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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

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ABSTRACT

Objective: To investigate the trends and the risk of developing type 1 diabetes in offspring of Swedes and immigrants by specific parental migration background, age, sex and birth cohort.

Design: Registry-based cohort study.

Setting: Using Swedish nation-wide data we analyzed the risk of developing type 1 diabetes in 3,457,486 female and 3,641,304 male offspring between 0-30 years of age, born to native Swedes or immigrants, and born and living in Sweden between 1969 and 2009. We estimated Incidence rate ratios (IRRs) with 95% confidence intervals using Poisson regression models. We further calculated age-standardized rates (ASRs) of type 1 diabetes, using the world population as standard.

Results: We observed a trend of increasing ASRs among offspring below 15 years of age born to native Swedes but not among offspring of immigrants. We further observed a shift towards younger age at diagnosis in younger birth cohorts in both groups of offspring.

Compared with offspring of Swedes, children (0 to 14 years) and young adults (15 to 30 years) with one parent born abroad had an overall 30% and 15% to 20% lower IRR, respectively, after multivariable adjustment . The reduction in IRR was even greater among offspring of immigrants if both parents were born abroad. Analysis by specific parental region of birth revealed a 45% to 60% higher IRR among male and female offspring aged 0–30 years of Eastern Africa.

Conclusions: Parental country of birth and early exposures to environmental factors play an important role in the etiology of type 1 diabetes.

Key words

Type 1 Diabetes, Birth Cohort, Incidence, Migration, Sweden

Article summary

Article focus

- The primary aim of the present study was to investigate if the risk of type 1 diabetes differs between offspring of Swedes and offspring of foreign born parents assuming that offspring of foreign born parents have similar environmental exposures as offspring of Swedes.

- The secondary aim was to investigate if age at onset of type 1 diabetes varies with ethnic background and between birth cohorts.

Key messages

- The observed increasing trend of type 1 diabetes and shift towards younger age at diagnosis in individuals younger than 15 years of age, suggests an important role of early exposures to environmental factors for the etiology of type 1 diabetes.

- The reduced Incidence rate ratio (IRR) among children (0 to 14 years) and young adults (15 to 30 years) with one foreign born parent, and even greater reduction if both parents were born abroad, also indicate the importance of parental country of birth in the etiology of type 1 diabetes.

Strengths and limitation of this study

- Study strengths include the nation-wide cohort design, nearly complete follow-up of type 1 diabetes occurrence over 40 years and avoiding misclassification bias through using unique Personal Identification Number (PIN) assigned to all Swedish citizens.

- A limitation with our study is the lack of specific ICD codes for type 1 diabetes in the earlier versions of ICD (i.e. 8th and 9th version of ICD). However, the prevalence of T2DM is low in Sweden and most likely the majority of diabetes cases diagnosed before 30 years of age are coded as type 1 diabetes.

INTRODUCTION

The epidemic of type 1 diabetes is accelerating in many parts of the world with large impact on the affected individual's life and also with great health economic consequences [1]. There is a wide variation in the incidence of type 1 diabetes between countries, ranging from 0.1 per 100 000 person years in China and Venezuela to more than 40 per 100 000 person years in Sweden and Finland, respectively [2-4].

The concordance rate of type 1 diabetes among monozygotic twins has been estimated to 27% [5]. Thus, in the etiology of type 1 diabetes, there is considerable room for influence of environmental factors acting on genetic predisposition. Investigating the occurrence of type 1 diabetes in immigrants and their offspring offers a unique possibility to explore and delineate the gene-environment interaction for the development of type 1 diabetes.

Over the past decades, a rapid rise in the incidence of type 1 diabetes among individuals below 15 years of age has been reported and also with a shift towards younger age at onset [6, 7]. These studies, however, have not distinguished between individuals born to parents with different migration background. If offspring of immigrants, with varying genetic background, experience the same change in age at onset as observed in offspring of natives, the importance of early environmental exposures for the development of type 1 diabetes would be further supported. We recently reported a decreased risk of type 1 diabetes among the majority of immigrants in Sweden compared with native Swedes. We also observed a tendency towards a convergence of risks for type 1 diabetes between offspring of immigrants as one group and native Swedes [8]. Since immigrants and their offspring are a

heterogeneous population, there is a need to explore if the risk of type 1 diabetes varies by specific parental country or region of birth.

