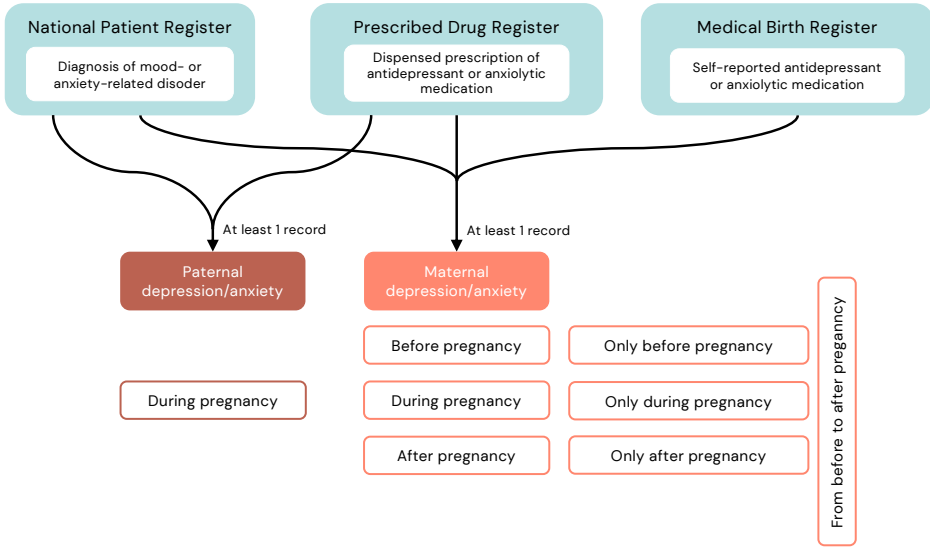

Figure 4 Register-based definition of depression or anxiety based on diagnosis or medication, and the various exposure periods before (1 year before), during, and after (1 year after) pregnancy

No validation study of this definition has yet been performed. It is reasonable to assume that cases of mood- or anxiety-related disorders registered in specialist in- or out-patient hospital care represent the more severe proportion of all afflicted individuals. A study of primary care diagnoses found that 81% of those with a primary care record for depression only had a registration in primary care, and not from specialist in- or out-patient hospital care (154). Reassuringly, the majority of cases of depression (79%) and anxiety (67%) handled in primary care had an identifiable prescription of antidepressants in the PDR and anxiolytics were prescribed to 54% or 64% of patients with depression or anxiety, respectively. Naturally, we cannot capture those who did not require treatment or were exclusively treated non-pharmacologically, those abstaining from dispensing a prescription, or for other reasons unknown not receiving medication prescriptions. Those missed ought, however, to be milder cases whose symptoms potentially may exert less of a biological stress effect *in utero*, and importantly, potential misclassification would be non-differential in relation to the outcome of offspring type 1 diabetes.

Additionally, for maternal depression/anxiety during pregnancy, we were also able to identify pregnancy exposure based on maternal self-reported medication use registered by midwives at routine visits during pregnancy weeks 10-12 in the MBR. A Swedish validation study examined the validity of medication recorded in the MBR and found that it corresponded well with records in the PDR (155). For antidepressant medication for instance, 88% of women who reported medication use at the first antenatal visit were found to have had a dispensed prescription within the preceding 180 days.

A limitation to this approach of defining maternal depression/anxiety is that it does not differentiate between any of the specific conditions included in the broad group of ICD codes for mood- or anxiety-related disorders. For *Paper I*, this was equally intentional as practical in reaching the aim of utilising a broad definition to capture any form of psychological stress resulting from psychiatric disease. Although one can surely argue that depression and anxiety are different psychiatric entities, our aim was not to study depression or anxiety per se, but rather the stress that they represent in the pregnant woman. We chose to limit to these affective disorders (and not include other psychiatric diagnoses) given their partially shared symptomatology, chronicity as well as similarities in treatment strategies.

Another limitation is that by basing the exposure definition on diagnosis or medication we could not differentiate between the role of the disease vs the medication. Again, this was reasonable in order to increase power, and intentional as addressing the effect of medication was beyond the scope of our research question.

Lastly, relating to register coverage with information on medication only available in the PDR from 1 July 2005 onwards, we are unable to identify milder exposure among the older individuals in our study population born 2001-2006. Exposure among these offspring

consequently certainly represents a more severe phenotype of maternal depression/anxiety, but we do not believe this fact to have entirely biased our results given the misclassification is purely due to data availability that is the same in regard to offspring type 1 diabetes, i.e., non-differential. Also, we found similar estimates when conducting a sensitivity analysis in a cohort with full register coverage.

3.3.3 Asthma and other allergic diseases

In *Papers II & III* we faced the task of defining the allergic diseases asthma, allergic rhinitis, and eczema from register data. Using only diagnoses from the NPR would not be feasible and certainly yield misclassification given that a large majority of patients with these conditions are followed in primary care. To this means, we therefore employed previously validated algorithms (156,157) designed to accurately define asthma and other allergic disease based a combination of diagnosis and medication codes (Table 2, p. 20).

3.3.3.1 On asthma

The definition of asthma (Figure 5, p. 27) was used in both *Papers II & III* and is derived from a 2013 validation study by Örtqvist et al. that compared records of diagnoses in the NPR and medication from the PDR to actual medical records and predefined diagnostic criteria of asthma by the Swedish Paediatric Society's section for allergy (156). They showed that around 95% of those with an asthma diagnosis in the NPR had at least one dispensed asthma medication prescription in the PDR. Furthermore, the positive predictive value for asthma (according to diagnostic criteria) among those fulfilling set asthma medication criteria was in general high; 0.94 in school-aged children (4.5-17 years of age) and 0.75 in pre-schoolers (<4.5 years of age). PPV was lower in the younger age group given that medication also reflects viral wheeze, proved by the PPV increasing to 0.87 when including obstructive bronchitis in the asthma definition. Similarly, in validating the diagnosis of asthma in the NPR compared to the predefined diagnostic asthma criteria upon review of medical records, PPV was 0.78 in pre-schoolers and increased to 0.89 when restricting to those children who also fulfilled the asthma medication criteria. For school-aged children, PPV was 0.99.

The definition of asthma therefore differs depending on age with the younger group <4.5 years of age required to have both diagnosis and medication, whereas the older group's asthma definition was valid based on either diagnosis or medication.

In *Paper II*, data availability was limited to information on diagnoses from the NPR up until 31st December 2013, but dispensed medication records up until 31st December 2015. To address this discrepancy and avoid misclassification in light of aforementioned differences in asthma definition by age, we constructed different follow-up time for children below compared to above 4.5 years of age. Only children who were older than 4.5 years of age were followed until 31st December 2015 given that we could confidently

base their asthma definition solely on medication. Children younger than 4.5 years were only followed until 31st December 2013 as we required information on asthma diagnosis.

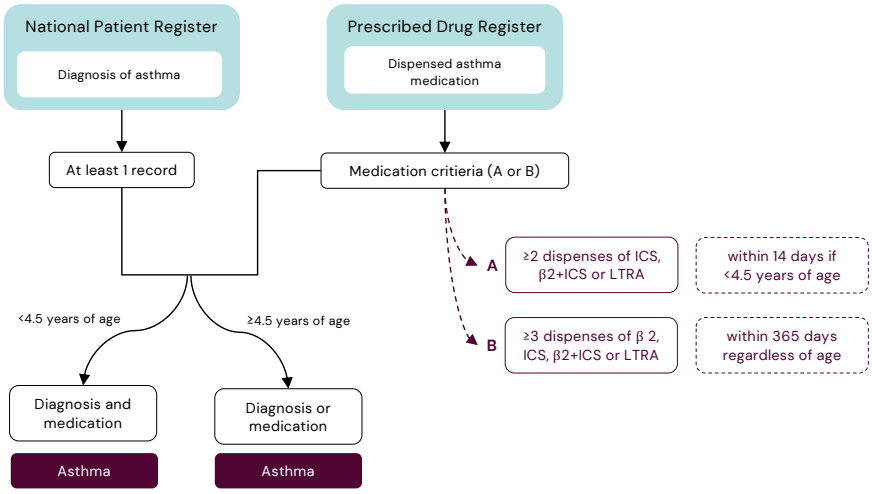

Figure 5 Definition of asthma based on diagnosis from the National Patient Register and dispensed asthma medication from the Prescribed Drug Register, according to algorithm by Örtqvist et al. *Abbreviations*: β2, Beta-2-receptor agonist. ICS, inhaled corticosteroid. LTRA, leukotriene receptor antagonist.

3.3.3.2 Defining other allergic diseases

For *Paper III* where we apart from asthma also studied other allergic diseases, we based the definition of allergic rhinitis and eczema on a 2015 study by Henriksen et al. (157). They defined allergic diseases according to algorithms based on disease-specific diagnosis and medication alongside criteria of repeated medication use given the chronic nature of the diseases as well as exclusion of other conditions also indicated for the medication (Table 2, p. 20). Details can be found in the supplement (Appendix 1A) of the Henriksen et al. article. The algorithms have been validated against a doctor's diagnosis, with high sensitivity and specificity (158).

3.3.4 Adult height outcomes

For *Paper IV* we studied adult height outcomes in relation to glycaemic control in childhood or adolescence among individuals with type 1 diabetes (Table 4, p. 28). Our primary outcome was final adult height measured in cm and data originated from the NDR. We defined adult height as height registered in adult age, i.e., after 18 years of age for females and 20 years of age for males. These age cut-offs were chosen based on Swedish growth references that indicate no significant additional growth after these ages (159). In line with previous population-based research on adult height (105,160), we excluded biologically implausible final heights less than 100 cm or greater than 240 cm (males) or

225 cm (females). Only 3.5% of our study population had missing final adult height in the NDR. While two of the largest previous studies on height among individuals with type 1 diabetes had greater number of included individuals, they only had final adult height for 3.5% (n=8101) (115) or near-adult height data for 7.4% (n=1685) (118) of their original study populations.

Table 4 Definition of adult height outcomes used in *Paper IV*

Adult height outcome	Definition
Final adult height	The largest height in cm registered at a specialist visit in the NDR in adult age, i.e., >20 years (males) or >18 years (females)
Short stature	Z-score for final adult height below -2 standard deviations
Change in Z-score for height	Difference between Z-score for height at first registration upon onset of type 1 diabetes (maximum 1 year between onset and registration) and Z-score for final adult height

While the national registers gather a plethora of data, population-based registration of height, especially in adult age, is lacking. For *Paper IV* this was an issue for availability to parental height of our study population, a predicting variable that could have enabled us to calculate target height. Distance to target height has been proposed as one of the most important criteria for following growth (161) given that it takes the individual's genetic height potential into account and could have been an alternative, clinically relevant, outcome measure.

Some population-based sources for height, apart from registers for specific patient groups such as the NDR, exist. For women who have given birth, self-reported height recorded by midwives at the first antenatal visit of pregnancy is registered in the MBR (124). We used this information for our maternal height covariate in *Paper IV.* In contrast, paternal height is not routinely measured. For Swedish men who underwent standardised testing ahead of military service, height (and other body measurements) was registered in the Swedish Military Conscription register (162). We did not have access to this register for this body of work. Finally, previous Swedish register-based research (105,160) has utilised information on adult height registrations from passport information held by the Swedish Police Authority. However, this information is not readily available for research purposes, and access was not granted for this study.

