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The risk of type 1 diabetes in immigrants and their offspring in Sweden: the influence of perinatal factors

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THE RISK OF TYPE 1 DIABETES IN IMMIGRANTS AND THEIR OFFSPRING IN SWEDEN: THE INFLUENCE OF PERINATAL FACTORS

Hozan Ismael Hussen



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In the name of God the Merciful the Compassionate

Dedicated to the loving memory of my Father

“Education is the most powerful weapon which you can use to change the world”

Nelson Mandela (1918-2013)

ABSTRACT

Aims: The overall aim of this study was to investigate the trend in and risk factors for type 1 diabetes, with particular reference to parental socioeconomic position (SEP) and country of birth of subjects and their parents. We examined the effects of maternal body mass index (BMI), maternal duration of residence and parental diabetes on the risk of type 1 diabetes among children and adolescents/young adults with native Sweden-born or immigrant parents.

Materials and methods: We used data from a nationwide dataset, The Migration and Health Cohort, in which information has been collected from national, longitudinal and clinical, health and sociodemographic registers (Studies I–IV). We followed the populations of children (0–14 years) and adolescents/young adults (15–30 years) born outside Sweden (immigrants), born in Sweden with at least one parent born outside Sweden (offspring of immigrants) and born in Sweden with both parents born in Sweden between 1969 and 2009. Incidence rate ratios with 95% confidence intervals for type 1 diabetes were estimated using Poisson regression models (Studies I–IV). We further calculated age-standardized rates of type 1 diabetes, using the world population as standard (Studies I and II).

Results: We observed an upward trend in type 1 diabetes incidence among children younger than 15 years of age, but not among adolescents/young adults aged 15 to 30 years (Studies I and II). We also observed a shift towards a younger age at diagnosis both in offspring born to native Swedes and those born to immigrants (Study II). Boys younger than 15 years with parents with a low level of education as an indicator for a low level of SEP had a 9% decreased risk of type 1 diabetes compared with boys with highly educated parents, whereas no effect of parental education was found among girls. By contrast, among adolescents/young adults aged 15–30 years, the risk of type 1 diabetes decreased with increasing parental level of education (Study I). Compared with children of Sweden-born parents, immigrants and their offspring had a lower risk of type 1 diabetes. The lower risk was more pronounced among offspring with both parents born abroad (Studies I and II). Among children and young adult immigrants born in Asia, South Europe, East Europe and Latin America, the risk of type 1 diabetes was between 40% and 85% lower than in individuals born in Sweden (Study I). Among offspring of Asian, European (except North European) and Latin and North American parents, the risk of type 1 diabetes was between 35% and 65% lower than among offspring of Sweden-born parents, whereas the risk was 45–60% higher in offspring of East African parents (Study II). In comparison to offspring of non-diabetic parents, a seven-fold increased risk of type 1 diabetes was observed in offspring of both Nordic and non-Nordic parents with type 1 diabetes (Study III). In the Nordic cohort, fathers with type 1 diabetes conferred a greater risk of type 1 diabetes to their offspring than mothers, whereas maternal type 1 diabetes conveyed a higher risk in the non-Nordic cohort (Study III). Maternal obesity was associated with a 36% increased risk of type 1 diabetes in offspring of non-diabetic parents (Study III). The risk of type 1 diabetes increased with increasing duration of residence of the mother before delivery. The highest risk was observed in offspring of East African mothers who had been resident in Sweden for at least 11 years (Study IV).

Conclusions: Country of birth is an important determinant of type 1 diabetes risk. The change in risks of type 1 diabetes over time and generations highlights the importance of lifestyle and environmental factors and their interaction with the genetic background in the aetiology of type 1 diabetes. Increasing prevalence of maternal overweight and obesity may partly explain the increasing incidence of type 1 diabetes in children of non-diabetic parents.

LIST OF SCIENTIFIC PAPERS

- I. **Hozan Ismael Hussen**, Dong Yang, Sven Cnattingius, Tahereh Moradi
Type 1 diabetes among children and young adults: the role of country of birth, socioeconomic position and sex.
Pediatric Diabetes. 2013 Mar; 14(2):138-48.
- II. **Hozan Ismael Hussen**, Martina Persson, Tahereh Moradi
The trends and the risk of type 1 diabetes over the past 40 years: an analysis by birth cohorts and by parental migration background in Sweden.
BMJ Open. 2013 Oct 31; 3(10):e003418.
- III. **Hozan Ismael Hussen**, Tahereh Moradi *, Martina Persson *
Maternal overweight and obesity increase the risk of type 1 diabetes in offspring of parents without diabetes regardless of ethnicity.
In revision.
- IV. **Hozan Ismael Hussen**, Tahereh Moradi, Martina Persson
The risk of type 1 diabetes among offspring of immigrant mothers in relation to the duration of residency in Sweden.
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* Both authors contributed equally to this work

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LIST OF ABBREVIATIONS

| | |
|---------|---|
| ADA | American Diabetes Association |
| AGA | Appropriate for gestational age |
| APC | Annual percentage change |
| ASR | Age-standardized rate |
| BMI | Body mass index |
| CI | Confidence interval |
| CTLA4 | Cytotoxic T lymphocyte antigen 4 |
| FGP | Fasting plasma glucose |
| GADA | Glutamic acid decarboxylase autoantibody |
| HbA1c | Glycated haemoglobin |
| HLA | Human leukocyte antigen |
| IAA | Insulin autoantibody |
| IA-2A | Insulinoma-associated 2 autoantibody |
| ICA | Islet cell autoantibody |
| ICD | International Classification of Diseases |
| IDF | International Diabetes Federation |
| INS | Insulin gene |
| IRR | Incidence rate ratio |
| LGA | Large for gestational age |
| LISA | The Longitudinal Integration Database for Health Insurance and Labor Market |
| MBR | Medical Birth Register |
| M&H Co. | Migration and Health Cohort |
| NPR | National Patient Register |
| PIN | Personal identification number |
| PTPN22 | Protein tyrosine phosphatase |
| SEP | Socioeconomic position |
| SGA | Small for gestational age |
| WHO | World Health Organization |
| ZnT8A | Zinc transporter autoantibody |

1 INTRODUCTION

1.1 DIABETES MELLITUS

Diabetes mellitus refers to a group of endocrine disorders characterized by hyperglycaemia and disturbances of carbohydrate, fat and protein metabolism, resulting from inadequate insulin secretion and/or insulin action. The main pathogenic processes involved in the development of diabetes include autoimmune destruction of the pancreatic beta-cells. The chronic hyperglycaemia and metabolic dysregulation associated with diabetes causes long-term impairment of various organs such as the eyes, heart, kidneys, nerves and blood vessels due to microvascular or macro vascular complications [1, 2].

1.2 CLASSIFICATION OF DIABETES MELLITUS

According to the American Diabetes Association (ADA) [3], diabetes is classified into four main types:

(1) Type 1 diabetes (previously known as insulin-dependent diabetes mellitus or juvenile diabetes) is the most common form of diabetes in children and adolescents, but it also may develop in adults. It accounts for 5–10% of all cases of diabetes. Type 1 diabetes is a multifactorial disease resulting from a complex interaction between genetic, environmental and immunological factors that eventually lead to the destruction of insulin-producing beta-cells and an absolute lack of insulin [4]. In this condition the body fails to produce insulin, a hormone needed to obtain energy from sugar and other foods. Individuals with this type of diabetes require daily insulin therapy to achieve good blood glucose level.

The clinical manifestation of type 1 diabetes may differ, depending on the rate of beta-cell destruction and age at onset. Patients with type 1 diabetes mostly present with the classical symptoms of polyuria, polydipsia, polyphagia, and weight loss. Some patients, especially children and adolescents, may present with diabetic ketoacidosis at the time of diagnosis. Diabetic ketoacidosis is a life-threatening condition that requires immediate hospitalization and medical treatment. In countries with poor health services, diabetic ketoacidosis is the primary cause of death in individuals with type 1 diabetes [5, 6].

(2) Type 2 diabetes (formerly non-insulin-dependent diabetes mellitus or adult-onset diabetes) is the most common form of diabetes accounting for about 90% of all cases. Type 2 diabetes is characterized by insulin resistance and relative insulin deficiency. The exact cause

of type 2 diabetes is not well understood but is likely to be a combination of genetic and lifestyle factors, such as excess weight and physical inactivity.

(3) Gestational diabetes is defined as any degree of glucose intolerance that develops during pregnancy but may disappear after delivery. Gestational diabetes occurs in 2–10% of pregnancies when insulin sensitivity is reduced by the action of various hormones produced by the placenta. This in turn causes rising blood sugar levels that can affect pregnancy and birth outcomes. Women with gestational diabetes are at risk of developing type 2 diabetes. Therefore, continuous monitoring and management of blood glucose levels during and few months after pregnancy are advised.

(4) Other specific types include genetic defects of beta-cell function or insulin action, diseases of the exocrine pancreas, endocrinopathies, drug-induced or chemical-induced diabetes, infections, uncommon forms of immune-mediated diabetes and other genetic syndromes sometimes associated with diabetes.

1.3 DIAGNOSIS

Diagnosis of diabetes mellitus can be established by one of the following four tests:

(1) The glycated haemoglobin (HbA1c) test shows the average blood glucose level over a period of weeks by measuring the percentage of blood glucose attached to haemoglobin. An HbA1c value of $\geq 6.5\%$ (≥ 48 mmol/mol) on two separate occasions indicates the presence of diabetes.

(2) The fasting plasma glucose (FPG) test is the most commonly used method for diagnosing diabetes because it is more convenient and less expensive than other techniques. The FPG test is performed after fasting (no caloric intake) for at least 8 hours. A FPG level of at least 126 mg/dL (7 mmol/L) on two separate occasions is considered indicative of diabetes.

(3) The oral glucose tolerance test is the most common method for determining glucose tolerance. This test should be performed according to the World Health Organization (WHO) guidelines using 75 g anhydrous glucose dissolved in water. A level of >200 mg/dL (11.1 mmol/L) 2 hours after the test suggests a diagnosis of diabetes.

(4) The random plasma glucose test measures the amount of circulating glucose in the blood at any given time. Unlike the FPG test, it is simple method that can be performed without

fasting. A random plasma glucose level ≥ 200 mg/dL (11.1 mmol/L) plus classical symptoms of hyperglycaemia or hyperglycaemic crisis suggests the presence of diabetes [1, 3].

1.4 MIGRATION IN SWEDEN

The number of immigrants and their descendants has increased in Sweden during the last decades (Figure 1). On 31 December 2013, the total population of Sweden was 9 644 864 with the foreign-born population estimated to be 1 533 493 (15.9%), including 748 366 and 785 127 foreign-born men and women, respectively. In Sweden there are 2 001 190 persons with a foreign-born background (individuals born outside Sweden or those born in Sweden with both parents born abroad), corresponding to 20.7% of the total population [7]. Between 1850 and 1930, Sweden was a country of net emigration, mainly to North America. Since 1930, migration to Sweden has increased because of various factors, including labour, social, religious and political reasons, and thus Sweden has changed to become a country of net immigration. In the 1940s, there was a rise in the Swedish population in the proportion of foreign-born individuals, most of whom were refugees from the Second World War [8]. During the 1950s and 1960s, demand for jobs within Swedish industry was the main reason for a large number of labour migrants from neighbouring Nordic countries, especially Finland, and also from South and Central Europe and Turkey [8].