In the present study, we used Swedish nation-wide data collected over 40 years to investigate the trend and the risk of developing type 1 diabetes in offspring of immigrants by specific paternal and maternal migration background and by birth cohorts. Since the incidence of type 1 diabetes varies with sex and age [9, 10], the analyses were stratified by offspring sex and age.

METHODS

Database

We used information from a newly established, nationwide dataset – The Migration and Health Cohort (M&H Co.) [11], where data from national, longitudinal clinical, health and socio - demographic registries have been compiled. This database was built by individual record-linkage between more than fifteen Swedish national registries to facilitate studies on diabetes, injuries, cancer, cardiovascular and psychiatric diseases among immigrants and their descendants in Sweden. The linkage was done using the Personal Identification Number (PIN), which is uniquely assigned to each individual that have resided in Sweden for longer than one year since 1947 [12]. The data used in this study are part of the M&H Co., including: 1) The Swedish Total Population Register, which covers the entire population registration in Sweden and is updated on a daily basis. The registry contains information on demographic variables, such as date and place of birth and data on emigration and immigration [13]. 2) The Cause of Death Register, which contains information on the date of death, the main and contributing causes of death [14]. 3) The National Patient Register, including the Inpatient Register which was established

in 1964 and with national coverage since 1987. Since 2001, the Patient Register includes information on all outpatient visits to specialist care and day visits to hospitals. The Patient Register contains data on the main diagnosis and up to eight secondary diagnoses [15, 16]. 4) The Multi-Generation Register contains links between children and their parents via PINs for all Swedish inhabitants born after 1931 who were alive in 1960 [17]. 5) The National Population and Housing Censuses and longitudinal integration database for health insurance and labor market studies (LISA), contains data on socio-economic, occupational and demographic variables [18, 19].

The linkages between the registers have been completed by Statistics Sweden and the National Board of Health and Welfare. To ensure confidentiality, the PINs have been replaced by person-unique serial numbers and a key code is kept at Statistics Sweden. The study was approved by one of the Regional Ethical Committees in Stockholm, Sweden (Dnr. 2009/2033-32).

Study cohort

The study population comprised 3,794,477 (51.4%) males and 3,593,765 (48.6%) females between 0 to 30 years of age, born and living in Sweden any time between January 1st, 1969 and December 31st, 2009. We excluded individuals whose parents had unknown information on country of birth and all individuals who had a history of type 1 diabetes, before entry into the cohort. The final cohort included 7,098,790 individuals (3,641,304 (51.3%) males and 3,457,486 (48.7%) females) aged 0-30 years and born in Sweden.

Follow-up

The cohort members were followed from date of birth or January 1st, 1969, whichever occurred last, until the date of diagnosis of type 1 diabetes according to the Swedish versions of International Classification of Disease (ICD-8: 250, 1969-1986; ICD-9: 250, 1987-1996; ICD-10: E10, 1997 and onwards), emigration, death or end of follow-up (December 31st, 2009), whichever occurred first.

Classification of offspring based on parental country of birth

The cohort was divided into four groups according to parental country of birth: individuals with mothers born outside Sweden (father could be born in Sweden, abroad or unknown) (n= 345,827); individuals with fathers born outside Sweden (mother could be born in Sweden, abroad or unknown) (n= 317,397); individuals with both parents born outside of Sweden (n= 435,045) and individuals with both parents born in Sweden (n= 6,000,521). We also classified parental country of birth into 6 continents: Africa (North, South, East, West and Middle 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) Northern America, and Oceania (Australia/New Zealand, Melanesia, and Micronesia/Polynesia). Based on the findings from our previous study among immigrant individuals [8], we categorized Africa into North, East and West Africa; Europe into Finland, North Europe without Finland, and South-, East-, and West Europe (the latter three as one group).