For secondary outcomes in *Paper IV*, we standardised final adult height values using a Swedish reference material (163). Based on these Z-scores, we were able to define two alternative outcome measures not requiring target height. Firstly, we defined short stature as a Z-score for final adult height lower than -2 standard deviations (SD) (164). There is no formal consensus on the definition of short stature (also referred to as growth retardation or growth failure) in past literature. Some studies have defined it as being below the 5th

centile (approximately <-1.64 SD) while others have used distance from target height more than 8 or 8.5 cm (160). Secondly, for a subpopulation with height registrations recorded in the NDR at diabetes onset, we calculated the change in Z-score for height from diabetes onset until adulthood. A change in Z-score over time (also referred to as height deflection) reflects a deviation from the expected channels of a growth curve and is an important clinical auxological parameter in detecting a growth disturbance.

3.4 Epidemiological approaches

3.4.1 Causal inference in observational studies

"Some scientists are reluctant to speak so blatantly about cause and effect, but in statements of hypothesis and in describing study objectives such boldness serves to keep the real goal firmly in focus and is therefore highly preferable to insipid statements about 'association' instead of 'causation'."

-Rothman, "Modern Epidemiology" (1986, 1st edition).

Randomised controlled trials are many times seen as the gold standard for understanding causal effects, but for practical and ethical reasons not always applicable for all research questions. As is the case throughout this thesis, *in utero* exposures, concomitant childhood diseases or levels of glycaemic control are not exposures that would be possible to randomly allocate. For that reason, we must rely on evidence from observational data.

Various study designs exist, but for this thesis all papers include a cohort study where exposed and unexposed individuals are compared in relation to an outcome. Given that exposure status is not randomly allocated – leading to an imbalance in risk of the outcome not due to the exposure – it is imperative that we use methods to deal with such confounding bias that may otherwise occur.

The question of causality is consequently central in epidemiology, no less so in all papers of this thesis. In *Papers I & IV* the causal questions are explicit, whereas the underlying causal relationships are more implicitly investigated in *Papers II & III*. Instead of attempting to adjust for factors hindering a causal interpretation as in *I & IV*, in *Papers II & III* we aimed to prove the existence of such unmeasured confounding. Estimating causal effects from observational studies is difficult and was not the aim of this thesis. However, even though association is often what we can measure, causation is many times the underlying objective. It is important to discuss these causal questions but not overinterpret findings.

3.4.1.1 Directed acyclic graphs

Directed acyclic graphs (DAGs) are a visual and cognitive aid to better understanding relationships between the exposure and outcome of interest, and how other factors relate to them and one another (165). Common relationship structures that can be identified using DAGs are confounders, mediators and colliders, which helps to inform decisions on which or which factors not to adjust for in models aiming to estimate a causal effect (Figure 6). This can be difficult since not all factors are known, measured or measurable, and their relationships to one another can be complex. While failure to adjust for important confounders can lead to residual confounding, adjusting for the wrong variables can also give rise to bias. For instance, adjusting for a mediator could open up backdoor pathways if the mediator shares a common cause with the outcome, so called collider stratification bias (166,167). Other variables also affecting the relationship between exposure and outcome are not as commonly represented in a DAG but can be important in their own right. An example is when the strength of the association between exposure and outcome differs depending on a third variable, i.e., an effect modifier.

DAGs were constructed (168) and used throughout the planning and analysis of all papers in this thesis, and were based on literature review and subject-matter knowledge of factors affecting exposure and outcome.

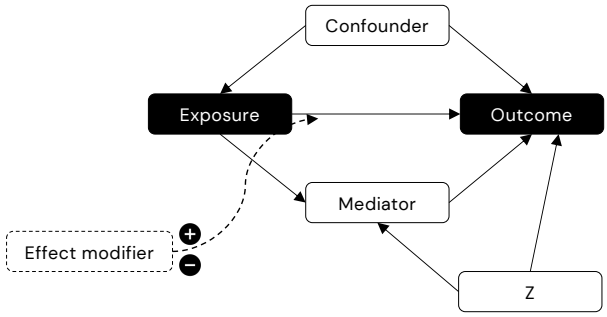

Figure 6 Example of a schematic directed acyclic graph. A confounder is causally related to both exposure and outcome, but does not lie on the causal path between them, as does a mediator. In the presence of a common cause of mediator and outcome (denoted Z), a mediator can be a collider and conditioning upon it opens up a backdoor biased pathway (collider stratification bias). Effect modifiers may alter the association between exposure and outcome

3.4.2 Family-based study designs – targeting confounding

There are multiple ways of dealing with bias due to confounding with the goal of nearing exchangeability between exposure groups. Common approaches include adjustment, stratification or matching in statistical analyses. However, not all confounders have been measured depending on data availability, neither are they all possible to measure, or even known to the researcher, which can result in residual, or unmeasured, confounding. It is possible to deal with this through study designs (169).

A so called quasi-experimental approach to addressing confounding through epidemiological design is the use of familial relations between study individuals, with their inherent similarities and differences (170). These family-based designs harness the genetic and environmental sharing between relatives to account for confounding structures to the associations that are shared within families, i.e., familial confounding. Using information on individuals who are genetically related, i.e., through genetically informative designs, is a way of addressing genetic confounding when genetic markers are not available. Various study designs to deal with unmeasured familial confounding were used in *Papers I–III* of this thesis and are briefly outlined below.

3.4.2.1 Paternal exposure as a negative control

Using negative control exposures (171,172) can in general help deal with unmeasured confounding if they share confounders with the exposure of interest. An association indicates the presence of confounding given that the negative control exposure is chosen for its own lack of association with the outcome. An application of this type of design useful for pregnancy-related exposures is a paternal negative control model, described in further detail by Brew et al. (173). We applied this type of design in *Paper I* when studying maternal depression/anxiety during pregnancy. In the presence of unmeasured familial confounding, we would expect to see an association between paternal depression/anxiety during pregnancy and offspring risk of type 1 diabetes.

3.4.2.2 Sibling comparisons

While matching on measured confounders can be a way to adjust for confounding, it is also possible to do so by design on individuals that are naturally similar or "matched", for instance within a cluster of relatives. An example is by comparing exposed individuals to their matched unexposed siblings in a sibling comparison design (174). Given that siblings share on average at least 50% of their segregating genes and can be assumed to share a large portion of environmental factors, especially during early life and childhood, such as parental, lifestyle and socioeconomic factors, a sibling comparison design inherently adjusts for factors (confounders and mediators, but not colliders (175)) shared between siblings.

In *Paper I*, a sibling comparison design was used to compare offspring exposed to early life stress in the form of maternal depression/anxiety during pregnancy to their unexposed siblings in order to adjust for shared familial factors that may be associated with both maternal depression/anxiety and offspring type 1 diabetes. Potential confounders that vary between pregnancies and siblings such as maternal BMI and age at delivery are not inherently adjusted for and were therefore included as covariates in the models.

By inherently adjusting for familial confounding, sibling comparisons can be a useful tool in understanding causal relationships (174). Nevertheless, sibling comparisons have several limitations that are important to consider when interpreting effect estimates from them. First, since only discordant siblings are informative, there can be a great loss of statistical power when many clusters are non-informative. If families with discordant siblings differ in terms of risk for the exposure/outcome compared to families with concordant siblings, selection bias may be present. Second, measurement error is amplified in sibling comparisons and can lead to biased estimates (176). Third, potential carryover effects such as the outcome in one sibling affecting the exposure of the other, can bias results (177). Lastly, limiting the population to siblings raises the question of generalisability of sibling comparisons estimates to the target population to which we aim to draw conclusions on. This did not seem to be an issue in *Paper I* with a sensitivity analysis resulting in similar estimates of the main association in the whole population and in the population of siblings.

3.4.2.3 Familial co-aggregation

While a sibling comparison aims to adjust for unmeasured familial confounding, a familial co-aggregation design aims to prove the existence of such shared familial factors, i.e., to detect a familial effect on the risk of two disorders.

The methodology for familial co-aggregation analysis has been thoroughly described by Hudson et al. (178), and applied in Swedish register-based data (179,180). If relatives of individuals with one disorder have an increased risk of the other disorder, we may assume that genetic or environmental factors shared by the relatives contribute to the co-occurrence of the two disorders and that familial co-aggregation is present. Figure 7 (p. 33) displays a DAG modified from Hudson et al. (178) to fit the research question of shared familial factors underlying an association between asthma and type 1 diabetes studied in *Papers II & III*.

By comparing the magnitude of associations across different relatives, it is possible to infer on what types of familial factors may be underpinning an association. For instance, given that full siblings share more segregating genes than half-siblings, stronger associations in full siblings may point to the influence of genetic factors. On the other hand, stronger estimates in maternal half-siblings than paternal half-siblings may indicate the importance of environmental factors, such as pregnancy-related ones.

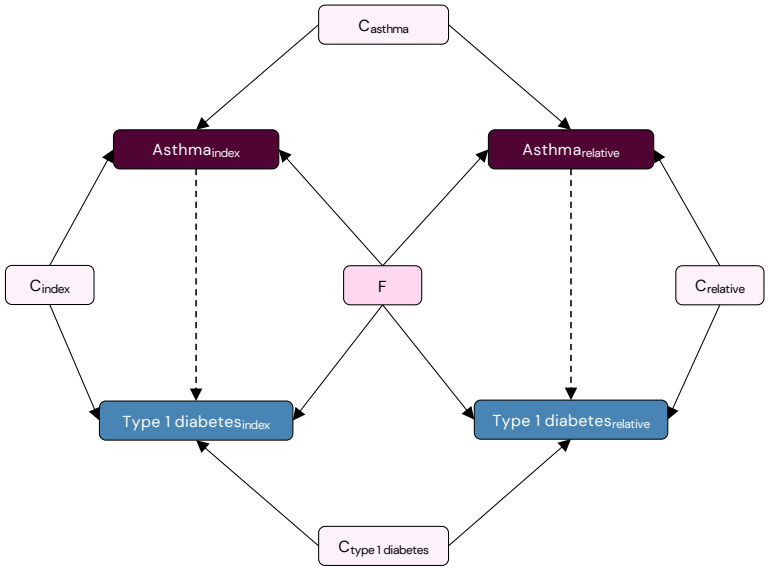

Figure 7 Directed acyclic graph of the relationship between asthma and type 1 diabetes in an index individual and their relative. F denotes shared familial factors for both asthma and type 1 diabetes. C denotes factors in the index individual (C_{index}) or relative ($C_{relative}$)that are non-shared confounders, and causes for asthma (C_{asthma}) or type 1 diabetes ($C_{type\ 1\ diabetes}$), that are shared by relatives. A sibling comparison design would adjust for all factors shared by the index individual and the relative (F, C_{asthma} and $C_{type\ 1\ diabetes}$). Familial co-aggregation designs aim to prove the existence of F. In an association between $asthma_{index}$ and $type\ 1\ diabetes_{relative}$, adjusting for the $asthma_{relative}$ deals with the direct effects of one disease on the other (dashed line), which further strengthens evidence for the presence of F.