From the 1970s to the 2000s, the nature of migration changed: immigrants were mainly refugees and asylum seekers due to political tension in different parts of the world. In the 1970s, refugees came from Uganda and South America. During the 1980s, immigration was predominantly from Asian countries, with refugees from Iran and Iraq. In the 1990s, refugees were mainly from the former Yugoslavia. In the 2000s, there was a rise in the number of asylum seekers to Sweden due to civil war in Iraq and Somalia [8, 9]. More recently a new wave of immigrants from Syria, as a result of civil war, has found a place of refuge in Sweden [10].

In 2013, Statistics Sweden reported that the 10 largest groups of foreign-born individuals in Sweden were from Finland, Iraq, Poland, the former Yugoslavia, Iran, Bosnia and Herzegovina, Somalia, Germany, Turkey and Denmark (Figure 2) [11].

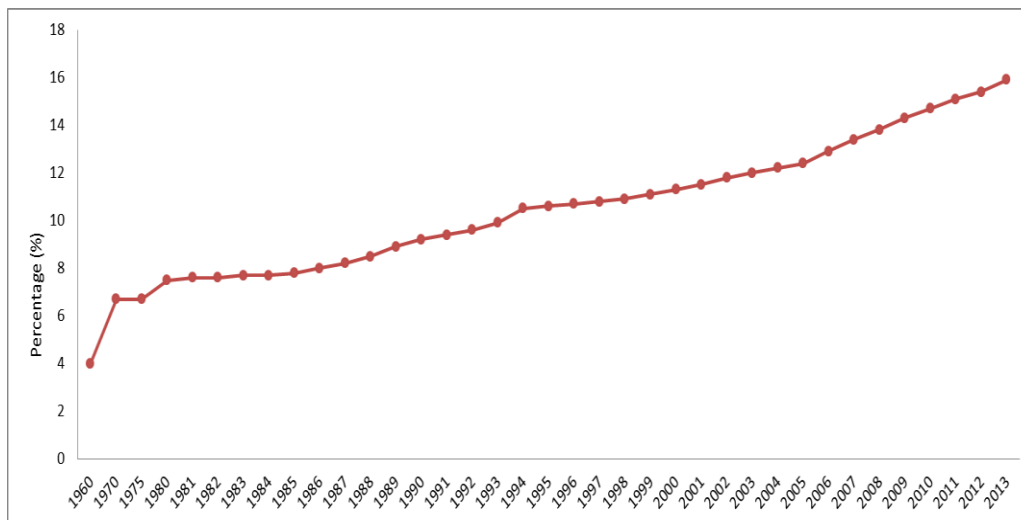


Figure 1: Proportion of foreign-born population in Sweden between 1960 and 2013 (Statistics Sweden).

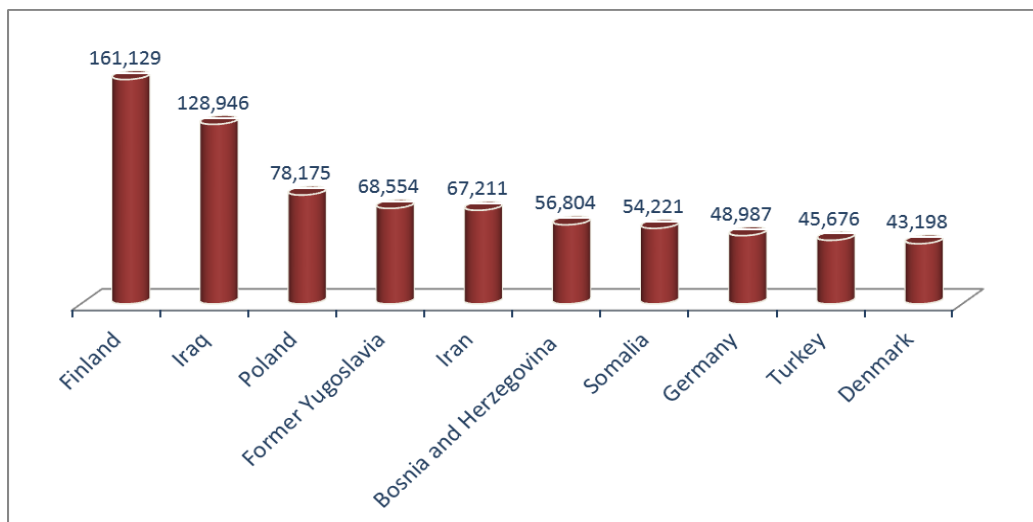


Figure 2: The 10 largest groups of foreign-born individuals in Sweden in 2013 (Statistics Sweden).

1.5 MIGRATION STUDIES

The incidence of type 1 diabetes has increased in populations that have moved from low-risk to high-risk regions [12-16]. The variation in the incidence of type 1 diabetes after migration suggests the importance of changes in environmental factors in the development of the disease. By contrast, variations in incidence between neighbouring areas with similar environmental exposure [17, 18] highlight the significant role of genetics in the development of type 1 diabetes. Thus, conducting studies among immigrants may be a valuable way to investigate the influence of gene–environment interaction on the occurrence of type 1 diabetes.

1.6 EPIDEMIOLOGY OF TYPE 1 DIABETES

The incidence of type 1 diabetes is increasing at an alarming rate in many countries worldwide [19-23]. The overall increase is estimated at around 3% annually with the greatest increase in the youngest age group [24-26].

In addition to secular trends over time, epidemiological investigations throughout the world have demonstrated wide geographical variations of type 1 diabetes incidence both between and within countries (Figure 3). The incidence ranges from the lowest in Asia and South America (0.1/100 000/year in China and Venezuela) [27, 28] to the highest in Europe, especially North Europe (more than 64/100 000/year in Finland) [29, 30].

Geographical variation has been reported within countries, including in Sweden [31, 32], Finland [33, 34], Norway [35], England [36], Italy [37], Germany [38] and Austria [39]. This variation in incidence rates of type 1 diabetes between countries and regions may be due to differences in distribution of environmental and genetic risk factors [25].

Worldwide, there are approximately 500 000 children younger than 15 years of age with type 1 diabetes, of whom 129 000 live in Europe and 108 700 in North America [25]. According to the recent estimates by the International Diabetes Federation (IDF), approximately 79 000 new cases of childhood type 1 diabetes were diagnosed in 2013 [40].

In Sweden, data have been recorded in a population-based register for more than 20 years [41]. After Finland, Sweden has the highest reported incidence of type 1 diabetes in the world. The current incidence rate of type 1 diabetes is estimated to be more than 40/100 000 person-years in children aged 0–15 years [42]. Studies from Sweden have demonstrated that the incidence of type 1 diabetes is increasing with a shift towards a younger age at onset. By

contrast, no increase in the incidence has been observed in individuals older than 15 years of age [23, 43]. In a recent study of individuals in Sweden aged 15–34 years, a decreasing incidence of type 1 diabetes was demonstrated [44], and this pattern has also been observed in studies from other parts of the world [45, 46].

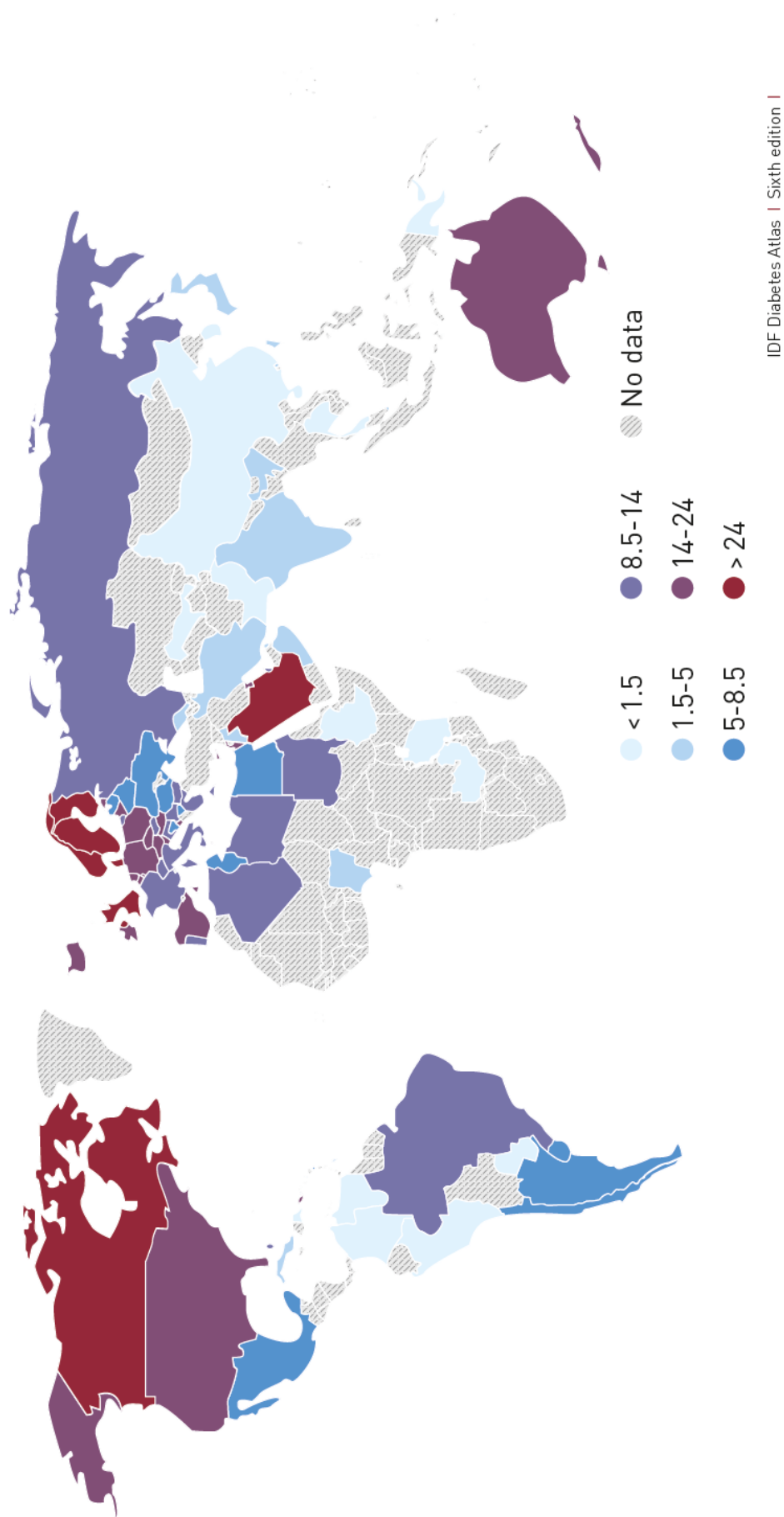


Figure 3: Worldwide incidence of type 1 diabetes per 100 000 persons per year in children aged 0–14 years (in 2013)

1.7 AETIOLOGY OF TYPE 1 DIABETES

The precise aetiology of type 1 diabetes is not yet completely understood. It is widely accepted that genetic predisposition plays a role, and exposure to one or several environmental factors may trigger the disease.