For the trend and the birth cohort analyses, we pooled all offspring of immigrants into one group.

Statistical analysis

We estimated Incidence rate ratios (IRRs) with 95% confidence intervals (CIs) using Poisson regression models. The analyses were adjusted for age at follow-up (in 5 years intervals 0-4, 5-9, 10-14, 15-19, 20-24, and 25-30 years), calendar years of follow-up (four categories: 1969-1978, 1979-1988, 1989-1998 and 1999-2009) and education of the mother or father (classified into four levels: 0-9 years, 10-12 years, 13 years or more and unknown). All analyses were performed for females and males separately. In addition, analyses were made separately for children (0-14 years) and young adults (15-30 years) where we did not distinguish specific parental region or country of birth. In further analyses, children and young adults (0-30 years) were pooled together as one category to allow reasonable statistical power for analyses by specific maternal and paternal regions or country of birth to test the hypothesis if the mother's and the father's background affect the offspring's risk of type 1 diabetes differently. We also analyzed risk of type 1 diabetes in children with both mother and father born in the same country/region. Those with parents from different regions or from Sweden were categorized as a mixed group.

Since we had no specific ICD codes before 1997 to distinguish between type 1 and type 2 diabetes, we repeated the analysis and confined our cohort to individuals living in Sweden between 1997 and 2009 where we could strictly identify type 1 diabetes according to ICD-10. The results were similar to the results of the entire cohort and thus not presented.

For the trend analysis, we further calculated age-standardized rates (ASRs), using the world population as standard [20]. We reported ASR in unit of per 100,000 person years.

We used Statistical Analysis System (SAS) version 9.3 for all the analysis.

RESULTS

On average, the age of onset of type 1 diabetes was similar in offspring of immigrants as in offspring of Swedes (mean ± SD; offspring of immigrants 14.31±7.70, offspring of swedes 15.47± 7.99).

Over the study period (1969 -2009), we observed a clear trend of increasing incidence of type 1 diabetes among offspring below 15 years of age born to native Swedes whereas, the increase was less evident among offspring of immigrants (Figure 1). In contrast, no increase or a slight decreasing trend was observed among young individuals between 15 to 30 years of age regardless of parental migration background (Figure 2).

The birth cohort analysis revealed a shift towards lower age at onset in individuals below 15 years of age in both offspring of Swedes and in offspring of immigrants (Figures 3A and 3B).

Compared with offspring of Swedish-born parents, boys and girls (0 to 14 years) with a foreign-born mother or father had about 30% lower IRR in the multivariable analyses adjusted for age, calendar period and parental education. Among boys and girls with both parents born abroad, corresponding risk reductions were about a 40% (Table 1).

Compared with young adults (15 to 30 years) of Swedish-born parents, young adults with only one parent born abroad had about 15% to 20% lower IRR of type 1 diabetes and among young adults with both parents born abroad, the risks were reduced by 25% to 30% (Table 1).

Next, we investigated risks of type 1 diabetes by parental region of birth. Compared with young offspring (0-30 years) of Swedish-born parents, male and female offspring of mothers or fathers born in Africa had about 20% to 40% higher IRR of type 1

diabetes (Table 2). The increased risk of type 1 diabetes was more prominent among individuals whose mothers or fathers were born in Eastern Africa. With a few exceptions, male and female offspring of mothers or fathers born in Asia, Europe (except Northern Europe), Latin America and Northern America (except female offspring to fathers from Northern America) had between 35% to 65% lower IRR than male and female offspring of Swedish-born parents (Table 2). These reductions in risks became even more prominent when we confined the analyses to parents born in the same region (Table 2). Offspring of Finnish immigrants and rest of Northern Europe had almost similar risks compared with offspring of Swedes (Table 2).

DISCUSSION

In this nation-wide cohort study of Sweden-born children and young adults, we observed a continuing increase of type 1 diabetes in individuals younger than 15 years of age over the past decades. This increase was, however, less evident among offspring of immigrants than in offspring of native Swedes. In contrast, no change in trend was observed among young individuals between 15 to 30 years of age, and regardless of parental country of birth.