3.4.3 Genetic epidemiology

Aforementioned family-based designs are examples of genetically informative methodology given that we can draw inference based on genetically related individuals. For instance, although siblings are not genetically identical, they share a large part of their genes enabling us to adjust to some extent for genetic confounding. Another way of dealing with genetic confounding is to use data on measured genetic markers in molecular genetic designs. The actual genetic variation is used instead of relying on assumptions in genetic differences between relatives.

3.4.3.1 Polygenic risk scores

The number of GWAS has increased dramatically over the past years making it possible to understand and identify specific common genetic variants (measured as SNPs) associated with disorders. Summary statistics from these GWAS can be used to construct polygenic risk scores (PRS) (181), without requiring information on family relations. PRS are, simply put, the sum of effects of multiple SNPs for a trait combined to a score and can help to provide an estimate of an individual's genetic liability to a disorder.

Genetic overlaps can then be explored by measuring associations between PRS for one disorder and phenotype of another disorder.

In this thesis, PRS of allergic diseases (asthma, allergic rhinitis, eczema) and type 1 diabetes were developed using summary statistics for the largest GWAS of the respective diseases to date (182–186). They were then applied on genotypic data from 30,880 individuals in the Swedish Twin Registry in *Paper III* to understand the association between PRS for allergic disease and risk of type 1 diabetes, and vice versa. Limitations of a PRS approach include that PRS cannot capture the entire genetic risk but only those due to common SNPs (187), as well as limited generalisability to non-European population given the lack of diversity in included populations in the underlying GWAS.

3.4.3.2 Genetic correlation

Using summary statistics, it is also possible to estimate a genetic correlation between two disorders without the need for individual-level genotyped data. In *Paper III*, this was done using linkage disequilibrium (LD) score regression (188,189) between each allergic disease (asthma, allergic rhinitis, eczema) and type 1 diabetes based on the same GWAS summary statistics as for the PRS.

3.5 Statistical methods

3.5.1 Regression models

3.5.1.1 Linear regression

Linear regression models estimate the change in a continuous outcome associated with a one unit change in the exposure. Potential confounders are adjusted for by inclusion in the model, giving an effect estimate of the association between exposure and outcome within the same stratum of the confounder, e.g., comparing children born the same year when adjusting for birth year. Linear regression was used in *Paper IV* when studying final adult height and change in Z-score for height. Models were presented crude, adjusted and stratified on sex. Effect modification by sex and age at onset of diabetes were tested for by including interaction terms in the model and performing likelihood ratio tests.

Linear regression assumes linearity of the association between exposure and outcomes. However, biological phenomena might not also follow a straight pattern. In *Paper IV*, we hypothesised that the impact of glycaemic control on adult height might differ across different levels of the exposure. We therefore used restricted cubic splines as a way of more flexibly modelling the data, allowing for non-linearity between exposure and outcome.

3.5.1.2 Logistic regression

Logistic regression models estimate the change in log-odds of a binary outcome associated with a one unit change in the exposure. Exponentiating the regression coefficients gives the odds ratio, i.e., the odds of the outcome among the exposed compared to the odds of the outcome among the unexposed. Logistic regression was used in *Papers II & III* to estimate the association between each allergic disease and type 1 diabetes within individuals and familial co-aggregation among relatives, and in *Paper III* to estimate the association between polygenic risk scores (per one SD increase) for one disease and phenotype of the other. It was also used in *Paper IV* when studying the binary outcome short stature. Models were presented crude and adjusted. In *Paper IV*, they were stratified on sex and included interaction terms for sex and age at onset of diabetes to test for effect modification.

Logistic regression is useful when there are no issues with censoring, and an equal amount of follow-up time for each individual. In *Paper II*, we applied conditional logistic regression stratified on date of birth. This extension of a logistic regression allows to in part take differing follow-up time into account by matching on date of birth.

3.5.1.3 Cox regression

As different lengths of follow-up among study participants may often be the case in a cohort study, other types of statistical approaches can also be useful. Cox proportional hazards model is a type of statistical model appropriate for time-to-event data such as cohort studies in that is takes time-at-risk into account. Individuals are followed from the start of follow-up (in our papers, from birth or 1 year of age) until the date of the outcome or censored at end of data availability, death or emigration. Cox regression models estimate the hazard ratio, i.e., the hazard (rate) of an event in the exposed group compared to the hazard (rate) of the event in the unexposed group, automatically adjusting for the underlying timescale.

Cox regression models were applied in *Papers I & II* and, in both, attained age was the underlying timescale meaning that the model only compared children of the same age. In *Paper II*, we modelled time-varying exposure. This means that since no study individuals were exposed at start of follow-up (birth), children remained unexposed until onset of disease (asthma or type 1 diabetes) and were then considered at risk.

An important aspect of Cox regression is the assumption of proportional hazards, i.e., that the rate of the event is constant over time. This was assessed by visual examination of log-hazard curves and tested based on Schoenfeld residuals. In *Paper II* we found that the proportional hazards assumption held, i.e., that the rate of type 1 diabetes among those with asthma was the same across all ages. In *Paper I*, on the hand, we uncovered time-varying effects. The rate of type 1 diabetes in offspring exposed to maternal

depression/anxiety during pregnancy differed depending on their age. We therefore split the model on attained age (1-8 or >8 years of age), assuming piece-wide constant effects.

For the sibling comparison analysis in *Paper I,* Cox regression stratified on sibling pair allowed to model a family-specific baseline hazard, thus only comparing between sibling pairs.

The interpretation and validity of hazard ratios has been discussed in the literature – is any biological phenomena really proportional over time? For example, Stensrud and Hernan (190) argued that hazards can never strictly be proportional throughout the entire follow-up period and that failure to find non-proportionality relates to sample size and length of follow-up.

3.5.1.4 Flexible parametric models

Another way of modelling time-to-event data, allowing for time-varying effects is by using flexible parametric modelling (191). This yielded a more flexible estimation of the time-varying HR than in Cox models merely split on two categories of attained age, and was suitable for producing a graphical representation. In *Paper I,* we applied flexible parametric models with cubic splines yielding smooth hazard estimates, and results are presented graphically as crude and adjusted hazard ratio curves with 95% CIs.

3.6 Ethical considerations

The ethical considerations related to this doctoral thesis with its four included papers have been thoroughly considered throughout the planning and execution of the studies, in order to adhere to the principles of autonomy, justice, beneficence, and non-maleficence to the study individuals. All studies within the thesis were approved by the Swedish Ethical Review Authority. In this section, a selection of ethical aspects related to register-based studies, clinical cohorts including biological material, and data from quality registers will be presented.

In general, when conducting studies, adequate measures should be taken in order to ensure the protection of the study participants' right to personal integrity and autonomy, for instance with informed consent, and to minimize the potential risk of injury (192). Potential risks should be weighed against potential benefits of the research conducted. As stated in the Ethical Review Act (2003:460), the Swedish law that regulates ethical review of human research: "*Research may only be permitted if the potential risks to the research subjects' health, safety and personal integrity are outweighed by the scientific value.*" Additionally, when reviewing research for ethical approval, the same law emphasises the importance of not approving research which if performed in an alternative manner could further minimise these risks. The law also recognizes the sanctity

of the individual's welfare over the needs of society or science (193). For this thesis, regulations relating to informed consent and the collection and handling of personal data, including biological samples and other sensitive data related to patient care, are of great importance and follow the European Union's General Data Protection Regulation.

For register-based research using individual-level data from the whole population, as in all four papers, one main concern is upholding data privacy in the handling of sensitive personal information, linked from multiple registers. This is addressed through the pseudonymization of the data, where the key file linking the personal identification number with the serial number used for analysis, is not held by the researchers but by the national government agency that has been responsible for matching the data. The key is only kept for a prespecified period of time before being destroyed. Although this hinders direct identification of the study participants, collecting data from multiple sources does increase the level of detail of personal information which could indirectly be tracked back to individuals. The potential breech of this integrity to personal information is handled via optimised data management and IT routines including encryption of codes, storage of data on secured servers, and limitations on who has access to which parts of the data as well as reporting aggregated statistics on a group, but never individual, level.

Another point to consider is informed consent. For all four papers, given that they were register-based, the requirement of informed consent was waived as long as an ethical approval had been made. This exemption has been discussed elsewhere, and is related to the fact that the register-based research only uses data collected routinely as part of normal clinical care, and that it does not involve direct contact with the study individuals (194). However, for additional data collection conducted by researchers, such as in twin studies from the STR and used in *Paper III*, informed consent is required and was obtained within each respective twin study. For children younger than 15 years old, parental consent was required, but the child should be involved in the discussion as much as possible in relation to their understanding of the study.

Another ethical consideration related to *Paper III* is the collection of biological material, which was used for genotyping. In this case, the DNA was extracted from saliva and blood samples that were not collected as part of routine healthcare. However, this sampling is a minimally invasive minor procedure, ought not to be associated with clinical risks, and did not affect any other aspects of future healthcare. Children or parents (for those under 15 years) provided informed consent for the testing of these samples after having received written information. Furthermore, samples were securely stored in KI Biobank, which follows the Swedish laws on biobanking under the Biobank Act (2023:38) (195). Despite the voluntary basis of inclusion of the study participants' data, individuals may eventually oppose the continued registering of their information, and can therefore anytime ask the Swedish Twin Registry to leave the twin study and not be contacted in further inclusions. Already collected material is allowed to still be used unless the study individual explicitly

revokes that consent. They also have the right to copies of any of their registered personal information.

Aggregated GWAS data for in *Paper III* were summarized by previously published studies and available from online repositories. Since no individual-level data is included, our use of this data ought not to pose any major ethical issues threats.

Compared to the other three papers, *Paper IV* had the additional linkage of the quality register for type 1 diabetes, which enriched our data with more detailed clinical information. All individuals registered in the NDR are provided with information upon inclusion in the quality register. However, individuals have the right to ask for reports of what data gave been collected, and to opt-out of continued inclusion in quality registers, or have already collected information permanently deleted (196). These measures increase the personal integrity and autonomy of study individuals.

Apart from the aforementioned risks, several benefits of conducting this thesis do exist as well. For instance, using register data allowed for identification of large study populations including pregnant women and children, whose data may otherwise not routinely be included in cohort studies or clinical trials. It also minimised bias in data collections, and enabled us to answer research questions that would be impossible to study using other methods, such as assessing prenatal exposures (*Paper I*), linking family members on a nationwide level, combining with genetic data (*Paper III*) and allowing for long follow-up periods over the life course from early life, through childhood, adolescence, and adulthood.

Scientific communication is also a key area in research ethics. Throughout this thesis, we aimed for an open and transparent scientific process. We analysed data according to a pre-specified analysis plan and followed departmental and institutional guidelines in documentation in order to achieve reproducible results. An additional step could have been to upload the analyses plans to an online repository ahead of time, similar to what is considered common practice for randomised controlled trials. Furthermore, we did not select results based on statistical significance and throughout all papers we tried to highlight and report null findings as well to discuss strengths and limitations in a nuanced manner.

While the main areas of a university institution are education and research, public outreach, sometimes referred to as the "third task" is equally as important and can be argued to be a part of an ethical approach to conducting research. It is important that research findings are conveyed to the public in a non-stigmatising and balanced way, not overemphasising conclusions while at the same time reporting key findings. For instance, relative estimates of associations may sound alarming although absolute risks are not greatly increased. Opportunities for outreach include dissemination of results in scientific and popular press, as well as patient involvement through feedback to study participants

on results or by reporting back to patient representatives, advocate groups, or funding agencies.