Type 1 diabetes can be subdivided into immune-mediated diabetes (type 1A) and idiopathic diabetes (type 1B). Type 1A is the most common disease type, accounting for approximately 80–90% of all type 1 diabetes cases. It generally results from cellular and humoral-mediated autoimmune destruction of insulin-producing beta-cells in the pancreas.

The rate of beta-cell destruction is rapid in infants and young children, and this may result in disease manifestation within a few months, whereas the process may take several years before the clinical presentation of overt disease in adults [3, 47, 48].

The majority of newly diagnosed patients with immune-mediated diabetes are positive for one or more islet-specific autoantibodies months to years prior to the clinical onset of the disease [49, 50].

Five autoantibodies are known to play an important role in the progression of beta-cell autoimmunity, including (1) islet cell autoantibodies (ICAs), (2) glutamic acid decarboxylase autoantibodies (GADAs), (3) insulinoma-associated 2 autoantibodies (IA-2As), (4) insulin autoantibodies (IAAs) and (5) zinc transporter autoantibodies (ZnT8As). The appearance of these autoimmunity biomarkers can be used to identify at-risk individuals during the pre-diabetic phase [51-53].

In the small group of patients with idiopathic or type 1B diabetes, the cause of beta-cell destruction is unknown. This form of diabetes has similar clinical features to type 1A disease, but there is no evidence of beta-cell autoimmunity [3, 54].

1.8 GENETICS OF TYPE 1 DIABETES

Genetic predisposition seems to be essential for the development of type 1 diabetes [51, 55]; however, the majority of patients do not have a family history of the disease [56, 57]. Type 1 diabetes runs in families and the risk increases significantly in first-degree relatives of patients with the disease. The risk of developing type 1 diabetes in individuals with no family history is approximately 0.4% [58]. Siblings of affected children with type 1 diabetes have a 3–6% risk of developing the disease. Children of affected mothers have a 2–4% risk, whereas those of affected fathers have a 5–8% risk and the offspring of two affected parents have

more than a 30% risk of type 1 diabetes [59, 60]. Genetic susceptibility for type 1 diabetes is greatest in childhood-onset disease and modest in disease that starts in adulthood [60, 61].

Susceptibility for type 1 diabetes is strongly associated with human leukocyte antigen (HLA) genes located on the short arm of chromosome 6 (6p21.3) [62, 63]. The HLA system is grouped into three classes (classes I, II and III), of which HLA class II DR3 (HLA-DRB1*0301 and DQB1*0201) and DR4 (HLA-DRB1*04 and DQB1*0302) genes are highly associated with the risk of type 1 diabetes [49]. The combination of these two alleles (DR3/DR4) produces the major genetic susceptibility for the disease [64].

In addition to HLA, several other non-HLA genes might also be involved in the aetiology of type 1 diabetes including the insulin gene INS on chromosome 11, the cytotoxic T lymphocyte antigen 4 (CTLA4) gene at the susceptibility locus and the protein tyrosine phosphatase (PTPN22) as well as other susceptibility loci [50, 51].

1.9 PERINATAL FACTORS

Current hypotheses of the pathophysiology of type 1 diabetes are based on the demonstration that environmental factors such as viral infections may initiate islet autoimmunity in genetically susceptible individuals. The process of beta-cell destruction may be accelerated by factors such as rapid postnatal growth, which increases the demand on the beta-cell mass resulting in the development of type 1 diabetes.

A number of perinatal factors such as parental age at delivery, birth order, birth weight, gestational age, preeclampsia, delivery by caesarean section, gestational infection and isoimmunisation due to blood group incompatibility have been considered to be risk factors for type 1 diabetes, and may contribute to the increasing incidence of type 1 diabetes [65-68]. However evidence regarding the influence of some of these factors remains conflicting and unclear.

Some studies have also demonstrated that high maternal body mass index (BMI) is a risk factor for type 1 diabetes in the offspring [69, 70]. High maternal BMI per se is associated with increased risk of a number of adverse pregnancy outcomes [71-74]. It has been proposed that being overweight during pregnancy, which often results in gestational diabetes, might lead to increased risk of type 1 diabetes in the offspring during early life [75]. Maternal diabetes and increased weight during pregnancy lead to overstimulation of the fetal pancreatic beta-cells. Insulin is an important growth factor, and rapid intrauterine growth is associated with increased insulin secretion [76]. It has been shown that hyperactive beta-cells

are more susceptible to immune-mediated destruction and predisposition towards type 1 diabetes [77].

In a Swedish register-based study, maternal-child blood group incompatibility was identified as the strongest perinatal risk factor for type 1 diabetes [78].

Strong associations between maternal BMI and both birth weight and BMI in childhood and adolescence have also been reported [79, 80]. Recently, Dahlquist reviewed the importance of high birth weight and rapid postnatal growth, as well-recognized estimates of overall wealth and lifestyle habits, as risk factors for type 1 diabetes, both between and within ethnic groups [81]. Others have also reported an association between high birth weight and increased risk of type 1 diabetes in children [82-84].

1.10 ENVIRONMENTAL FACTORS

The observed increasing trend and international variation in the incidence of type 1 diabetes cannot be attributed to genetic factors alone, but rather may reflect a critical role of changes in lifestyle and environmental factors in the aetiology of type 1 diabetes [70, 85]. The process by which environmental factors trigger/and or accelerate the immune-mediated attack of the beta-cells is not fully understood.

Environmental factors that have been proposed to have a pathophysiological role in the development of type 1 diabetes include viral infections, particularly enteroviruses, rubella, mumps, rotavirus, parvovirus and cytomegalovirus [86-88], nutrition in early life, such as early introduction of cow's milk, low vitamin D levels, nitrates and early or late introduction of cereals and gluten [89-91], and a number of perinatal complications [66, 68, 92, 93].

These environmental factors may initiate and accelerate islet autoimmunity, leading to excessive beta-cell destruction and the clinical onset of type 1 diabetes.

The crucial role of environmental factors in the pathogenesis of type 1 diabetes is suggested by several findings, including (1) rapid changes in incidence of type 1 diabetes among children over time, (2) a low concordance rate of type 1 diabetes of 30–50% for monozygotic twins, (3) a more than 10-fold difference in incidence of type 1 diabetes in children younger than 15 years of age in countries within Europe, (4) a decrease in the proportion of individuals with high-risk HLA among newly diagnosed cases of type 1 diabetes, compared to an increase in the proportion of those with low-risk HLA genotypes over the past decades

and (5) an increased incidence of type 1 diabetes in populations after moving from low-risk to high-risk areas, as shown in migration studies [47, 94].

Other risk factors such as age and sex are also associated with an increased incidence of type 1 diabetes. In most populations, the highest risk is observed in children below 15 years of age [95, 96]. The incidence peaks during puberty between the ages of 10 and 14 years, then decreases after puberty and seems to reach a steady state after 20 years of age [31, 35, 45].

A specific pattern of male predominance of type 1 diabetes has been observed in high-risk countries, whereas female predominance is reported in countries with a low risk of disease [60, 97]. In Sweden, the pattern of male excess of type 1 diabetes has been observed only in individuals aged 15–39 years and not in children younger than 15 years of age [98].

1.11 SOCIOECONOMIC POSITION

The impact of socioeconomic position (SEP) on the risk of type 1 diabetes has been investigated both at the individual and regional level [99-103].

Epidemiological studies of the association between SEP and incidence of type 1 diabetes have shown contradictory results. Some studies have reported a higher risk of type 1 diabetes in more wealthy areas [104, 105], whereas others have demonstrated a greater risk in deprived areas [106].

Living in urban areas and high SEP at the time of diagnosis have been independently associated with an increased risk of type 1 diabetes in Western Australian children [107]; by contrast, no association between indicators of SEP and the risk of type 1 diabetes was found in other studies [108, 109]. An ecological analysis of population-based European registers over a wide range of incidence rates of type 1 diabetes showed that the incidence of the condition was strongly correlated with the official estimates of gross national product [81].

Parental level of education, as a commonly used indicator of SEP, has also been shown to affect children's health. Low levels of parental education have been associated with increased risk of type 1 diabetes in children in some studies [100, 106, 110]; however, in other studies, a low level of education was associated with a reduced risk of type 1 diabetes in children aged 4-14 years [111].

2 AIMS AND HYPOTHESES

2.1 GENERAL AIMS

The overall aim of this thesis was to investigate the trend in and risk factors for type 1 diabetes, with particular reference to subjects' country of birth and parental country of birth and level of education. Further, we investigated the effect of perinatal factors, maternal duration of residence and parental diabetes on the risk of type 1 diabetes among children and young adults with Sweden-born or immigrant parents.

2.2 SPECIFIC AIMS AND HYPOTHESES

The specific aims were to study the risk of type 1 diabetes among children and young adults in relation to the following variables.

Parental SEP

- Does the incidence of developing type 1 diabetes differ between children and young adults with different parental level of education? (Study I).

Country of birth of cases

- Do the incidence of and trend in type 1 diabetes differ between Sweden-born and foreign-born children and young adults? (Study I).
 - We hypothesized that by moving to Sweden the risk of type 1 diabetes in foreign-born children and young adults would become similar to that of native Swedes.

Parental country of birth

- Does the risk of developing type 1 diabetes differ between children and young adults with Sweden-born (both mother and father) and foreign-born (mother or father) parents? (Study I).

- Do the trend in and risk of developing type 1 diabetes differ between children and young adults born in Sweden with Sweden-born (both mother and father) and foreign-born (mother only, father only or both) parents? (Study II).
 - We hypothesized that the risk of developing type 1 diabetes in offspring of immigrants would be higher than the risk in immigrants, and closer to that of offspring of Sweden-born parents.

Birth cohorts

- Is there a shift towards younger age at diagnosis of type 1 diabetes in offspring of immigrants? (Study II).
 - We hypothesized that if environmental exposures are important for the development of type 1 diabetes, one would observe the same change in age at onset of type 1 diabetes in offspring of immigrants as in offspring of native Swedes.

Perinatal factors

- Is the risk of developing type 1 diabetes modified by parental diabetes in offspring of parents with different migration background? (Study III).
- Is the risk of developing type 1 diabetes modified by maternal overweight or obesity in offspring of parents with and without diabetes and of different migration backgrounds? (Study III).
 - We hypothesized that the combination of any type of maternal diabetes and being overweight or obese during early pregnancy will be associated with an increased the risk of type 1 diabetes in the offspring, regardless of parental migration background.

Maternal duration of residence in Sweden

- Does the duration of residence in Sweden of a foreign-born mother before delivery affect the risk of the offspring developing type 1 diabetes? (Study IV).
 - We hypothesized that the risk of type 1 diabetes in the offspring of immigrants would increase with increasing duration of residence of the mother in Sweden.