An interesting finding in the present study was an almost identical pattern with a shift towards lower age at onset of type 1 diabetes by younger birth cohorts in both offspring of foreign born parents and Swedes.

Over the past decades, a rapid rise in the incidence of type 1 diabetes has been demonstrated [21, 22]. The finding of an increased incidence rate of type 1 diabetes between 1969 and 2009 among individuals below 15 years of age, and a decreasing or steady incidence rate among young adults, is in line with previous studies from Sweden [6] and other parts of the world [7]. The finding of an almost identical pattern

with a shift towards lower age at onset of type 1 diabetes in both offspring of foreign born parents and Swedes indicates the exposure to similar environmental factors in both groups. It has been hypothesized that this developments is due to increased exposures in early life to factors that initiate and/ or accelerate beta cell destruction, including viral infections, rapid postnatal growth and nutritional factors [23, 24].

We further found that offspring with one or two parents born abroad had a reduced risk of type 1 diabetes compared with offspring to Sweden-born parents. The reduction in risk was similar between sexes and was more apparent among individuals where both parents were foreign born. Stratification by specific parental region/country of birth, however, revealed that this reduction was confined to offspring of immigrants from Asia, Latin and North America, South-, West- and East Europe. In contrast, the IRR for type 1 diabetes was increased in individuals with African parents, particularly so if the parents were born in Eastern or Northern Africa.

The primary strength of our study is the nation-wide cohort design with nearly complete follow-up of type 1 diabetes occurrence over several decades. Using a unique PIN assigned to all Swedish citizens, we were able to correctly assess exposure (parental country of birth) and thus avoiding misclassification bias.

The observed increased risk among offspring of Africans in this study is also observed in Swedish residents born in Africa [8, 25]. It is unclear if these findings reflect a high risk of type 1 diabetes in the countries of origin, thus rating Eastern and Northern Africa as the areas with the highest incidence of type 1 diabetes in the world.

The reported low number of type 1 diabetes diagnoses in Africa [26] is most likely to be underestimated due to lack of diagnostic measures [27], and high mortality among uncontrolled type 1 diabetes cases as a result of limited access to insulin

treatment [28]. Moreover, priorities are mostly given to the high burden of communicable diseases in African countries [29], especially in busy emergency hospitals. As a consequence, children with diabetic ketoacidosis at the time of diagnosis [30] could be misdiagnosed as cerebral malaria or meningitis [31] which would also lead to an underestimation of type 1 diabetes cases. The observed higher risk in African offspring in the present study and the increased risk of type 1 diabetes in Swedish residents born in Africa [8] might be due to genetic propensity interacting with environmental factors in the new home country.

Offspring of Swedish residents born in Asia, Latin and North America, South-, West- and East Europe retained the low risk profile we recently observed in young immigrants in Sweden born in these areas [8]. This risk reduction was independent of maternal or paternal birth region but was stronger if both parents were born in the same region.

The importance of parental country of birth for the risk of developing type 1 diabetes has also been observed in other studies [32-35] and may indicate the role of genetic factors [36, 37]. Children of Sardinian heritage (a high risk area), born and living in Lazio (a low risk area) retained the high risk profile of Sardinia [38]. The risk for type 1 diabetes in children of Yugoslavian, Italian and Greek heritage in Germany was closer to the reported incidence in those countries than in Germany [39] However, the importance of life style or environmental factors interacting with genetic factors cannot be ruled out [40] as studies of immigration from regions with low to high incidence of type 1 diabetes have been associated with increased incidence of type 1 diabetes [33] .

We lacked specific ICD codes for type 1 diabetes in the earlier versions of ICD (i.e. 8th and 9th version of ICD). However, the prevalence of type 2 diabetes is low in

Sweden [41, 42] and most likely the majority of cases of diabetes diagnosed before 30 years are type 1 diabetes. Moreover, the results of the analysis limited to only cases of type 1 diabetes according to ICD 10 for the years 1997 and forward were similar to the results for the entire period of the study.