In summary, several ethical considerations have been discussed and include the right to personal integrity, autonomy, adding societal benefit, and reducing harm to study participants. Several precautions have been taken and it is deemed that the benefits of the scientific knowledge gained by studying the epidemiological aspects of type 1 diabetes in this thesis outweighed the risks.

4 Results and discussion

4.1 Summary

The main findings from this thesis (Figure 8) are the increased risk of type 1 diabetes among offspring whose mothers experienced depression or anxiety during pregnancy (*Paper I*); the comorbidity between type 1 diabetes and allergic diseases which, at least for asthma and allergic rhinitis, seems to share a familial liability but not a great genetic overlap (*Paper II & III*); and the lower adult height among children with poor glycaemic control of their type 1 diabetes during childhood or adolescence (*Paper IV*). Using large-scale, high-definition, population-based data in combination with several epidemiological approaches including family-based study designs enabled us to adjust for unmeasured confounding and address causal relationships (*Paper I*), triangulate evidence based on multiple methodology (*Paper II & III),* as well as utilise clinical measurements on a nationwide level (*Paper IV*). In this section, the main findings relating to each research aim are highlighted as well as a brief discussion on potential mechanisms and implications. Results with all tables and figures alongside a detailed discussion in comparison to the literature can be found in the attached papers.

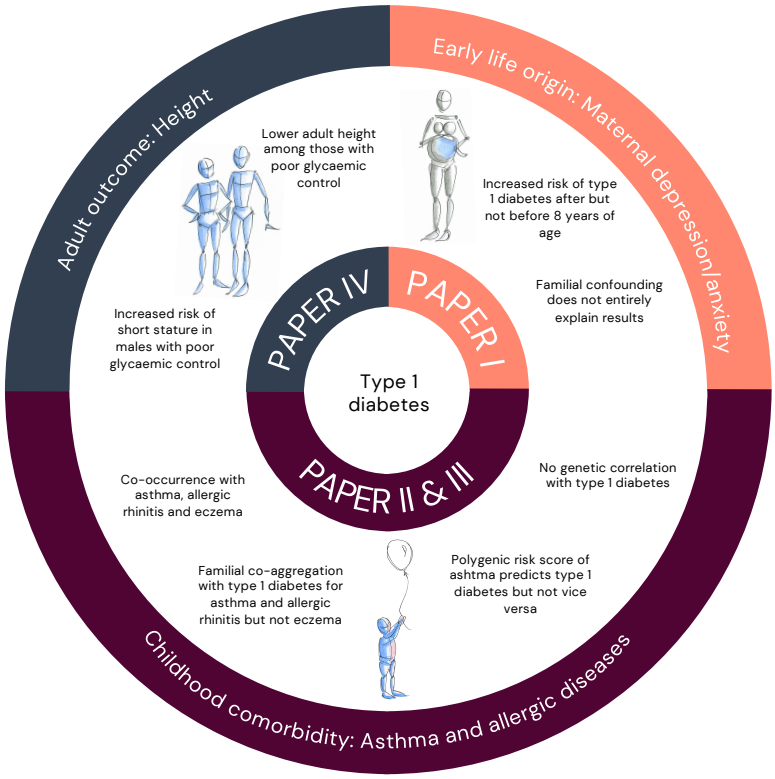

Figure 8 Overview of the main findings of this thesis

4.2 Early life stress – maternal depression or anxiety during pregnancy

4.2.1 Time-varying effects and mechanisms

In *Paper I*, in our study population of 1,807,309 mother-offspring pairs, 6.3% were exposed to maternal depression/anxiety during pregnancy, which is similar to other Swedish estimates of perinatal depression (70). Overall, among those exposed, 0.4% developed type 1 diabetes compared to 0.5% in the unexposed group. When examining the data, we observed evidence for non-proportional hazards, i.e., the rate of type 1 diabetes differed by age (the underlying timescale). We therefore modelled the association allowing for time-varying effects using flexible parametric models (*Paper I*, Figures 1 & Supplemental Figure S4). The HR increased above 1 from approximately 8 years of age and onwards implying an increased risk in those exposed vs unexposed.

In Cox regression models, allowing for time-varying effects in two groups of attained age (1-8 or >8 years of age), this corresponded to a crude HR of 1.27 (1.09, 1.45) after 8 years of age, and 1.21 (1.03, 1.42) after adjustment for offspring birth year and sex as well as maternal early pregnancy BMI, parity, age at delivery, type 1 diabetes, and highest level of educational attainment (Table 5).

Table 5 Association between maternal depression or anxiety during pregnancy and offspring type 1 diabetes presented as hazard ratios (HR) with 95% confidence intervals (CI)

	Maternal depression/anxiety during pregnancy		**Offspring type 1 diabetes**	
Age at onset of type 1 diabetes	Exposed, no. (incidence rate per 10,000 person-years)	Unexposed, no. (incidence rate per 10,000 person-years)	Crude HR (95% CI)	Adjusted HR (95% CI)
1–8 years	228 (4.13)	4171 (4.43)	0.95 (0.83, 1.08)	0.91 (0.79, 1.04)
>8 years	176 (8.60)	3607 (6.73)	1.27 (1.09, 1.48)	1.21 (1.03, 1.42)

The findings of no difference before 8 years of age, but an increased risk of type 1 diabetes after 8 years of age potentially point to different risk factors for the onset of diabetes at different ages. This is in support of the notion of different endotypes of type 1 diabetes, i.e., different aetiologies and timing underlying the disease (197,198). Genetic susceptibility may be associated with an earlier onset of disease (27), whereas other environmental factors may only trigger disease after a certain age, for instance in predisposed individuals (18).

Our findings of an association between a proxy for early life stress and type 1 diabetes are in line with other studies that have found an increased risk among children exposed to various serious life events during pregnancy including bereavement, unemployment,

family conflict or divorce during pregnancy (63,64). In another study, however, no association was found (57). The methodological differences between the studies makes the comparison difficult and conflicting results may be due to severity, definition and timing of the stressor or sample size issues. Potential pathways that might explain our findings are outlined in the following sections and summarised schematically in Figure 9 (p. 44).

An intuitive thought may be that an exposure occurring during pregnancy and exerting an early life effect on the unborn child *in utero*, should be associated with an earlier onset of disease in infancy/childhood. We did not find evidence to support this in our data. However, it is known that the autoimmune disease processes behind type 1 diabetes, including circulation of antibodies, rather than the overt disease itself, can begin as early as the first six months of life (29), and may well therefore have been programmed during pregnancy. Thus, one potential mechanism explaining our findings is that exposure to early life stress is associated with such foetal programming of autoimmunity. Mechanisms are not yet completely understood, but immune dysregulation and proinflammatory processes via the HPA axis may be involved (199).

Given the large-scale population-based nature of this study we were not able to collect blood samples from study individuals. It would have been interesting to see if maternal depression/anxiety increased the risk of detectable autoantibodies early in life, even if we could not demonstrate a higher risk of type 1 diabetes before 8 years of age. We cannot rule out that among those who developed type 1 diabetes after 8 years in our study some already had signs of diseases processes earlier in life that were attributable to the pregnancy exposure. Evidence supporting this hypothesis come from a study of genetically at-risk individuals followed within The Environmental Determinants of Diabetes in the Young (TEDDY) study that found an association between stressful maternal major life events during pregnancy and the appearance of first-appearing autoantibodies (66).

Another potential mechanism other than foetal programming of autoimmunity is that early life stress increases the risk of other factors that may trigger type 1 diabetes disease progression. Instead of a more direct cause as in programming of actual autoimmune disease processes, this mechanism would be an indirect path, mediated through downstream maternal or childhood factors. For instance, maternal stress during pregnancy is associated with childhood asthma (70), infections (200), and obesity (46), all known-risk factors for type 1 diabetes (96,201,202).

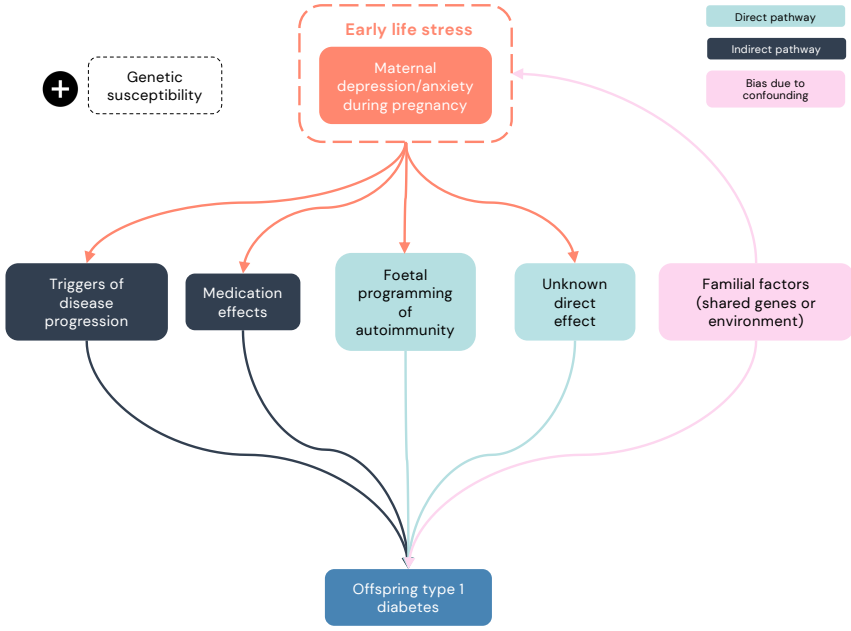

Figure 9 Schematic overview of potential pathways underlying the association between maternal depression or anxiety as a proxy for early life stress and offspring type 1 diabetes, based on the findings of this thesis alongside previous literature

Furthermore, the impact of early life stress on type 1 diabetes may differ depending on genetic susceptibility for type 1 diabetes and this may be driving the association found maternal depression/anxiety during pregnancy and offspring type 1 diabetes risk. Many studies on the environmental origins of type 1 diabetes have focused on studying potential determinants in genetically at-risk individuals (18,20). A limitation of our study is consequently that we did not have genetic information available. Unfortunately, power was too low to investigate the demonstrated associations in a subpopulation who had at least one first-degree relative with type 1 diabetes, which otherwise would have been a possible proxy for genetic risk.

While we utilised maternal depression/anxiety as a proxy for early life stress, it is possible the observed association is specific to the maternal psychiatric illness, or medication to treat the illness itself. As discussed in Methodological considerations 3.3.2.1, we did not differentiate between underlying diseases or medication subtypes. While selective serotonin reuptake-inhibitors have been studied in relation to a range of adverse perinatal outcomes with a consistently demonstrated small increased risk of preterm birth and small-for-gestational age (69), their safety in regard to childhood type 1 diabetes has not been investigated. A small exploratory animal study reported reduced pancreatic beta-cell mass in rats exposed to SSRI due to altered gene expression in islet cell regulation (203). Taken together with our findings, this warrants further epidemiological investigation (see Points of perspective 6.1).

In short, there may be several possible mechanisms underlying an association between maternal depression/anxiety during pregnancy and offspring risk, including direct or indirect pathways that may differ among genetically predisposed. Other alternative biased pathways, including due to familial confounding, are discussed below.