3 MATERIALS AND METHODS

3.1 DATABASES

The data used for the studies in this thesis are based on the information available in a nationwide dataset, The Migration and Health Cohort (M&H Co.) [112]. This database was created by individual record-linkage between more than 15 Swedish, national, longitudinal, clinical, health and sociodemographic registries (Figure 4). The linkage has been completed using the Swedish 10-digit unique personal identification number (PIN), which is provided by the National Tax Board for all individuals who have resided in Sweden for longer than 1 year since 1947. The PIN has been replaced by serial numbers and the key code is kept by Statistic Sweden to ensure confidentiality. The purpose of the M&H Co. is to facilitate studies on diabetes, cancer, cardiovascular and psychiatric diseases among immigrants and their offspring and among socially disadvantaged populations in Sweden.

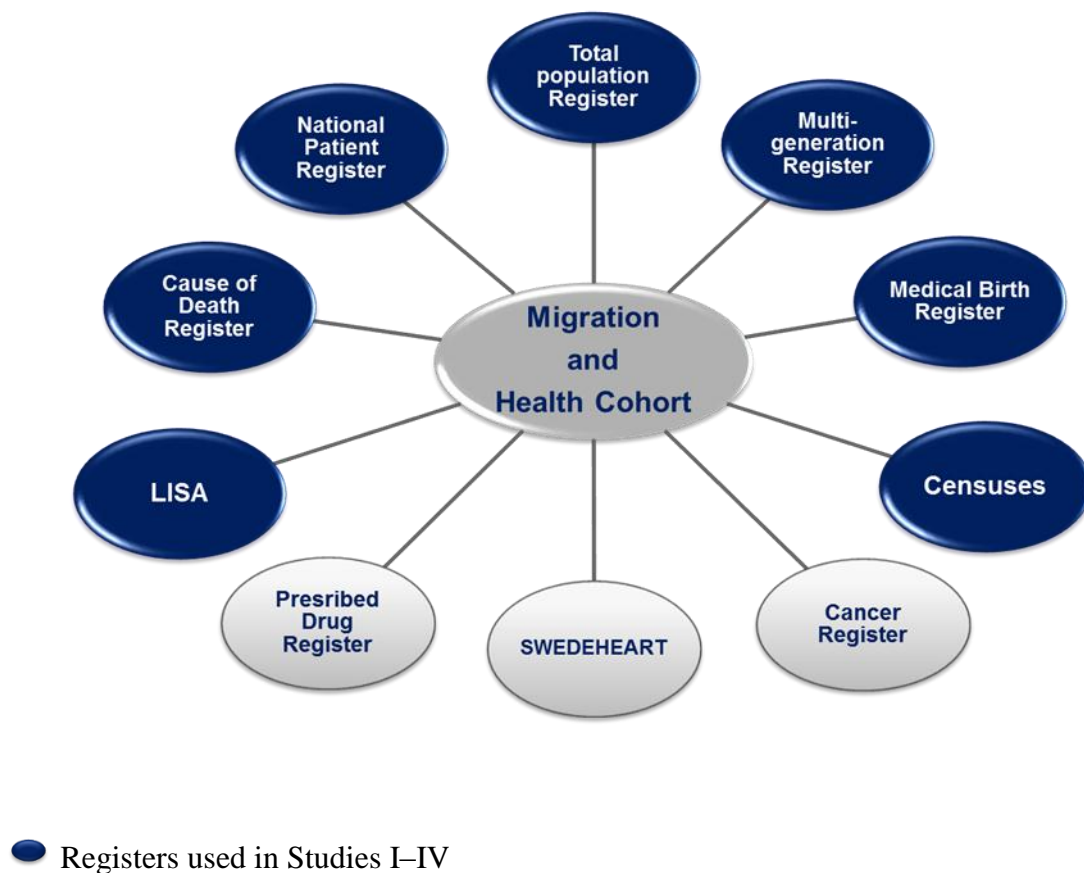


Figure 4: The Migration and Health Cohort

The data used in this thesis, as part of the M&H Co., were obtained from the following registries:

3.1.1 The Total Population Register

Population registration in Sweden dates back to the 17th century and was originally started by the Church of Sweden [113]. The Swedish Total Population Register (TPR) was established in 1968 by Statistics Sweden, which stores a large amount of historical data and information on changes within the population from the registers at the country administrative boards. Population registration was computerized at the same time as the control digit was introduced into the PIN. Most individuals who were born in or who moved to Sweden are registered in the TPR and remain registered in Sweden until the date they emigrate or die [114].

The register contains the following information for each person:

- Name
- Address
- PIN and co-ordination number
- Country of birth
- Citizenship
- Civil status
- Spouse, children, parents, guardians and adoption data
- Property, parish and municipality of registration
- Immigration to Sweden
- De-registration information (emigration from Sweden and address abroad, or death and burial site).

The Swedish TPR covers the entire population in Sweden and is updated on a daily basis. However, both under-coverage (due to lack of information about birth and immigration) and over-coverage (due to deficiencies in the reporting of death and emigration) exist, although to what extent is not clear [113].

3.1.2 The National Patient Register

The National Patient Register (NPR) covers inpatient and outpatient care at public and private hospitals in Sweden, and is considered a main source of data for many research projects.

The Inpatient Register, also known as the Hospital Discharge Register, was established in 1964, with national coverage since 1987. The National Board of Health and Welfare collects

data on all discharges from any hospital in Sweden for all residents by completing a specific form for all patients without exception. These forms are computerized locally; the data are first collected in administrative registers held at the hospitals and by the county administrations and are then delivered to the National Board of Health and Welfare annually. In addition to the PIN and other administrative information, such as admission and discharge dates and hospital and department codes, one primary discharge diagnosis is recorded with up to eight secondary diagnoses, coded according to the Swedish versions of the International Classification of Diseases (ICD) (the 9th version (ICD-9) during the years 1987–1996 and the 10th version (ICD-10) from 1997).

Since 2001, the NPR has contained information on all registered outpatient visits to specialist care and hospital day care.

The quality and completeness of data available in the NPR are checked on a regular basis by the Swedish National Board of Health and Welfare. The result of the latest validation showed that the diagnoses are valid in 85–95% of cases for the Inpatient Register and for about 80% of all visits for specialized outpatient care [115, 116].

3.1.3 The Swedish Medical Birth Register

The Swedish Medical Birth Register (MBR) is a national register established in 1973 by an act of the Swedish parliament, and contains data on more than 98% of all pregnancies in Sweden. The register contains prospectively collected data on maternal demographic characteristics, medical history, pregnancy, delivery and neonatal period for nearly all infants born in Sweden and their mothers. The register is considered to be a valuable source of data for epidemiological studies of reproduction.

The data in the MBR have been collected in two phases. During the first phase (1973–1982), data were obtained from a summary sheet (Medical Birth Reports), with the contents of the medical records summarized on a standard form; during the second phase (1982 onwards), copies of the medical records from antenatal care clinics, delivery units and paediatric examination of neonates have been transferred to the MBR. The Swedish National Board of Health and Welfare repeatedly evaluate the quality of data in the MBR at regular intervals in order to keep the register at a high standard. The MBR has also been subjected to yearly quality checks. The conclusion of the most recent extensive validation was that the quality of the variables used in this thesis, including maternal height, maternal weight and smoking

habit in early pregnancy, the diagnosis of preeclampsia, maternal age, gestational age, parity, stillbirth/live birth, and infant congenital malformation and birth weight was high [117, 118].

3.1.4 The Cause of Death Register

The Cause of Death Register has been administered by the Swedish National Board of Health and Welfare from 1961, and is updated annually. The register provides data for all deceased individuals who at the time of death were registered in Sweden, whether the death occurred within or outside Sweden. Individuals who died during a temporary stay in Sweden or those who had not yet received a residence permit, stillbirths, and emigrants from Sweden who are no longer registered in Sweden are not included in the register. The international version of the ICD adopted by WHO is used for the diagnosis in the Cause of Death Register.

The register contains the PIN, data on the date of death, the main and contributing causes of death, place of death, nature of any injury, sex, age and marital status.

The quality of the Cause of Death Register can be affected by the age and diagnosis of the deceased person. For example, elderly individuals may have more than one health problem; therefore, it may be more difficult for a physician to issue a death certificate with the precise cause of death for an older person compared to a younger individual.

New regulations for forensic death investigation allow families a greater opportunity to reject an autopsy. Therefore, the proportion of autopsies, as an important source of information about causes of death, has decreased from around 50% in the early 1970s to about 12% in recent years. The proportion of missing data in the Cause of Death Register was estimated to be around 0.5% for all deaths, with no missing data since 1997 [119, 120].

3.1.5 The Multi-Generation Register

The Multi-Generation Register contains information of biological and adoptive links between children and their parents through the PINs for all Swedish inhabitants born after 1931 and who were alive in 1960. The register can be used for identification of country of birth, SEP and possible disease diagnosis for parents and siblings through linkage to other registers in the M&H Co. including the TPR, the NPR, National Population and Housing Censuses and the Longitudinal Integration Database for Health Insurance and Labor Market (LISA) [121].

3.1.6 *The National Population and Housing Censuses*

The National Population and Housing Censuses collected data on individuals and households in Sweden every 5 years between 1960 and 1990. The information in the Population and Housing Censuses was obtained partly from a questionnaire sent to every Swedish household, and also from available records. The Censuses contained demographic, socioeconomic and occupational data for individuals. In addition, household information such as number of residents, housing status and overcrowding was also collected [122].

3.1.7 *LISA*

The LISA was established in 1990 and includes all individuals aged 16 years and older who were registered in Sweden at the end of each year.

The database comprises integrated data from the labour market and educational and social sectors, and is updated annually. The LISA contains information on demographic, occupational and socioeconomic factors including individual, family and capital income, level of education and marital status. Other information on individuals in the database includes employment, employment compensation, unemployment, place of employment, studies, national military service, sick leave, parental leave, labour market activity, rehabilitation, early retirement, partial retirement, private and occupational pensions, social assistance, country of birth, latest year of immigration and place of residence [123].

3.2 ETHICAL ISSUES

The studies included in this thesis were approved by one of the regional boards of the Ethics Committee in Stockholm, Sweden (Reference no. 2005/726-31 and amendment 2009/2033-32). Linkages have been completed via the PIN by Statistics Sweden and the National Board of Health and Welfare. To ensure confidentiality and maintain data anonymity for research, the PINs have been replaced by serial numbers with the code held at Statistics Sweden.

3.3 STUDY POPULATION AND FOLLOW-UP

Study I

The study population consisted of 8 952 861 children (0–14 years) and adolescents/young adults (15–30 years) living in Sweden at any time between 1 January 1969 and 31 December 2008.

The cohort members were followed from the date of birth (for Sweden-born individuals), date of immigration (for immigrants) or 1969, whichever occurred last, until the date of diagnosis of type 1 diabetes, emigration, death or end of follow-up (31 December 2008), whichever came first.

Study II

The study population comprised 7 388 242 children (0–14 years) and adolescents/young adults (15–30 years) born and living in Sweden at any time between 1 January 1969 and 31 December 2009.

The cohort members were followed from the date of birth or 1 January 1969, whichever occurred last, until the date of diagnosis of type 1 diabetes, emigration, death or end of follow-up (31 December 2009), whichever came first.