Our findings of a lower IRR of type 1 diabetes among children and young adults with one or two foreign born parents, with the notable exception of offspring of African immigrants, and the shifting of age of diagnosis towards younger age in both offspring of Swedes and of immigrants highlight the important role of environmental factors and its interaction with genetic background in the etiology of type 1 diabetes.

Further studies of exploring early exposures to environmental factors and studies on offspring of immigrants from African countries, in particular from Eastern Africa, might improve our understanding on the etiology of the disease.

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Competing interests

No potential conflicts of interest relevant to this article were reported.

Contributors

H.I.H. designed the research, drafted the manuscript, analyzed data, and interpreted results.

M.P. designed the research, interpreted the results critically reviewed and edited the manuscript.

T.M. designed the research, interpreted the results, critically reviewed and edited the manuscript, handled research data and funding, and supervised.

Data Sharing

There are no additional data available.

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Figures

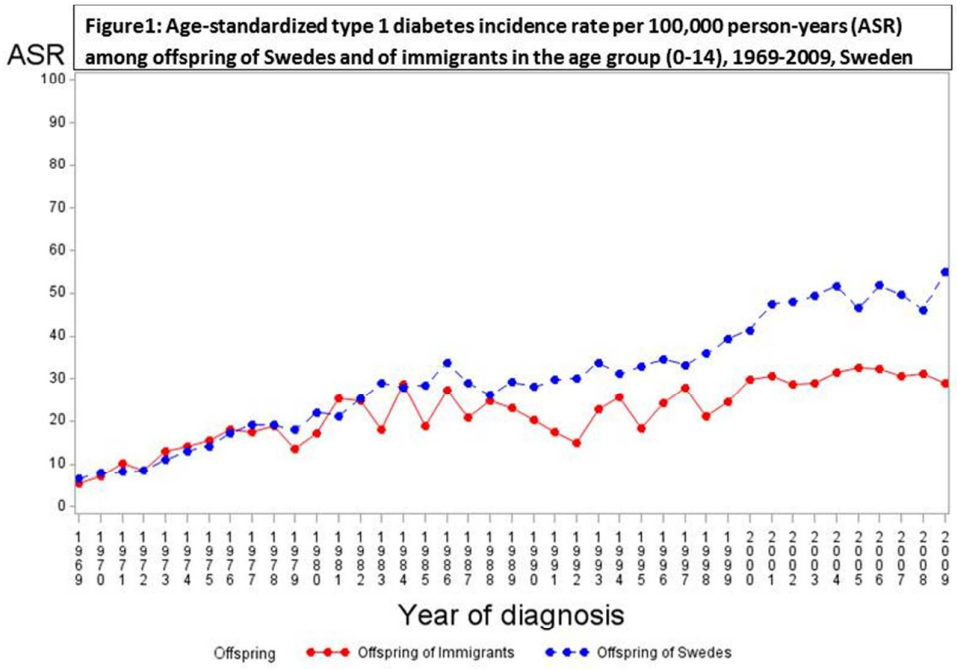

Figure1: Age-standardized type 1 diabetes incidence rate per 100,000 person-years (ASR) among offspring of Swedes and of immigrants in the age group (0-14), 1969-2009, Sweden