4.2.2 Addressing causality

In order to substantiate the potential causal arguments discussed above, we rely also on the results of several epidemiological approaches targeting confounding that we applied in *Paper I*.

4.2.2.1 Timing of exposure

First, we addressed time-stable confounding, i.e., from maternal factors constant over time and related to both maternal depression/anxiety and offspring diabetes, but not specific to the pregnancy period. This was done by comparing exposure *during* to exposure *before* and/or *after* pregnancy (for an overview of exposure periods used see *Paper I*, Figure 1). The rationale was that if associations were still observed in models studying exposure before pregnancy, confounding may be present since maternal factors in the pre-pregnancy window do not have a direct *in utero* effect. Findings are summarised in Figure 10.

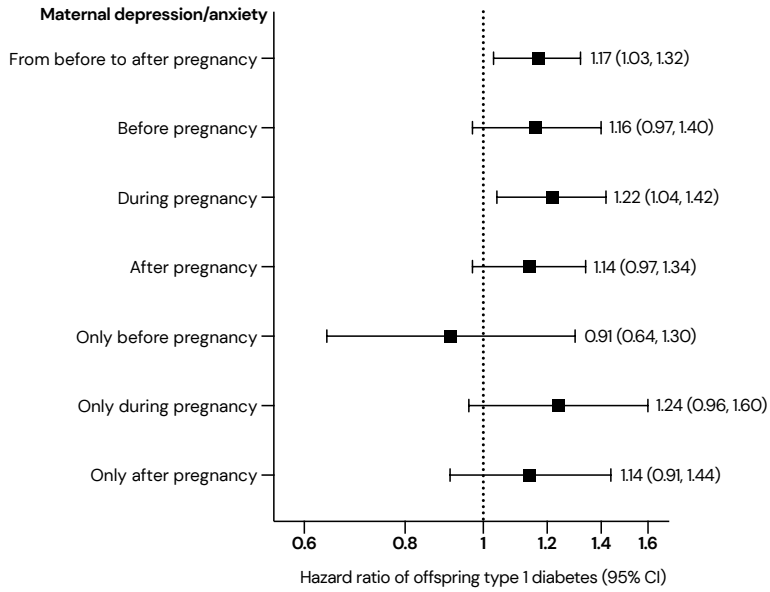

Figure 10 Associations between maternal depression/anxiety in different exposure periods in and around pregnancy and offspring type 1 diabetes after 8 years of age, presented as hazard ratios with 95% confidence intervals. Cox regression models are adjusted for offspring birth year and sex, and maternal early pregnancy BMI, parity, age at delivery, type 1 diabetes, and highest level of educational attainment

For any exposure where the pregnancy period itself might also have been involved (i.e., *from before to after*, *before* pregnancy, *after* pregnancy) we saw a similar pattern of a trend to an increased risk of diabetes. In the exposed *before* pregnancy group, 62.5% was exposed also *during* pregnancy, while in the exposed *after* pregnancy group, 55.6% had been exposed *during* pregnancy. On the other hand, exposure periods in which no recorded exposure had occurred *during* pregnancy, such as *only before* pregnancy, were not associated with an increased risk of type 1 diabetes and time-stable confounding from before pregnancy cannot entirely explain our findings. *Only after* pregnancy was also associated with an increased risk of type 1 diabetes, but this does not contradict our findings given that depression/anxiety after pregnancy often constitutes a different phenotype, such as postpartum psychiatric illness that in itself may be related to type 1 diabetes, and cannot be involved in foetal programming. Maternal stress during the first year of life has been associated with offspring type 1 diabetes in previous studies (63). Also, we cannot rule out that women we defined has exposed *only after* pregnancy, in fact had been exposed to symptoms of depression /anxiety *during* pregnancy but did not have records of medication dispense or diagnosis, making it impossible for us to identify them.

4.2.2.2 Familial confounding

Our second approach at targeting confounding was by using a paternal negative control model. Similarly, to addressing timing-of-exposure in relation to pregnancy, paternal exposure during the mother's pregnancy cannot logically directly influence the unborn child in utero. So, if an association is present between paternal exposure and offspring type 1 diabetes, this would also point to unmeasured familial confounding. Our findings showed that exposure to paternal depression/anxiety did not seem to be related to offspring type 1 diabetes (adjusted HR 0.96, 0.73, 1.26; Table 6, p. 47). In other words, familial confounding structures similar in mothers and fathers did not seem to be present.

Another way of addressing familial confounding was our third approach using a sibling comparison design. In our population n=1,265,116 were siblings. Of them, we could only identify n=297 exposure-discordant pairs on whom to base the analysis. By comparing them, we inherently adjusted for all factors shared between siblings. Models remained positive and of comparable magnitude (adjusted HR 1.37, 0.83, 2.28, Table 6, p. 47) indicating that familial confounding might not entirely explain our results. We cannot however rule out that some residual confounding may still be present, given the low statistical certainty of our estimates stemming from the great loss of power associated with the sibling comparison design.

Table 6 Addressing familial confounding in the association between maternal depression/anxiety during pregnancy and offspring type 1 diabetes using paternal depression/anxiety as a negative control and comparing with unexposed full siblings in a sibling comparison model

		Depression/anxiety during pregnancy		Offspring type 1 diabetes	
		Exposed, no. (incidence rate per 10,000 person-years)	Unexposed, no. (incidence rate per 10,000 person-years)	Crude HR (95% CI)	Adjusted HR (95% CI)
	Age at onset of type 1 diabetes				
Paternal negative control	*>8 years*	52 (7.17)	3731 (6.79)	1.04 (0.79, 1.37)	0.96 (0.73, 1.26)
Sibling comparison	*>8 years*	93 (7.97)	2410 (6.74)	1.18 (0.74, 1.89)	1.37 (0.83, 2.28)

In support of a shared familial liability are results demonstrating a familial co-aggregation between subsequent depression/anxiety/stress-related disorders in parents or full siblings of individuals with type 1 diabetes (204). Subsequent quantitative genetic modelling, however, provided little evidence for genetic or shared environmental contributions, with the correlations between diseases mainly explained by individual-specific factors (205). Recent Swedish studies have found an increased risk of type 1 diabetes among offspring whose mothers (but not fathers) had a history of any psychiatric illness ever in life prior to the child being born. In light of our results, these findings may well be explained by (71,72) exposure during pregnancy.

In summary, we believe that by applying several approaches to deal with unmeasured confounding we have strengthened evidence to support an association between maternal depression/anxiety during pregnancy as a proxy for early life stress and offspring type 1 diabetes. The association may have causal components, although we cannot entirely rule out alternative explanations.

4.3 Comorbidity with asthma and other allergic diseases

4.3.1 Co-occurrence of diseases

4.3.1.1 Asthma and type 1 diabetes

In *Paper II* (n=1,284,748) we first examined the comorbidity between asthma and type 1 diabetes by quantifying their co-occurrence (Figure 11). We found that children with either of the diseases, more often also had the other disease, compared to unaffected individuals. At the end-of-follow-up, the OR (adjusted for sex and date of birth) for the association between asthma and type 1 diabetes was 1.15 (95% CI 1.05–1.27). This finding was replicated in *Paper III* (n=3,199,242); adjusted OR of 1.11 (1.07–1.15) with narrower confidence intervals representing the larger population. Allowing for a minimum amount of follow-up by estimating the associations among children reaching a certain age (5–8 years of age respectively) yielded similar results with ORs ranging from 1.32–1.42 (*Paper II*, Table 2).

Upon finding these results, we were then interested in understanding if it mattered which of the diseases first occurred in the individual, i.e., the sequential appearance of disease. Using time-to-event analysis with time-varying exposures we assessed the risk of subsequent type 1 diabetes after asthma onset as well as, oppositely, the risk of subsequent asthma after type 1 diabetes onset. We found an increased risk of type 1 diabetes among those with pre-existing asthma (adjusted HR 1.17, 1.07–1.28), whereas no differences in asthma risk among those who debuted with type 1 diabetes first could be found in our sample (adjusted HR 0.91, 0.75–1.11).

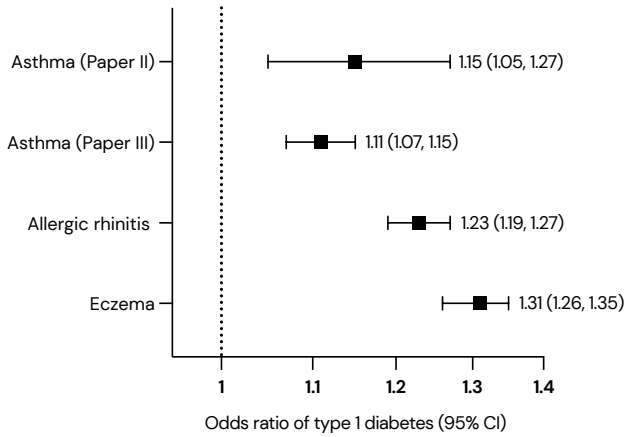

Figure 11 Association between allergic diseases and type 1 diabetes within-individuals presented as odds ratios with 95% confidence intervals, adjusted for sex and birth year

4.3.1.2 Other allergic diseases and type 1 diabetes

In *Paper III*, we expanded upon the findings from *Paper II* by also studying the co-occurrence of other allergic diseases – allergic rhinitis and eczema – with type 1 diabetes, given the known overlap between asthma and other allergic diseases (83). In individuals with allergic rhinitis (28.9%) or eczema (16.2%), type 1 diabetes was more frequent than in those without the respective allergic disease (Figure 11, p. 48) Results were estimated at end-of-follow-up and were symmetrical: OR of allergic rhinitis-type 1 diabetes (or vice versa) 1.23 (1.19–1.27) and OR of eczema-type 1 diabetes (or vice versa) 1.31 (1.26–1.35).

4.3.2 Association, causation, or misclassification?

The co-occurrence of allergic disease and type 1 diabetes has been a debate for several years in the literature. Despite the converging and large body of heterogenous research (see Background 1.3) making it difficult to draw conclusions, one could argue that the comorbidity remains biologically plausible. Th1- and Th2 immune responses do not seem to be as mutually exclusive as previously thought with multiple examples of overlap (206). For instance, signallers of both immune responses act in both allergic disease and type 1 diabetes. The question that ensues is, however, to understand what this comorbidity is due to. Does the association demonstrated represent a causal relationship? Is their unmeasured (including familial) confounding? Or what sources of misclassification may have biased the results? Potential mechanisms are outlined in Figure 12 (p. 50) and discussed in the following sections.

For asthma, the results of an increased risk of type 1 diabetes after previous asthma onset are in line with several studies, including a recent Danish nationwide register study that reported a HR of 1.32 (1.08, 1.61) (207). As in other studies, our findings may suffer from residual confounding by factors specific to the individual affecting both asthma and type 1 diabetes such as diet, microbial exposure, infections, or pregnancy-related factors including early-life stress. They may also represent a causal pathway that could be due to severity of the asthma disease itself, mediated through treatment for asthma such as inhaled corticosteroids (208), or may be explained if there are factors known to be a consequence of asthma that in themselves are triggers of type 1 diabetes. The hypothesis of a causal relationship is strengthened by findings of a bidirectional Mendelian randomization study that found evidence for a causal effect of asthma on type 1 diabetes, but not vice versa (209).