Studies III and IV

The study population comprised 1 263 358 infants, children and adolescents (0–18 years) born and living in Sweden at any time between 1 January 1992 and 31 December 2004.

The cohort members were followed from the date of birth, until the date of diagnosis of type 1 diabetes, emigration, death or end of follow-up (31 December 2009), whichever came first.

3.4 EXCLUSION CRITERIA

In Studies I and II, individuals with a lack of information on parents' country of birth and those with a history of type 1 diabetes before entry into the cohort were excluded from the study population.

In Studies III and IV, children with any congenital malformation, and those from multiple births, delivered before 28 or after 43 completed weeks of gestation, with missing data on birth weight or gestational age, or with a birth weight >6 standard deviations above or below the mean were excluded from the study population. In addition, records with missing data on maternal weight and height or with extreme values of maternal age (<13 years), weight (<40 or ≥ 200 kg) or height (<120 or ≥ 200 cm) were also excluded from the study population. In Study IV, we further excluded women with an invalid immigration date.

3.5 OUTCOME VARIABLE

In all four studies of this thesis, the main outcome of interest was diagnosis of type 1 diabetes in children and young adults using the NPR.

Type 1 diabetes cases were identified according to the Swedish versions of the ICD (eighth version (ICD-8) and ninth version (ICD-9) code 250 between 1969 and 1996, and tenth version (ICD-10) code E-10 from 1997). However, before 1997 it was not possible to distinguish between type 1 and type 2 diabetes due to the lack of a specific ICD code. In Sweden, the majority of diabetes cases diagnosed before 30 years of age are most likely to be type 1 diabetes.

3.6 EXPOSURE VARIABLE

Study I

The main exposures of interest in this study were country of birth of the index person and parental country of birth and level of education. The cohort members were classified into three groups: immigrants (individuals born outside Sweden), offspring of immigrants (individuals born in Sweden with at least one parent born outside Sweden) and Sweden born (individuals born in Sweden with both parents also born in Sweden).

We classified foreign-born individuals into groups by country of birth into six continents and further subdivided into 19 world region, as defined by the United Nations Population Division: Africa (North, South, East, West and Central Africa), Asia (East, West, South-Central and South-East Asia), Europe (North, South, East and West Europe), Latin America (Caribbean, Central America and South America), North America and Oceania

(Australia/New Zealand, Melanesia and Micronesia/Polynesia) [124]. Only countries with five or more cases of type 1 diabetes were reported in order to ensure enough statistical power. Countries with less than five cases were grouped together and are presented as “Other” for each geographical region.

We used parental level of education attained as an indicator of SEP. Levels of education were determined separately for mothers and fathers from the National Population and Housing Censuses and the LISA database, and the highest parental education level for either the mother or father was used. For example, if the mother had a high level of education and the father had a low level, the parental education level was considered to be high. The levels of education were classified as: 0–9 years (compulsory school education), 10–12 years (upper secondary school), 13 years or more (post-secondary school) and unknown.

Study II

The main exposure variable in this study was parental country of birth. We classified the cohort into four groups according to parental country of birth as offspring (1) of mothers born outside Sweden, (2) of fathers born outside Sweden, (3) with both parents born outside Sweden and (4) with both parents born in Sweden. We also classified parental country of birth into six main geographical regions: Africa, Asia, Europe, Latin America, North America and Oceania, and further into 19 world sub regions according to the United Nations Population classification [124]. Furthermore, we classified Africa into North, East and West Africa and Europe into Finland, North Europe excluding Finland, and South, East and West Europe.

Study III

The main exposure variable was maternal BMI, calculated as weight divided by the square of the height (kg/m^2), in early pregnancy. Mothers were classified according to the WHO classification of BMI cut-off values as underweight ($<18.5 \text{ kg/m}^2$), normal weight (between ≥ 18.5 and $<25 \text{ kg/m}^2$), overweight (between ≥ 25 and $<30 \text{ kg/m}^2$) and obese ($\geq 30 \text{ kg/m}^2$) [125].

In this study, we further explored the combined effect of maternal BMI and maternal and/or paternal diabetes on the risk of type 1 diabetes in the offspring of parents from different birth countries.

Information on diagnoses of parental diabetes was obtained from the NPR according to the Swedish versions of the ICD as maternal diabetes (pre-gestational type 1 diabetes, type 2 diabetes or other specified or unspecified types of diabetes: ICD-9 codes 250 and 648A and ICD-10 codes E10, E11, E13, E14 and O240-O243), gestational diabetes (ICD-9 code 648W and ICD-10 code O244) and paternal diabetes (type 1 diabetes, type 2 diabetes or other specified or unspecified types of diabetes: ICD-9 code 250 and ICD-10 codes E10, E11, E13, E14).

Parental country of birth was categorized as Sweden (both parents born in Sweden) and foreign (both parents born outside Sweden). Due to similar environmental exposures in the Nordic countries, we further categorized parental country of birth as Nordic (both parents born in Sweden, Norway, Denmark, Finland or Iceland) and non-Nordic (both parents born in other countries).

Study IV

The main exposure variable was maternal duration of stay in Sweden before delivery stratified by parental country of birth.

Maternal duration of stay was categorized as 0–5 years, 6–10 and ≥ 11 years. Parental country of birth was first classified as foreign (only mothers or both parents born abroad) and Sweden (both parents born in Sweden). We further categorized foreign-born parents into other Nordic (Finland, Norway, Denmark and Iceland) and East African.

3.7 EXPLANATORY VARIABLES

3.7.1 SEP

In Studies I, II and IV, parental education level was used as an indicator of SEP. Level of education was classified as: 0–9 years (compulsory school education), 10–12 years (upper secondary school), ≥ 13 years (post-secondary school) and unknown.

3.7.2 Sex and age at follow-up

We adjusted for sex and age of the case at follow-up in all four studies.

In Studies I and II, age at follow-up was divided into six groups (0–4, 5–9, 10–14, 15–19, 20–24 and 25–30 years).

In Studies III and IV, age at follow-up was divided into three groups (0–5, 6–11 and 12–18 years).

3.7.3 Calendar years of follow-up

We adjusted for calendar years of follow-up in Studies I and II as follows.

In Study I, the study period was divided into four time periods (1969–1979, 1980–1989, 1990–1999 and 2000–2008), and in Study II the study period was divided into four time periods (1969–1978, 1979–1988, 1989–1998 and 1999–2009).

3.7.4 Maternal age

In Studies III and IV, the risk estimates were adjusted for maternal age at delivery categorized in four age groups (<20, 20–24, 25–29 and ≥ 30 years).

3.7.5 Maternal smoking

In Studies III and IV, the analyses were adjusted for maternal smoking habits in early pregnancy, defined as no smoking, 1–9 cigarettes/day, ≥ 10 cigarettes/day and unknown.

In Study III, we also adjusted for **size of the infant at birth** categorized as appropriate for gestational age (AGA, defined as birth weight between the 10th and 90th percentile), small for gestational age (SGA, birth weight below the 10th percentile) and large for gestational age (LGA, birth weight above the 90th percentile) according to the Swedish reference curves for normal fetal growth [126].

In Study IV, the analyses were additionally adjusted for **maternal BMI** in early pregnancy (categorized as underweight, BMI <18.5 kg/m²; normal weight, BMI between ≥ 18.5 and <25 kg/m²; overweight, BMI between ≥ 25 and <30 kg/m²; and obese, BMI ≥ 30 kg/m²), **parity**

(1, 2–3 or ≥ 4) and **preeclampsia** diagnosis according to the Swedish versions of the ICD codes (ICD-9 codes 642E–642G and ICD-10 codes O14 and O15).

3.8 STATISTICAL ANALYSIS

3.8.1 *Poisson regression*

We used Poisson regression models to calculate incidence rate ratios (IRRs) with 95% confidence intervals (CIs) of type 1 diabetes for all four studies in this thesis. This means that all person-years are aggregated and considered of equal value within the limits given by age and calendar period.

Poisson regression is a form of regression analysis in which the outcome variable is assumed to follow the Poisson distribution, which describes the probability of a given number of events in a fixed time interval. In Poisson regression, follow-up time is divided into time intervals and a separate rate parameter is estimated for each interval, thereby allowing for the probability that the rate is changing with time, but Poisson regression assumes that the rate is constant within each time interval.

Poisson distribution assumes that the mean is equal to its variance. However, in certain situations, such as in an inappropriate model, the observed variance is greater than the mean and this is known as over-dispersion.

3.8.2 *Age-standardized rates*

For the trend analyses, Age-standardized type 1 diabetes incidence rates (ASRs) of type 1 diabetes incidence between 1969 and 2009 stratified by sex and parental education (Study I) and by parental migration background (Study II) were calculated for children younger than 15 years and adolescents/young adults aged 15 to 30 years from the numbers of new cases divided by the estimated numbers of person-years at risk in 5-year age groups. To ensure comparability and to adjust for differences in age in the study population, ASRs were directly calculated using truncated weights based on the world population as the standard, which assumes equal numbers in each age group (0–4, 5–9, 10–14, 15–19, 20–24 and 25–30 years). ASRs are presented per 100 000 person-years.

3.8.3 *Joinpoint regression*

The Joinpoint regression model was used in Studies I and II to evaluate the trends in type 1 diabetes incidence rates. Joinpoint regression analysis fits several different joined lines on a log scale to the incidence rate data and also tests for a significant change in the trend. The annual percentage change (APC) was also estimated by this method to describe and test the statistical significance of the trends. The null hypothesis in this analysis is that the trend in incidence rates is the same over time (no change in trend over time) [127].

4 RESULTS

4.1 STUDY I. TYPE 1 DIABETES AMONG CHILDREN AND YOUNG ADULTS: THE ROLE OF COUNTRY OF BIRTH, SEP AND SEX

We followed a cohort of 4 469 671 male and 4 231 680 female children and young adults aged 0–30 years, living in Sweden at any time between 1 January 1969 and 31 December 2008. Among this group, 1 533 082 were immigrants and 1 036 724 were offspring of immigrants.

During the study period (1969–2008), there were 15 022 cases of type 1 diabetes among Sweden-born children younger than 15 years of age, compared to 464 cases among immigrants and 2 308 among offspring of immigrants within the same age group. Among those aged 15–30 years, a total of 14 956 cases of type 1 diabetes were observed in the Sweden-born group, 1491 cases among immigrants and 1600 cases among offspring of immigrants.

Among children aged 0–14 years, the risk of type 1 diabetes was about 40% lower in immigrants and about 25% lower in offspring of immigrants, compared to Sweden-born children.

Compared to those with parents with a high level of education (≥ 13 years), male children with a low level of parental education (≤ 9 years) had a 9% decreased risk of type 1 diabetes (IRR=0.91, 95% CI 0.84–0.98); however, no effect of parental education was observed among female children. We also found an increasing risk of type 1 diabetes with increasing age (p for trend <0.0001) and with calendar years of follow-up (p for trend <0.0001) among children of both sexes.

Among adolescents and young adults (15–30 years), the risk of type 1 diabetes was about 30% lower in immigrants and about 15% lower in offspring of immigrants, compared to their Sweden-born counterparts. Further, we observed that the risk of type 1 diabetes decreased with increasing age and parental level of education. Adolescents and young adults of both sexes with parents with a low level of education (0–9 years) had about a 20% increased risk of type 1 diabetes compared to those with parents with at least 13 years of education. Moreover, the risk of type 1 diabetes increased with calendar years of follow-up in young men, whereas the risks were highest in the earlier years of follow-up among young women (p for trend <0.0001).

At the country level, the risks of type 1 diabetes in men and women born in countries within Asia, South Europe (except women born in Spain), East Europe and Latin America (except women born in Uruguay) were between 40% and 85% lower compared with Sweden-born individuals. Similar reduced risks were also observed among men born in West Africa and North America and in women born in Ethiopia, the United Kingdom and Greece. Immigrants from other countries had basically similar risks of type 1 diabetes as Sweden-born individuals.

We used Joinpoint regression analysis to evaluate trends in both age groups. Over the study period, we found increasing trends in the incidence of type 1 diabetes by year of diagnosis for all levels of parental education in children younger than 15 years. However, among adolescents and young adults aged 15 to 30 years, the trend varied by sex and parental level of education.

4.2 STUDY II. THE TRENDS AND THE RISK OF TYPE 1 DIABETES OVER THE PAST 40 YEARS: AN ANALYSIS BY BIRTH COHORTS AND BY PARENTAL MIGRATION BACKGROUND IN SWEDEN

We followed a cohort of 3 641 304 male and 3 457 486 female offspring aged 0–30 years born and living in Sweden any time between 1 January 1969 and 31 December 2009.

On the basis of Joinpoint regression analyses, we observed an increasing trend in the incidence of type 1 diabetes among children younger than 15 years born to native Swedes and to immigrant parents (offspring of Swedes: APC=3.9, $p<0.001$; offspring of immigrants: APC=2.2, $p<0.001$). By contrast, among adolescents and young adults aged 15–30 years, no increase or a tendency towards a decreasing trend was observed, regardless of parental country of birth (offspring of Swedes: APC=−0.0, $p=0.9$; offspring of immigrants: APC=−0.7, $p=0.08$).

In an analysis by birth cohort, a shift towards younger age at diagnosis was observed in both groups of offspring aged 0–14 years. However, no clear effect of birth cohort was seen in the adolescents and young adult groups.

Compared with children (0–14 years) of Sweden-born parents, the risk of type 1 diabetes was about 30% lower in children with one foreign-born parent and about 40% lower in those with both parents born abroad, after multivariable adjustment for age, calendar period and parental education.

Compared to adolescents and young adults born to Swedish parents, the risk of type 1 diabetes was about 15–20% lower in adolescents and young adults with only one foreign-born parent and about 25–30% lower in those with both parents born abroad.

A stratified analysis by specific parental country/region of birth revealed 20–40% higher IRR values among male and female offspring aged 0–30 years of mothers or fathers born in Africa compared with offspring of Swedes. The increased risk was even more pronounced in individuals with parents from East Africa, with a 45–60% higher risk compared with offspring of Swedes. With a few exceptions, IRR values were between 35% and 65% lower in offspring of any parent born in Asia, Europe (except North Europe), Latin America and North America (except female offspring of fathers from North America) than in offspring of Swedes. This decrease in risk of type 1 diabetes was more prominent among individuals whose mothers and fathers were born in the same region.

Offspring of Finnish immigrants and parents from other countries within North Europe had similar risks to offspring of Sweden-born parents.

4.3 STUDY III. MATERNAL OVERWEIGHT AND OBESITY INCREASE THE RISK OF TYPE 1 DIABETES IN OFFSPRING OF PARENTS WITHOUT DIABETES REGARDLESS OF ETHNICITY

During the study period between 1992 and 2009, a total of 4 588 children and adolescents were diagnosed with type 1 diabetes.

Compared with offspring of non-diabetic mothers, the risk of type 1 was increased three-fold in offspring of Swedish and Nordic mothers with any type of diabetes, after adjustment for paternal diabetes, maternal early pregnancy BMI, maternal age, gestational age, smoking habits in early pregnancy and age at follow-up.

In an analysis stratified by type of parental diabetes, the risk was increased six- to seven-fold in offspring of mothers with type 1 diabetes compared with offspring of mothers without diabetes, regardless of maternal country of birth. Among offspring of mothers with type 2 or gestational diabetes, the risk was increased approximately two-fold compared with offspring of mothers without diabetes born in Sweden or a Nordic country. However, we found no association between maternal type 2 or gestational diabetes and risk of type 1 diabetes in offspring of mothers born outside Nordic countries (IRR=1.01, 95% CI 0.53–1.92).

We observed the same pattern but a stronger association with paternal types of diabetes if fathers were born in Sweden or another Nordic country. The risk of type 1 diabetes in

offspring of non-Nordic fathers with type 1 diabetes was elevated compared with non-Nordic, non-diabetic fathers (IRR=3.11, 95% CI 1.28–7.55), but this increase was smaller than in offspring of mothers with type 1 diabetes. In contrast to the lack of association between the risk of type 1 diabetes in offspring and maternal type 2 diabetes if mothers were born outside the Nordic countries, the risk was elevated in offspring of fathers with type 2 diabetes (IRR=2.08, 95% CI 1.23–3.53).

High maternal BMI was associated with increased risk of type 1 diabetes in the offspring, regardless of parental country of birth and after multivariable adjustment for potential confounders. The risks of type 1 diabetes were 30% higher in offspring of obese mothers born in Sweden or a Nordic country and about 50% higher in offspring of obese mothers born abroad or in non-Nordic countries, compared with offspring of normal-weight mothers. However, in a stratified analysis by parental diabetes, we found that the increased risk of type 1 diabetes in offspring with increasing maternal BMI was confined to children with non-diabetic mothers and fathers, and almost regardless of parental region of birth. Overall, offspring of non-diabetic parents with obese mothers had a 36% higher IRR of type 1 diabetes compared with offspring of non-diabetic parents with normal-weight mothers.

High maternal BMI was associated with a reduced risk of type 1 diabetes in offspring of mothers diagnosed with any type of diabetes (maternal BMI ≥ 30 kg/m²: IRR=0.59, 95% CI 0.42–0.84). This protective effect was confined, however, to offspring of diabetic mothers born in Sweden or a Nordic country.

When the analyses were stratified by type of maternal diabetes, the risk of type 1 diabetes was significantly decreased in offspring of overweight and obese mothers with type 2 diabetes (overweight: IRR=0.20, 95% CI 0.04–0.93; obese: IRR=0.23, 95% 0.07–0.74). Within the Nordic cohort, there was an increase in the proportions of women with type 2 or gestational diabetes with increasing BMI. The risks of type 1 diabetes in offspring of overweight and obese mothers with type 1 or gestational diabetes did not significantly differ from the risk in offspring of women of normal weight.

No significant effects of maternal age or size of the infant at birth on the risk of type 1 diabetes in the offspring were observed.

In offspring of Nordic mothers, maternal heavy smoking (≥ 10 cigarettes per day) in early pregnancy was associated with a significantly decreased risk of type 1 diabetes.

4.4 STUDY IV. THE RISK OF TYPE 1 DIABETES AMONG OFFSPRING OF IMMIGRANT MOTHERS IN RELATION TO THE DURATION OF RESIDENCY IN SWEDEN

A total of 4 825 Sweden-born children and adolescents aged 0 and 18 years were identified with a diagnosis of type 1 diabetes during the study period between 1992 and 2009.

Compared with offspring of Sweden-born mothers, the risk of type 1 diabetes was about 45% and about 30% lower in offspring of foreign-born mothers resident in Sweden for up to 5 years and for more than 5 years, respectively, after multivariable adjustment for maternal age, maternal BMI, smoking at enrolment, parental education, parity, preeclampsia, and sex and age at follow-up in the offspring.

When the analyses were confined to offspring of foreign-born mothers, we found that those with mothers resident in Sweden for 5 years or less had a 23% lower risk of type 1 diabetes compared with offspring whose mothers had been living in Sweden for at least 11 years.

In comparison with offspring of Swedish mothers, those of mothers born in East African countries who had been resident in Sweden for 11 years or more had a two-fold increased risk of type 1 diabetes.

In the analyses confined to a cohort of offspring of mothers born in East African countries, we observed approximately a 60% lower risk of type 1 diabetes among those whose mothers had been resident in Sweden for up to 5 years, compared with offspring of mothers who had been living in Sweden for at least 11 years.

In offspring of mothers from other Nordic countries, no statistically significant association between maternal duration of stay in Sweden and risk of type 1 diabetes in the offspring was observed.

5 DISCUSSION

5.1 MAIN FINDINGS

5.1.1 *Study I*

In this nationwide cohort study of immigrants, offspring of immigrants and Sweden-born individuals, we observed an increasing trend in type 1 diabetes over the study period between 1969 and 2008 among children aged 0 to 14 years, whereas no change in trend was found among adolescents and young adults aged 15 to 30 years. We also found that the risk of type 1 diabetes was clearly reduced among immigrants, as well as among offspring with at least one parent born abroad, compared with Sweden-born individuals. The effect of parental education level was different among children and young adults. While parental education had a small or no effect on the risk of type 1 diabetes among children, the risk decreased with increasing level of parental education in adolescents and young adults. Among children aged 0 to 14 years, the incidence of type 1 diabetes rose with increasing age, whereas the inverse was observed among adolescents and young adults. At the regional level, children and young adults born in countries within Asia, South Europe, East Europe and Latin America had lower risks of type 1 diabetes than Sweden-born individuals.

5.1.2 *Study II*

This population-based cohort study of offspring of Swedes and of immigrants demonstrated an increasing trend in type 1 diabetes in children younger than 15 years of age during the study period between 1969 and 2009. By contrast, no change in trend was observed in either group of adolescents and young adult offspring aged 15 and 30 years. We also observed a shift towards a lower age at diagnosis in the younger birth cohorts of offspring of foreign-born and Swedish parents. We further found a reduced risk of type 1 diabetes in Sweden-born children and adolescents/ young adults with at least one parent born abroad, compared with individuals with native Swedish parents. This reduction in risk was, however, more prominent among individuals with two foreign-born parents and was observed for both sexes. Compared with offspring of native Swedes, the risk of type 1 diabetes was decreased in offspring of immigrants from Asia, Latin and North America and South, West and East Europe. Another finding in this study was that, in contrast to all offspring of immigrants who had a reduced risk of type 1 diabetes compared with offspring of Swedes, the risk was increased in individuals with African parents, especially those born in East or North Africa.

5.1.3 Study III

In this nationwide cohort study of all children born between 1992 and 2004 in Sweden, we observed that parental diabetes and maternal overweight and obesity were associated with increased risks of type 1 diabetes in the offspring regardless of parental birth place. We also found that paternal type 1 diabetes conferred a higher risk of type 1 diabetes to their offspring compared with maternal type 1 diabetes among Nordic parents. By contrast, maternal type 1 diabetes conferred the greatest risk of type 1 diabetes in offspring compared with paternal type 1 diabetes in non-Nordic parents.