A Finnish study examining the bidirectional sequential appearance also noted an increased risk of subsequent type 1 diabetes (HR 1.41, 1.28–1.54) and found a decreased risk of subsequent asthma after type 1 diabetes (HR 0.82, 0.69–0.98), with confidence intervals overlapping ours (96). We concluded that type 1 diabetes is more common after asthma onset but not the other way around, due to a younger age at onset of asthma compared to type 1 diabetes. Metsälä et al. hypothesised that their findings of a

decreased risk of asthma may be indicative of a protective effect of type 1 diabetes, as supported by other older examples of research in the field (89). The fact that both diseases co-occur does not necessarily contradict that one disease may be protective of the other. Differences depending on age at onset remain to be investigated. Would findings be the same among those who had an early-onset diabetes? Or a later-onset asthma?

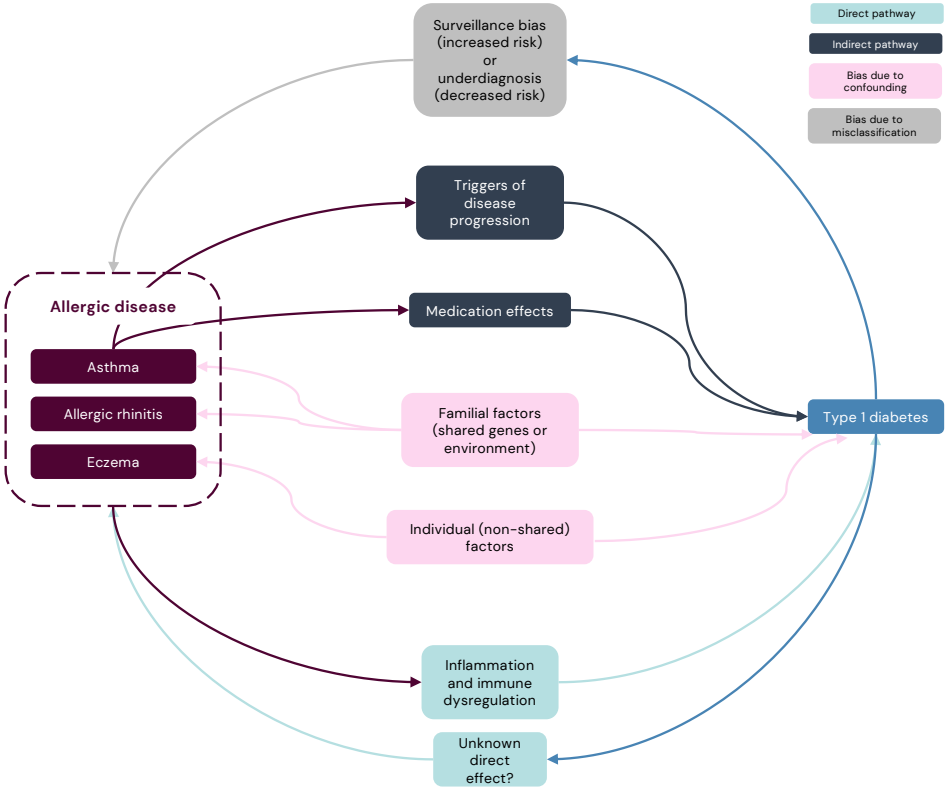

Figure 12 Schematic overview of potential pathways underlying an association between allergic disease and type 1 diabetes, or vice-versa, based on the findings of this thesis and previous literature.

Aside from an underlying biological mechanism, it may be possible that the finding of no or a lower risk of asthma among those with previous type 1 diabetes is due to misclassification. This could include underreporting (in retrospective studies) or underdiagnosing (in prospective register-based studies) symptoms of asthma in patients with type 1 diabetes, and might arise if physicians for instance more easily overlook milder issues when focusing on the treatment and care for diabetes. On the other hand, due to the frequency and continuity of hospital visits in a child with type 1 diabetes, bias, if any, ought to arise from more often being in contact with healthcare providers and would have resulted in an association in the opposite direction.

This type of surveillance bias may, however, be at play in the case of the co-occurrence between allergic rhinitis or eczema, and type 1 diabetes. There is a risk that children with type 1 diabetes more often are diagnosed or receive treatment for these milder conditions due to the increased number of physician contacts associated with type 1 diabetes care. To the best of our knowledge, there is no confirmed mechanistical explanation as to why children with type 1 diabetes might more often have an allergic disease. Speculations include a pro-inflammatory state that predisposes to both diseases as well as a dysregulation of immune response. For allergic rhinitis or eczema, it is possible that similar mechanisms as for asthma are at play in type 1 diabetes comorbidity. Since children with allergic rhinitis and eczema more often have asthma (210), it is also possible that co-occurring asthma itself is driving the comorbidity with type 1 diabetes. A bidirectional Mendelian randomization study found evidence in support of a causal relationship between eczema and type 1 diabetes, strengthening the possibility of an immune-mediated cause (211).

Taken together, the co-occurrence of allergic diseases and type 1 diabetes may have certain underlying causal pathways or be explained by residual confounding or misclassification. Aside from this, an alternative explanation is that these findings may also represent unmeasured familial confounding – which we attempted to deal with in the following analyses described below.

4.3.3 Familial co-aggregation points to shared familial factors

One of the main focus points of both *Papers II & III* was to understand if there was a familial liability to both allergic diseases and type 1 diabetes due to shared genetic or environmental factors. In order to do that we set out to examine the familial co-aggregation of the diseases. As outlined in more detail in Methodological considerations 3.4.2, this type of family-based design attempts to find proof of the presence of shared familial factors, in contrast to adjusting for it, in for instance a sibling analysis. For asthma, we found a familial co-aggregation between parent-offspring, full siblings and cousins. The pattern of the association with decreasing estimates upon increasing genetic distance and less shared factors indicates that either genes or environment may underlie the association (Figure 13, p. 52).

Familial co-aggregation was also present for allergic rhinitis, pointing to shared familial factors in that relationship as well, but could not be found for eczema and type 1 diabetes. This indicates that, for an eczema, a possible comorbidity with type 1 diabetes is more likely due to non-shared factors specific to the individual or a causal relationship as described previously.

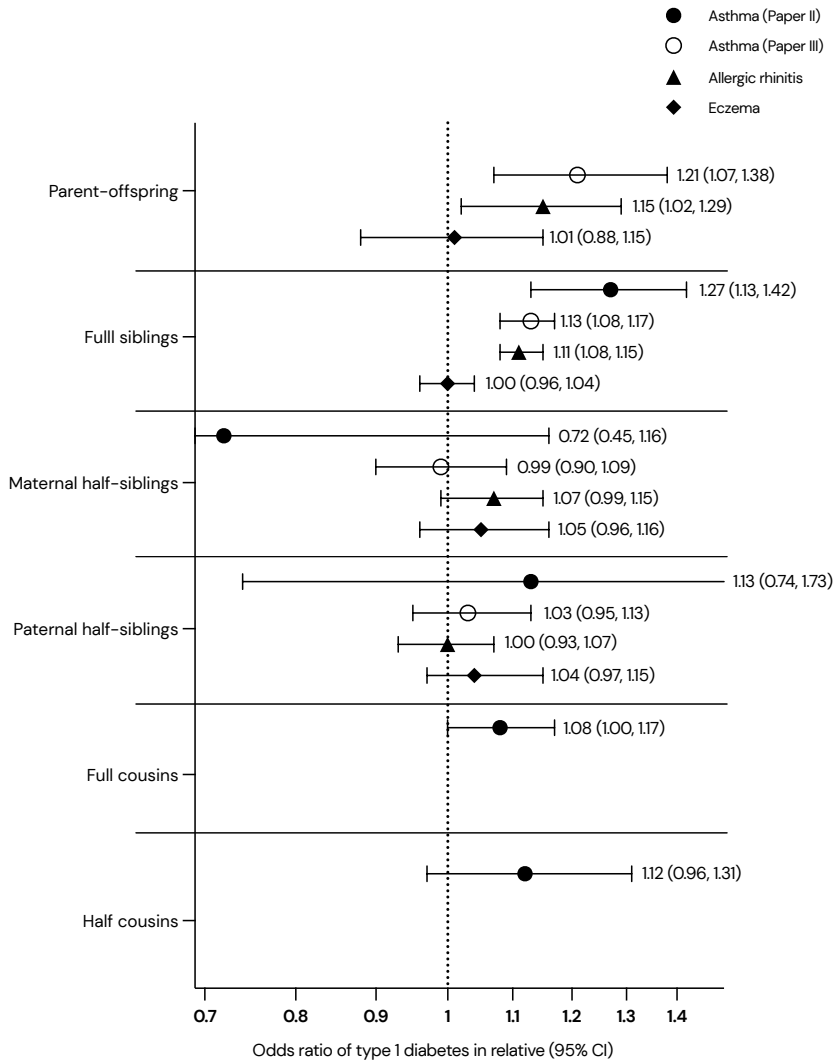

Figure 13 Results of familial co-aggregation between allergic diseases (asthma, allergic rhinitis, eczema) and type 1 diabetes from *Papers II & III.* Twins from *Paper III* are not displayed due to low sample size. Odds ratios with 95% confidence intervals represent the risk of type 1 diabetes in relatives of individuals with an allergic disease

4.3.4 Molecular genetic analyses

As performed in many studies, the next step upon finding evidence for shared familial factors is often to estimate how much is due to genes, environment or individual-specific (non-shared) factors using quantitative genetic modelling. As discussed in further detail in the attached paper, this was, mainly for power reason, not possible in *Paper III.* Instead, results from two molecular genetic analyses enabled us to better understand the genetic overlap.

First, in LD score regression analyses we found only weak, non-statistically significant genetic correlations between any of the allergic diseases and type 1 diabetes (see *Paper III*, Table 2). Second, polygenic risk scores for asthma were associated with higher odds of type 1 diabetes (ORs ranging 1.32–1.34), although confidence intervals included the null (Figure 14). In contrast, PRS for type 1 diabetes was not associated with asthma. This is interesting as if there truly were shared genetic factors underlying the relationship, results of PRS ought to have been bidirectional, i.e., PRS for either disease associated with the other disease phenotype. This one-sided association instead strengthens evidence for a potential causal relationship between asthma and type 1 diabetes. Neither allergic rhinitis nor eczema and type 1 diabetes were associated in PRS analyses. However, the predicting ability of the PRS especially for allergic rhinitis and eczema was limited (see *Paper III*, Figure S1), which might have contributed to the null findings.

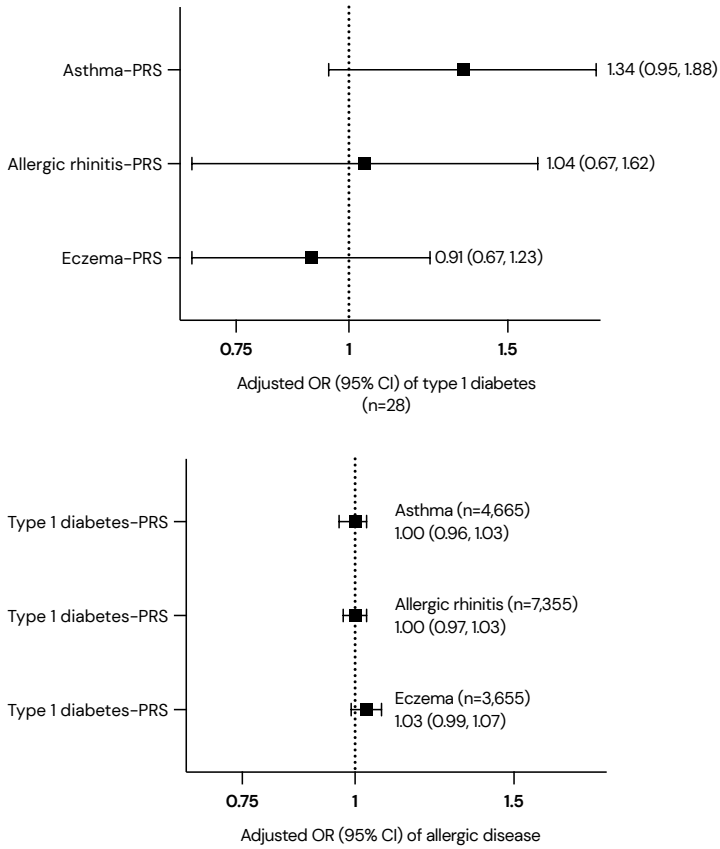

Figure 14 Association between polygenic risk scores for each allergic disease and type 1 diabetes phenotype (A), and between polygenic risk scores for type 1 diabetes and each allergic disease phenotype. Odds ratios with 95% confidence intervals were estimated from logistic regression models adjusted for adjustment for sex, birth year, and including interaction terms for the top five principal components and from which twin cohort in the Swedish Twin Registry the individual originated

4.3.5 Triangulating evidence

In summary, throughout *Papers II & III* we applied multiple study designs and methodologies, each with its own inherent strengths and limitations, in an attempt to better understand the comorbidity between allergic diseases and type 1 diabetes. Overall, taking our results and the body of literature together, current evidence is consistent with both a potential causal relationship of asthma on type 1 diabetes (but not type 1 diabetes on asthma) as well as shared familial factors contributing to their co-occurrence. For allergic rhinitis, shared familial factors may also play a role. For eczema, individual-level (non-shared) factors and/or a causal relationship may explain an association. Shared genes do not seem to be of great importance for any of the diseases given little evidence for a genetic overlap found using the molecular genetic methods applied. Of note is that although we demonstrate a co-occurrence of diseases with a relative increase of type 1 diabetes in individuals or relatives with an allergic disease, the absolute risk difference is small. For instance, in *Paper III*, 0.62% of those without asthma had type 1 diabetes, compared to 0.69% among those with asthma, i.e., a difference of 7 cases in 10,000 children.

4.4 Adult height outcomes

4.4.1 Description of study sample and their glycaemic control

In *Paper IV*, in our study sample of 12,095 individuals (55.4% males) with type 1 diabetes followed with HbA1c measurements in childhood or adolescence, and at least one height registration in adult age, 16.7% of males and 19.2% of females had a mean HbA1c of >75 mmol/mol, categorised as poor glycaemic control (Table 7, p. 55). Among those with poor glycaemic control, it was more prevalent to have had diabetes onset in earlier calendar years and at an earlier age in life, often before puberty (*Paper IV*, Table 1).

4.4.2 Final adult height

On average, those with poor glycaemic control reached lower height in adult age (Figure 15, p. 56). In males, mean adult height was 181.7 cm in those with optimal glycaemic control (>53 mmol/mol) compared to 178.7 cm in those poor control, corresponding to a mean difference in height of -2.91 cm (-3.48, -2.33). In adjusted models, covariates, including age at type 1 diabetes onset, explained some but not all of the association; adjusted mean difference -1.59 cm (-2.16, -1.01). However, the relationship between HbA1c and adult height was not fully linear, demonstrated by the pattern of mean height difference curves when modelling the data using restricted cubic splines (*Paper IV*, Figure 2). This more flexible approach showed that reductions in height were more pronounced per increase of HbA1c at mean HbA1c levels between 50–70 mmol/mol compared to differences per HbA1c increase at lower or higher values. This illustrates the

importance of maintaining an optimal glycaemic control and not only addressing those with extreme high values. Furthermore, in males, mean differences in height were similar irrespective of at what age in relation to puberty onset of diabetes occurred (p-value for interaction with age at onset 0.08; *Paper IV*, Table 3).

Table 7 Measures of glycaemic control and adult height outcomes presented by sex

	Males (n=6,699)	**Females** (n=5,396)
Measures of glycaemic control		
Category of mean HbA1c, no. (%)		
Optimal	1,309 (19.5)	847 (15.7)
Suboptimal	4,271 (63.8)	3,512 (65.1)
Poor	1,119 (16.7)	1,037 (19.2)
Mean HbA1c, mmol/mol (SD)	64 (12.9)	65 (13.0)
Time with poor glycaemic control, years (SD)	1.4 (2.3)	1.2 (1.8)
Mean HbA1c before puberty, no. (%)		
Optimal	3,993 (73.0)	2,966 (68.8)
Suboptimal	1337 (24.4)	1224 (28.4)
Poor	143 (2.6)	124 (2.9)
Mean HbA1c during puberty, no. (%)		
Optimal	2,051 (34.5)	1,316 (27.4)
Suboptimal	3,171 (53.3)	2,861 (59.5)
Poor	727 (12.2)	632 (13.1)
Mean HbA1c after puberty, no. (%)		
Optimal	1270 (19.0)	768 (14.2)
Suboptimal	4,079 (60.9)	3,401 (63.0)
Poor	1,350 (20.2)	1,227 (22.7)
Height outcomes		
Final adult height, mean (SD)	180.5 (7.3)	167.0 (6.6)
Short stature, no. (%)	174 (2.6)	117 (2.2)
Change in Z-score, mean (SD)	-0.1 (0.8)	0.0(0.7)

In females, similar associations between poor glycaemic control and adult height were found, with certain exceptions. Mean adult height was lower in those with poor (165.8 cm) compared to those with optimal glycaemic control (167.7 cm), mean difference -1.83 cm (-2.42, -1.23) in crude and -0.94 cm (-1.54, -0,34) in adjusted models (Figure 15, p. 56). These reductions in height were disproportionately less to the reductions in males. Yet for each year of poor glycaemic control during follow-up both males and females had on

average -0.27 cm lower height, i.e., a disproportionate effect in females compared to males in relation to their adult height. Also, in females, poor glycaemic control was only associated with final adult height in those with diabetes onset before puberty (-3.01 cm [-4.09, 1.94]; p-value for interaction with age at onset <0.001; *Paper IV,* Table 3).

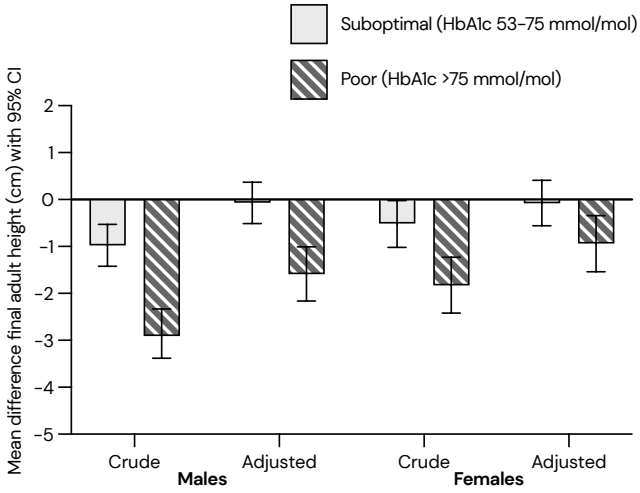

Figure 15 Mean difference in adult height comparing poor/suboptimal to optimal glycaemic control. Linear regression models are adjusted for age at onset of diabetes, calendar year of onset, any other autoimmune disease, asthma, maternal height, parental type 1 diabetes, parental country of birth, and highest level of parental education

In line with the finding of differences of the impact of age at onset in males and females, other sex-specific associations uncovered were in relation to the effect of mean HbA1c, separately studied, before, during, or after puberty in relation to final adult height (Figure 16, p.57). For males, associations with adult height were only apparent between mean HbA1c *during* or *after* puberty. For females, associations were only found if mean HbA1c had indicated poor glycaemic control *before* puberty.

Reasonably, these differences in males versus females stem from the natural differences in physiological growth between the sexes. Pre-pubertal growth is of greater importance in the attainment of final adult height in females, with peak growth velocity reached earlier than in males (159). Also, studies have shown that pubertal growth velocity in females with type 1 diabetes is reduced compared to their male peers (212–214), indicating that there is less growth potential in the pubertal and post-pubertal period compared to males. In addition, the findings ought not be explained by differences in levels of glycaemic control between the sexes given that females on average had worse glycaemic control before, during and after puberty compared to males (Table 7, p. 55).

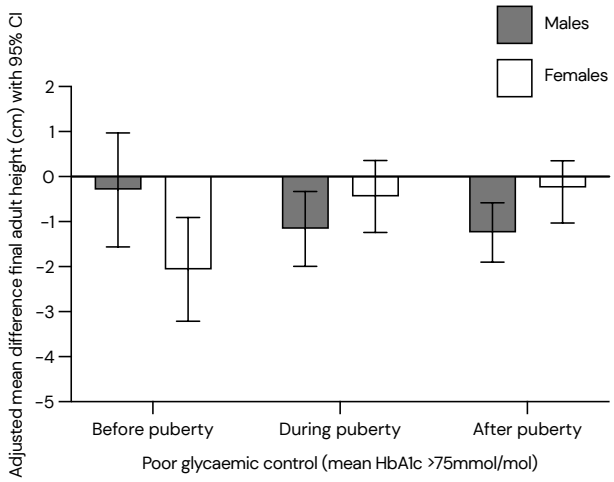

Figure 16 Mean difference in adult height comparing poor to optimal glycaemic control (suboptimal not shown). Linear regression models are adjusted for age at onset of diabetes, calendar year of onset, any other autoimmune disease, asthma, maternal height, parental type 1 diabetes, parental country of birth, and highest level of parental education

4.4.3 Short stature

To the best of our knowledge we also reported, for the first time, an association between poor glycaemic control and risk of short stature (Figure 17). In our sample, we defined short stature as a final adult height less than -2 SD from the mean, i.e., corresponding to being within the 2.3% shortest of the population. Males with poor glycaemic control had a roughly 3 times increased risk of short stature (OR 3.11 [1.87, 5.18]) which was statistically significantly higher than in females (OR 1.03, [0.56, 1.90], p-value of test for interaction by sex 0.01). The difference in risk for short stature between the sexes represents the larger impact of glycaemic control on height found in males compared to females.

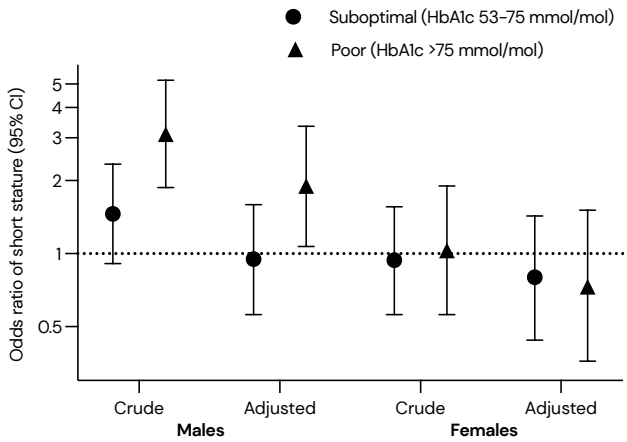

Figure 17 Association between category of glycaemic control (mean HbA1c during follow-up) and short stature in males and females, presented crude and adjusted for aforementioned covariates.