A novel finding in this study was that the increased risk of type 1 diabetes associated with high maternal BMI was confined to offspring of parents without diabetes, and particularly those with foreign-born parents.

Within the Nordic cohort, we further observed that maternal overweight and obesity were not associated with increased risk of type 1 diabetes in offspring of mothers with type 1 or gestational diabetes. However, in offspring of mothers with type 2 diabetes, maternal overweight and obesity were associated with a significantly reduced risk of type 1 diabetes.

5.1.4 Study IV

In this nationwide cohort study from Sweden between 1992 and 2009, we observed that maternal duration of residency in Sweden before delivery was associated with increased risk of type 1 diabetes in the offspring.

In comparison with offspring of Sweden-born mothers and those of mothers who had lived in Sweden for at least 11 years, offspring of mothers resident for up to 5 years had the lowest risk of type 1 diabetes. Offspring of East African mothers residing in Sweden for at least 11 years had a two-fold higher risk of type 1 diabetes, compared with offspring of Sweden-born mothers. In a sub cohort of East African parents, the lowest risk of type 1 diabetes was observed in offspring of mothers living in Sweden for up to 5 years.

5.2 INTERPRETATION OF FINDINGS

The finding of an increasing trend in type 1 diabetes among children younger than 15 years of age but no increase in adolescents and young adults aged 15–30 years (Studies I and II) was consistent with the results of studies from Sweden [23, 128] and other countries worldwide [12, 45]. By contrast, studies from Finland and Italy showed an increasing incidence of type 1 diabetes in both children and young adults [129, 130].

Environmental exposures in utero and in early life have been proposed to explain the increasing trend and earlier diagnosis of type 1 diabetes among children younger than 15 years of age [70, 81, 92, 107, 131-133]. Alternatively, the results of our study could be due to the completeness of ascertainment of the NPR; this register did not have national coverage until 1987, thus there is a possibility of missing information about type 1 diabetes cases before this time. Therefore the lower incidence of type 1 diabetes in the earlier years of this study could be due to missed or undiagnosed cases of type 1 diabetes. However, we observed the sharpest increase in incidence among individuals below 15 years of age after 1997 when the inpatient register had full coverage and when the ICD-10 were able to disentangle different types of diabetes.

The observed decreased risk of type 1 diabetes among immigrants, with a smaller reduction in risk among offspring with at least one parent born abroad (Studies I and II), indicates the importance of parental country of birth as well as changes in lifestyle and environmental factors in the aetiology of this disease. This finding is in line with the results from some previous migration studies demonstrating that the incidence of type 1 diabetes in children moving from a low-risk to a high-risk area was close to that of children in the host country [13, 14, 16, 105, 134, 135]; however, other studies have demonstrated the opposite result [17, 136].

The incidence of type 1 diabetes in offspring with one foreign-born and one Sweden-born parent was between that of children with either two foreign-born or two Sweden-born parents. This might be explained by genetic admixture [137, 138], or it is possible that foreign-born parents from low-risk regions maintain the cultural lifestyle of their country of origin, and thereby reduce the exposure to risk factors in the family. It has been argued that increased exposure to risk factors and adoption of the typical lifestyle of the new country could have contributed to the increased risk of type 1 diabetes in immigrants and their offspring. By contrast, new immigrants may maintain their lifestyle from the country of origin, thus providing a temporary protective effect against the disease [9, 139].

The finding of increased risk of type 1 diabetes in offspring of African mothers or fathers, compared with offspring of Swedes (Study II), was consistent with the results of another Swedish study [140]. This might reflect the true type 1 diabetes risk in the countries of origin. However, epidemiological data regarding the incidence of type 1 diabetes in most low and middle income countries in sub-Saharan Africa are scarce, and it is not clear whether the reported incidence rates of the disease in these regions are reliable [28]. Indeed, the diagnosis might be missed due to lack of diagnostic measures and high rates of mortality among individuals with uncontrolled type 1 diabetes as a result of poor access to insulin treatment [141, 142]. In addition to genetic variation, therefore, poor living conditions and limited access to health care services in African countries might contribute to the observed differences in the risk of type 1 diabetes.

The observed increased risk of type 1 diabetes with decreasing level of parental education in adolescents and young adults (Study I) might be due to differences in unmeasured lifestyle factors such as diet, breastfeeding practices and hygiene standards [19, 143]. However, our knowledge of such factors in Sweden, especially among immigrant groups, is limited. In developed countries, it has been demonstrated that a shorter duration of breastfeeding in mothers with low SEP is associated with increased risk of type 1 diabetes in children [111].

The variation in incidence of type 1 diabetes over time and generations implies that the observed lower risk of the disease in immigrants and their offspring cannot be attributed to genetic differences alone, but rather to complex interactions between genetic and environmental factors.

The observed increased risk of type 1 diabetes in offspring of mothers with type 1 diabetes (Study III) is in line with the results of previous studies [56, 144]. Maternal type 2 or gestational diabetes were also significant risk factors for type 1 diabetes in the offspring, which is in agreement with some [56, 145] but not all [144] previous studies. The greater risk of type 1 diabetes in the offspring of mothers with type 1 diabetes, as compared with other types of maternal diabetes, is likely to be a reflection of differences in genetic susceptibility between these two groups of offspring.

Our finding of a greater risk of type 1 diabetes in the offspring of fathers with type 1 diabetes compared to those with mothers with the disease in the Nordic cohort is in accordance with the results of previous studies [146-149]; however, the underlying mechanism is not fully understood. Within the non-Nordic cohort, maternal type 1 diabetes is associated with a

higher risk of type 1 diabetes in the offspring than paternal type 1 diabetes. However, the number of cases in this population is too few to allow any clear conclusion to be drawn.

Previous studies have reported conflicting results regarding the effect of maternal overweight and obesity on the risk of type 1 diabetes in the offspring. The association between high maternal BMI and increased risk of type 1 diabetes in offspring found in our study has been observed in some [69, 70], but not all [150, 151], previous studies.

The novel finding that the increased risk of type 1 diabetes associated with high maternal BMI is confined to offspring of parents without diabetes, and particularly offspring of foreign-born parents, indicate the importance of heredity in the occurrence of this disease in the offspring.

The decreased risk of type 1 diabetes in offspring of overweight and obese mothers with type 2 diabetes might reflect the differences in genotypic characteristics associated with type 1 and type 2 diabetes.

Maternal overweight and obesity may lead to greater placental transfer of glucose and other nutrients during fetal development. This would result in overstimulation of the fetal pancreatic beta-cells and increased insulin secretion [152, 153]. Maternal overweight and obesity also influence the fat status of the fetus and newborn infant which in turn is associated with fetal insulin resistance [154, 155]. This is a possible mechanism that may contribute to the increased risk in genetically predisposed offspring of overweight and obese mothers.

It has been demonstrated that the children of obese mothers are more likely to be overweight or obese [152, 156, 157]. The association between high childhood birth weight/or BMI and increased risk of type 1 diabetes has repeatedly been reported in previous studies [82, 84, 158].

It has recently been shown that low-risk alleles for type 1 diabetes are associated with increased BMI. Moreover, there has been an increase over time in the proportion of the low-risk HLA genotypes among newly diagnosed type 1 diabetes patients, which is in parallel with an increased proportion of overweight or obese patients [159-161].

There was no evidence of a significant impact of neonatal size at birth on the subsequent risk of type 1 diabetes in either cohort. However, in previous studies, birth weight adjusted for gestational age was associated with the risk of type 1 diabetes in the offspring [41, 66, 84, 162].

No association between maternal age and risk of type 1 diabetes in the offspring was observed, which is consistent with the findings of some earlier studies [150, 163, 164].

However, an association between high maternal age and increased risk of type 1 diabetes in the offspring has been reported by others [70, 78, 165].

A reduced risk of type 1 diabetes among offspring whose mothers smoked during early pregnancy has previously been demonstrated by some [78, 150, 166], although not all [83, 167, 168], studies. The mechanism underlying this inverse association between maternal smoking and offspring risk of type 1 diabetes observed by some is unclear. A higher prevalence of preeclampsia among non-smoking mothers has been reported [169]. Because preeclampsia has been associated with increased risk of type 1 diabetes in the offspring [92, 170], it has been hypothesized that the possible association between maternal smoking and reduced risk of type 1 diabetes in the offspring might be due to immunological disturbances associated with preeclampsia [78]. Another possible explanation for this association could be that mothers who smoke tend to have smaller infants, and a reduced risk of type 1 diabetes has been reported in offspring who were small at birth [171, 172]. It is well established that maternal smoking during pregnancy is related to an elevated risk of maternal complications and adverse neonatal outcomes. Therefore, the finding of this possible association needs to be interpreted with caution.

In our study to investigate the association between maternal duration of residency in Sweden and the risk of type 1 diabetes in their offspring (Study IV), we observed that the risk increased with longer maternal duration in Sweden. Although the reason for such an association is yet to be investigated, it could be speculated that mothers with a longer duration of stay have a higher exposure to environmental risk factors and this may result in the higher incidence of type 1 diabetes in their offspring. At the same time, the effect of variations in genetic expression on the development of type 1 diabetes cannot be ruled out. Immigrants moving to high income countries such as Sweden are exposed not only to a new culture and environment but also to new health services and dietary habits. It has been demonstrated that changes in dietary habits and physical inactivity in certain immigrant groups with longer duration of stay in Sweden are linked to a rise in obesity in these populations [9, 173].

Viral infections during pregnancy as well as in childhood have been associated with increased risk of type 1 diabetes in children [86, 174-176]. Moreover, certain dietary factors such as low vitamin D intake, breastfeeding for short periods and early exposure to cow's milk, cereals and gluten were also associated with an increased risk of islet cell autoimmunity [89, 90, 177-179]. Interaction between two or more environmental factors such as exposure to enterovirus infection and introduction of cow's milk in early life has been linked to the

initiation or acceleration of islet autoimmunity and type 1 diabetes in genetically susceptible individuals [180]. The frequent occurrence of viral infections in the cold climate as well as a high intake of gluten-containing foods and milk in Sweden may, therefore, partly explain the increased incidence of type 1 diabetes in children of mothers with a longer duration of residence.

As stated above, the higher risk of type 1 diabetes has been observed in offspring of East African parents [23, 24]. The finding of a two-fold higher risk of type 1 diabetes in offspring of East African mothers resident in Sweden for at least 11 years, compared to offspring of Sweden-born mothers, could be due to variations in genetic background. On the other hand, this finding might be due to lifestyle changes and environmental factors associated with increased maternal BMI in mothers with a longer duration of residence in Sweden, if this is indeed a key risk factor for type 1 diabetes in this population, or due to unexplored interactions between these factors in the host country.

No significant association was found between maternal duration of stay in Sweden and the risk of type 1 diabetes in the offspring of Nordic mothers. A possible explanation is that all Nordic countries are geographically close to Sweden and have similar risks of type 1 diabetes [28, 181]. In terms of environmental exposure and lifestyle habit, all Nordic countries would be more similar to Sweden than non-Nordic countries. Thus, the influence of these factors on the risk of type 1 diabetes in this group of immigrants might also be similar.