4.4.4 Change in Z-score for height

In a subsample with height registrations available near the onset of type 1 diabetes (n=4,227 males, 3,443 females) we were able to study the association between glycaemic control and change in Z-score for height (from onset to adulthood). Comparing poor to optimal glycaemic control, mean difference in the change in Z-score in males was -0.19 SD (-0.26, -0.12) and in females -0.12 SD (-0.19, -0.04). We were not able to find previous examples in the literature of studies evaluating differences in changes of Z-scores over time among patients with type 1 diabetes. Nevertheless, others have previously reported Z-scores for adult height of -0.30 SD among those with HbA1c >8.0% (no comparison group) (118) and 0.15 SD higher Z-scores for adult height in those with HbA1c <7.5% compared to >9.0% (115).

In summary, our findings support the hypothesis that poor glycaemic control is associated with lower adult height and short stature in individuals with type 1 diabetes. Comparison with previous literature is difficult given large differences in methodology concerning measurement of both glycaemic control and final adult height, but has in general reported an impact of glycaemic control or type 1 diabetes itself on growth or adult height (143,215). Previous research suggests that duration of diabetes affects final adult height (114,216–218). Our results are line with this given the attenuation after adjustment for age at onset, but also show that duration does not entirely explain the association. While strategies for treatment have advanced greatly over the past decade it seems that poor glycaemic control remains prevalent and has an impact on final adult height.

Our findings largely expand on the existing literature by more consistently reporting and uncovering sex-specific estimates, addressing age at onset in relation puberty, as well as studying associations for glycaemic control at different ages in relation to puberty. Nevertheless, we were bound by the clinical data available from the NDR and were therefore lacking information from growth charts such as peak height velocity for onset of puberty estimation or target height based on mid-parental height. It is possible that the shortest heights in our sample simply were consistent with those individuals' genetic expectations. However, we have not selected on height or genetic potential and as long as the inherent height potential does not affect glycaemic control, which we do not believe it does, target height ought not be a large source of residual confounding.

4.5 Overarching discussion

Throughout this thesis I have attempted to highlight strengths and limitations of the presented research through an integrated discussion throughout the sections 3

Methodological considerations and 4.2–4.4 Results and discussion. Further specific remarks can be found in the attached papers. Some general comments on internal and external validity are outlined in this section.

4.5.1 Internal validity

Important areas for addressing systematic errors that could pose a threat to the internal validity of the papers are misclassification, confounding and selection. Misclassification of the specific measures used in this thesis is discussed in 3 Methodological considerations, and confounding is addressed in sections related to family-design studies.

4.5.1.1 Misclassification

In register-based research we rely heavily on data availability and the quality of recorded data in defining exposures, outcomes and covariates. It is therefore of importance that these measures are valid in terms of sensitivity and specificity, and that we define and discuss variables in regard to risk of potential misclassification or measurement error. While many algorithms for identifying diseases from registers have been validated, including some used in this thesis, other medication and diagnoses combinations such as those we applied for depression/anxiety and type 1 diabetes have not yet been. Validating these disease definitions using the national healthcare registers should be a priority for Swedish research going forward, especially in relation to subtypes of phenotypes and severity.

The impact on the results that bias due to misclassification can have is sometimes hard to foresee. In the papers, misclassification of the exposure may have arisen in *Paper I* for the definition of maternal depression/anxiety or in *Papers II & III* for the definition of allergic disease, although we do not believe it to be differential in regard to the outcome of type 1 diabetes, and if present would have underestimated our estimates. Further, by conducting sensitivity analyses in different birth years, and across different disease definitions throughout the papers, the interpretations of the respective findings remained the same. Methods such as quantitative bias analysis (219) could have been useful in a scenario with differential misclassification in order to understand the magnitude and direction of bias that otherwise may not be intuitive.

4.5.1.2 Confounding

Complete confounder adjustment is oftentimes illusive in an observational research setting. To counter that in this thesis, we were able to apply several powerful and unique family-based designs throughout *Papers I–III* with the aim of adjusting for factors shared within families, or illustrating the presence of shared familial factors contributing to the co-occurrence of a comorbidity. While these designs can partially adjust for unmeasured confounding, residual confounding may always be present.

Related to data availability in the registers, lifestyle factors are notoriously tricky to adjust for. In this thesis, we lacked information on environmental tobacco exposure, diet, physical activity and other behaviours to name a few, which might have resulted in residual confounding. Advantageously, thanks to the plethora of information available in the registers spanning several generations we were able to adjusted for multiple known confounders in each paper.

4.5.1.3 Selection

Bias due to selection can arise from mechanisms, such as inclusion, exclusion, loss-to follow-up or missingness of data, that alter the balance between exposure and outcome in the study sample compared to the target population to which we aim to apply our findings. All papers of this thesis were population-based cohort studies using prospectively collected data with limited loss-to-follow-up or missingness, which has limited the risk of selection bias. Nonetheless, certain aspects can be discussed.

For instance, in *Paper IV,* we had a sample of individuals selected based on their inclusion in the quality register (the NDR). It is possible that a factor influencing participation in the NDR, such as socioeconomic status, also impacts glycaemic control and is associated with adult height.

Even among those participating in the NDR, selection bias may occur. As an example, in *Paper IV,* we had information on final adult height for 98% of the study population. We calculated the distribution of glycaemic control among the individuals we excluded due to missing adult height registrations as a way of a assessing the risk of selection bias in an exploratory analysis. We would have also been interested in assessing their near-adult height to see if missingness was related both to glycaemic control and height, but did not have that data due to differences in frequency and timing of height registrations. There were more females with height registrations who had poor glycaemic control (19.2% compared to 8.3%) which may reflect the fact that those with worse glycaemic control are monitored more closely with less time between check-ups and have a greater chance of their height being registered. While we can further only speculate on other underlying reasons of missingness, selection mechanisms do not seem to strongly contribute to bias given the small number of individuals excluded and that we only observed a different distribution of glycaemic control among females with missingness, but not males. Furthermore, even if our sample with adult height data had potentially worse glycaemic control, that does not necessarily mean that the results are not generalisable.

4.5.2 External validity

A major strength of the papers in this thesis is the population-based nature, resulting in a high generalisability to the Swedish population. Our findings are consequently most likely generalisable to other similar countries, especially in Scandinavia, that have comparable

demographics and healthcare systems. However, genetic susceptibility to type 1 diabetes, as well as to asthma or other allergic diseases, varies between individuals, and we cannot refute that the demonstrated associations may differ in high-risk populations. When possible, future studies should take this into account by including information on family history, HLA-subtype or polygenic risk scores. High-risk populations may benefit from directed interventions, screening or specific follow-ups with the goal of preventing onset of diabetes or mitigating complications.

5 Conclusions

The work presented in this thesis has helped expand on type 1 diabetes knowledge by focusing on three understudied areas of the disease's epidemiology, namely early life stress, allergic disease comorbidity, and adult height outcomes.

More specifically:

- Maternal depression or anxiety during pregnancy, used as a proxy for early life stress, is associated with offspring type 1 diabetes after 8 years of age. Paternal negative control and sibling comparison indicate that the findings are not fully explained by familial confounding.

- Allergic diseases, including asthma, allergic rhinitis, or eczema, co-occur with type 1 diabetes which could, for asthma and allergic rhinitis, partly be due to a shared familial liability, but does not seem to stem from a large genetic overlap.

- Poor glycaemic control in children and adolescents with type 1 diabetes is associated with lower final adult height in both males and females, and an increased risk of short stature in males. Age at onset of disease and timing of glycaemic control, both in relation to puberty, have an impact on the associations.

By harnessing the breadth of nationwide Swedish healthcare and sociodemographic registers, we were able to answer research questions that otherwise would have been impossible to study in an interventional setting, and have demonstrated the strengths of using a range of epidemiological approaches including family-based designs.

6 Points of perspective

In this section some specific ideas for future research alongside examples of clinical implications of this thesis are outlined in relation to each research aim.

6.1 Maternal stress as an early life origin

- Consistency across multiple definitions of early life stress could help strengthen evidence of the demonstrated associations. Alternative measures of stress should incorporate various biological phenomena as well as a range of severity and chronicity of symtoms. Alternative already-utilised register-based proxies of stress include bereavement, cancer diagnosis or stress-related disorders. Other diseases that may entail stress could be burnout, malaise or fatigue, post-Covid syndrome, or chronic pain conditions.
- Further investigation into the mechanisms underlying an association between maternal depression or anxiety duing pregnancy is warranted and should aim to delineate disease pathways mediated by symtoms, from treatment effects. Testing the safety of antidepressant medication on long-term health outcomes in children, such as the risk of type 1 diabetes, is important for physicians prescribing and patients taking these drugs.
- Prospective cohort studies with clinical measurements and biomarkers could help to better understand the associations between early life stress, including subjective and objective measures such as perceived stress or cortisol levels, and markers of autoimmunity preceding disease onset.

6.2 Childhood comorbidity with asthma and other allergic diseases

- The burden of disease can be high for children with type 1 diabetes, and can be accentuated by comorbidities. Understanding outcomes of the demonstrated comorbidity with asthma and other allergic diseases is of clinical relevance and of importance to those affected in order to identify those in need of targeted interventions. Aspects that may be of relevance include those related to health such as disease control, severity, treatment and complications, to socioeconomic measures such income, academic performance, or to quality of life. Measures of lung function and allergic sensitization could contribute with a more in-depth understandning of the comorbidity.
- A more in-depth analysis of the potential causal relationship between asthma and type 1 diabetes is warranted. Approaches for exploring this might include a sibling- or co-twin control model or a mediation analysis to separate direct from indirect medication effects. Using the target trial emulation framework (220) could help better design studies of the effect of asthma medication on subsequent diabetes development.

- Taking the results of *Paper I–III* together, understanding epidemiological similarities in terms of common risk factors for both type 1 diabetes and allergic diseases is of importance. What role does foetal programming play in the comorbidity? Could early life or childhood infections be shared risk factors? Is this modified by genetic risk and could PRS play a role in screening or preventative measures?

6.3 Adult height outcomes

- It is possible that large fluctuations in HbA1c are more detrimental for health outcomes than stable trajectories and measures such as glycaemic variability (221–223) may represent this better than means of time. How do different treatment strategies impact this and what are the consequences on growth and adult height?
- Qualitative research could bring valuable complementary perspectives to the research field and help identify what outcomes are important for individuals living with type 1 diabetes and their experience of the constant goal of optimal glycaemic control as well as an increased understanding of behaviours, societal and healthcare-related factors that impact these individuals.
- The findings from this study can be used in informing patients, parents and healthcare providers on the importance of glycaemic control in reaching adult height. For some, the findings that final adult height does not differ greatly may be reassuring. For others, they may be an added incentive in maintaining optimal glycaemic control. Regardless of the individual's personal stance or view of the importance of adult height, having a stable glycaemic control is of utmost importance for all and should remain a priority.

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