6 METHODOLOGICAL CONSIDERATIONS

6.1 STRENGTHS

The major strength of this thesis is that all four studies were based on high-quality data from a nationwide register including all cases of type 1 diabetes in Sweden. The NPR and Cause of Death Register ensured complete follow-up of all patients with type 1 diabetes.

Moreover, the large sample size and the cohort design with a long follow-up period in our studies made it possible to adjust for several potential confounding factors and to explore the strength of associations between exposure and outcome.

Almost complete information was available on the main exposure of the study (individual country of birth) over a large and heterogeneous population of all immigrants in Sweden coming from high-risk and low-risk areas. This enabled us to indirectly investigate the effect of gene–environment interactions on the risk of type 1 diabetes.

6.2 LIMITATIONS

Generally immigrants who move to Sweden are self-selected; they are a subgroup of the original population and might not represent the whole population in their countries of birth. Furthermore, immigrants might come from specific regions or have specific ethnic, socioeconomic and religious backgrounds with different reasons behind their migration and over different time periods. Therefore the interpretation of findings in migration studies can be limited. It is certainly possible that the findings in our studies might not be generalizable to the whole population in their home countries.

In addition, the healthy migrant effect should always be considered in migration studies; the authors of one Swedish study stated that “individuals with type 1 diabetes have tended to refrain from migration” [16].

6.2.1 Bias

The quality of diagnosis of type 1 diabetes in the NPR is lower in the earlier years of the study period compared to the later years. The diagnoses of type 1 and type 2 diabetes have only been differentiated since 1997 and the introduction of ICD-10. Therefore, the difficulty in correctly classifying diabetes into types especially in individuals over 15 years of age

during the period before 1997 is a potential source of misclassification in our studies, and some patients with type 2 diabetes may have been misclassified as having type 1 diabetes, and vice versa (Studies I–IV). It is possible that the true number of type 1 diabetes cases was either underestimated or overestimated, and this may influence the calculated risks of type 1 diabetes in our studies. However, in Sweden, the prevalence of type 2 diabetes in the population younger than 30 years of age is low. Thus we believe that the effect of this potential bias is small. In addition, the results of sensitivity analysis confined to periods after 1997 where we were able to disentangle type 1 and type 2 diabetes were similar to the reported results in the main analysis for the entire period of the study.

The uncertainty of self-reported data on maternal height may affect the accuracy of BMI as the main exposure variable (Study III). Because women tend to overestimate their height, the finding of an association between maternal BMI and risk of type 1 diabetes is likely to be underestimated. Moreover, data on maternal BMI was missing for 16% of the women (Study III). The observed risks of type 1 diabetes associated with maternal BMI, therefore, could be biased if there are differences in prevalence of maternal overweight and obesity among women with available data on BMI compared to those without BMI data. The risk would be underestimated if women with missing BMI data were more overweight or obese than women with information on BMI.

To elucidate this, we performed a sensitivity analysis by determining the distribution of BMI classes (normal weight/overweight/obese) in a subgroup of women with two pregnancies during the study period. We found that the distribution was very similar in the first and second pregnancies, regardless of whether or not BMI was recorded in the second pregnancy. Thus, we consider the risk of potential selection bias to be very small.

6.2.2 Confounding

A confounder is a factor that distorts the true association between the exposure and the outcome. It occurs when the exposure variable is also correlated with another risk factor.

In order for a variable to be a confounder, it must be associated with the exposure under study and independently associated with the outcome. In addition it should not be a step in the causal pathway [182].

In this thesis, several potential confounding factors were identified and adjusted for in the analyses of the association between country of birth and risk of type 1 diabetes. The two non-modifiable variables age and sex are the most important confounders in epidemiological

studies. Differences in age distribution between countries and regions and also between immigrants, offspring of immigrants and the Swedish population might confound the comparison of type 1 diabetes risk. For this reason, age at follow-up as a potential confounder was controlled by age standardization in the trend analyses. The effect of sex as another potential confounder was also controlled either by stratification or by adjustment in the model.

The impact of level of education as an indicator of SEP on the risk of type 1 diabetes was also considered as another potential confounder in measuring the effect of country of birth (Studies I, II and IV).

Another plausible confounding factor that should be considered is the geographical variation in type 1 diabetes risk between countries, which might be a possible source of confounding. In all four studies, data are reported by comparisons between countries or regions, but not by ethnicity. However, one country may comprise different ethnic groups, or a homogeneous ethnic group may be present in many countries.

In addition, there are still other factors that might confound the association between exposure and outcome in our studies, including diet, breastfeeding practices and hygiene standards. However, reliable data of these lifestyle factors among foreign-born individuals is not available at national level in Sweden.

We did not have information on paternal BMI and family history of obesity, which might be helpful to identify a specific pattern to reveal the environmental and genetic effects on the risk of development of type 1 diabetes in the offspring. Moreover, information about other important covariates such as differences in pregnancy-/birth-related complications, autoantibodies and HbA1c levels were also not available. Therefore, it was not possible to estimate the extent of these factors which could have affected our results (Study III).

Finally, we lacked information on lifestyle and environmental factors such as physical activity, growth pattern and viral infections (Study IV), which might have an impact on the risk of type 1 diabetes. However, the factors that modulate the risk of type 1 diabetes over time are probably complex. It is important to note that it is difficult to investigate the slow changes in lifestyle and environmental factors after only a short period in the new environment. Furthermore, immigrants have been living in Sweden for varying periods of time and thus the effect of different factors in determining risk changes over time might also differ.

7 CONCLUDING REMARKS AND FUTURE PERSPECTIVES

- An increasing trend in type 1 diabetes among children younger than 15 years of age but not among adolescents and young adults aged 15–30 years indicates the importance of early life exposure to environmental factors in the aetiology of type 1 diabetes. From this perspective, further investigations with more information on environmental factors such as early life growth patterns, dietary habits and viral infections might expand our understanding of the aetiology of the disease.
- The shift in type 1 diabetes towards a younger age at diagnosis in offspring below 15 years of age indicates the importance of factors that accelerate rather than trigger islet autoimmunity.
- The observed association between maternal overweight and obesity and risk of type 1 diabetes in children with non-diabetic parents might be a consequence of increasing maternal overweight and obesity. Studies exploring the combined effect of a specific type of diabetes and maternal BMI in genetically diverse populations might increase our understanding of the effect of maternal overweight and obesity and hyperglycemia in utero on type 1 diabetes risk.
- The observed lower risk of type 1 diabetes among immigrants and the smaller reduction in risk among their offspring highlight the importance of environmental factors and their interaction with genetic background in the aetiology of type 1 diabetes.
- The increased risk of type 1 diabetes in offspring of African parents, especially those from East Africa, suggests the need for collection of reliable data on the incidence of type 1 diabetes in these countries to confirm that these differences in incidence are genuine and not due to underestimation.
- The finding that longer maternal duration of stay in Sweden is associated with increased risk of type 1 diabetes in the offspring of immigrants suggests the need for studies to identify the environmental factors that influence the aetiology of type 1 diabetes.

SAMMANFATTNING PÅ SVENSKA

Syfte: Den övergripande målsättningen med detta avhandlingsarbete var att studera incidensen av och riskfaktorer för typ 1 diabetes hos invandrare och deras barn i Sverige. Betydelsen av föräldrarnas socioekonomiska position (SEP), barnens och föräldrarnas födelseland och eventuell förekomst av diabetes hos föräldrarna för risken att utveckla typ 1 diabetes undersöktes. Risken för typ 1 diabetes analyserades också i relation till moderns body mass index (BMI) i tidig graviditet och vistelsetid i Sverige före förlossningen. Risken för typ 1 diabetes jämfördes mellan barn till svenskfödda föräldrar och barn till invandrade föräldrar.

Material och metoder: Vi använde data från en nationell databas, Migrations och hälsa kohorten, med information från sociodemografiska och hälso-sjukvårdsregister. Vi följde populationer av barn (0-14 år) och ungdomar/unga vuxna (15-30 år) födda i Sverige eller utomlands mellan 1969 och 2009 med a) båda föräldrarna födda utanför Sverige (invandrare), b) med minst en förälder född utanför Sverige (barn till invandrare) och med båda föräldrarna födda i Sverige. Incidens rate ratios med 95% konfidensintervall för typ 1-diabetes beräknades med Poissons regressionsmodeller (studie I-IV). Vidare beräknade vi age standardized rate för typ 1-diabetes och använde världens befolkning som standard (studie I och II).

Resultat: Vi observerade en uppåtgående trend i incidensen av typ 1 hos barn yngre än 15 år, men inte bland ungdomar/unga vuxna i åldern 15 till 30 år (studie I och II). Vi observerade också en förskjutning mot yngre ålder vid diagnos, både hos barn till infödda svenskar och hos barn till invandrare (Studie II). Pojkar under 15 års ålder och med föräldrar med låg utbildningsnivå som indikator för SEP hade en 9% minskad risk för typ 1-diabetes, jämfört med pojkar med högutbildade föräldrar. Föräldrarnas utbildningsnivå påverkade inte risken för typ 1 diabetes hos flickor under 15 år. Hos unga vuxna i åldern 15-30 år, minskade risken för typ 1 med stigande utbildningsnivå hos föräldrarna (Studie I). Jämfört med barn till svenskfödda föräldrar hade barn till invandrare lägre risk att drabbas av typ 1 diabetes. Den lägsta risken observerades hos barn med båda föräldrarna födda utomlands (Studies I och II). Bland barn och unga vuxna invandrare födda i Asien, Sydeuropa, Östeuropa och Latinamerika, var risken för typ 1-diabetes mellan 40% och 85% lägre än hos personer födda i Sverige (Studie I). Barn till asiatiska, europeiska (utom nordeuropeiska), latin och nordamerikanska föräldrar, hade en 35-65% lägre risk för typ 1 diabetes än barn till svenskfödda föräldrar. Barn till föräldrar från Östafrika hade en 45-60% högre risk för typ 1 diabetes än barn till svenskfödda föräldrar (Studie II). Typ 1 diabetes hos någon av föräldrarna var associerat med en sju gånger ökad risk för typ 1 diabetes hos barnet (Studie III). Hos barn till nordiska föräldrar var paternell typ 1 diabetes förenad med den största risken för typ 1 diabetes hos barnet. Hos barn till icke nordiska föräldrar var maternell typ 1 diabetes förenad med den största risken (Studie III). Maternell övervikt var associerat med en 36% ökad risk för typ 1-diabetes hos barn till föräldrar utan diabetes (Studie III). Risken för typ 1 diabetes hos barnet ökade med längden på mammans vistelsetid i Sverige före förlossning. Den högsta risken för typ 1 diabetes fanns hos barn till föräldrar från Östafrika och som bott i Sverige i minst 11 år före barnets födelse. (Studie IV).

Slutsatser: Födelseland har stor betydelse för risken att utveckla typ 1 diabetes. Förändringen av risken över tid och mellan generationer tyder på att samverkan mellan arv och miljö har patofysiologisk betydelse för utvecklingen av typ 1 diabetes. En ökande förekomst av maternell övervikt och fetma kan möjligen bidra till den ökande förekomsten av typ 1 diabetes hos barn till föräldrar utan diabetes.

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