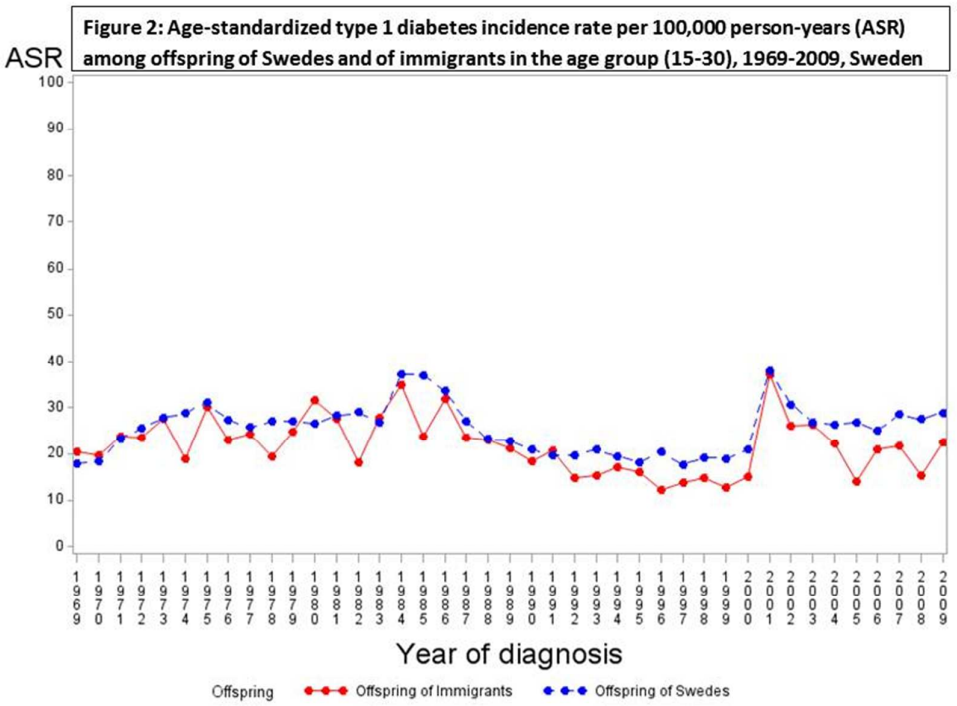

Figure 2: Age-standardized type 1 diabetes incidence rate per 100,000 person-years (ASR) among offspring of Swedes and of immigrants in the age group (15-30), 1969-2009, Sweden

Figure 3.A. : Incidence of type 1 diabetes by age at diagnosis (0-30 years) and birth cohorts 1960-2009 among offspring of Swedes in Sweden

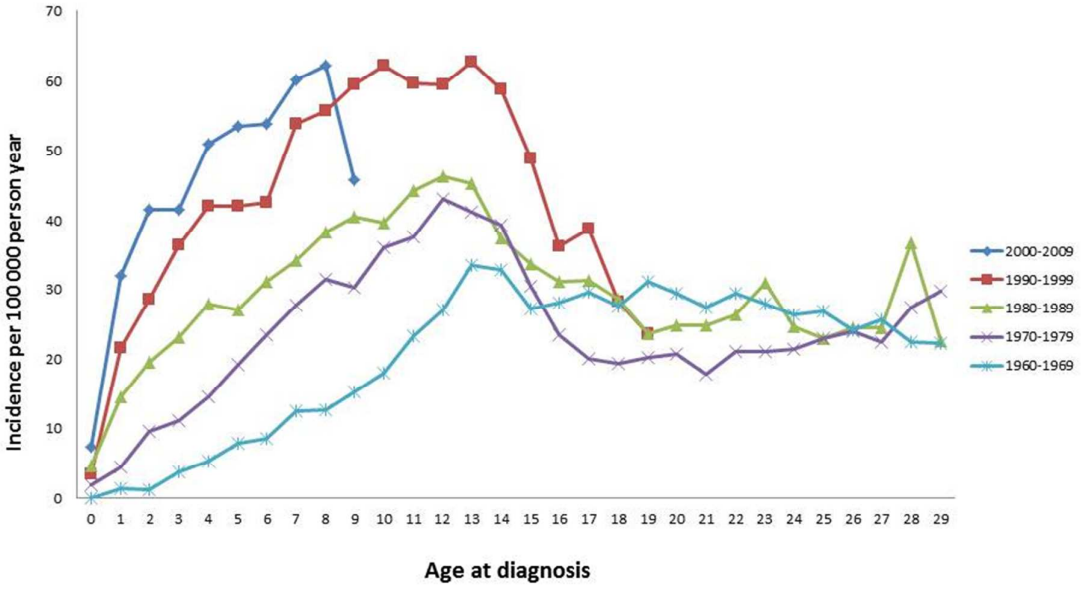

Figure 3.B: Incidence of type 1 diabetes by age at diagnosis (0-30 years) and birth cohorts 1960-2009 among offspring of Immigrants in Sweden

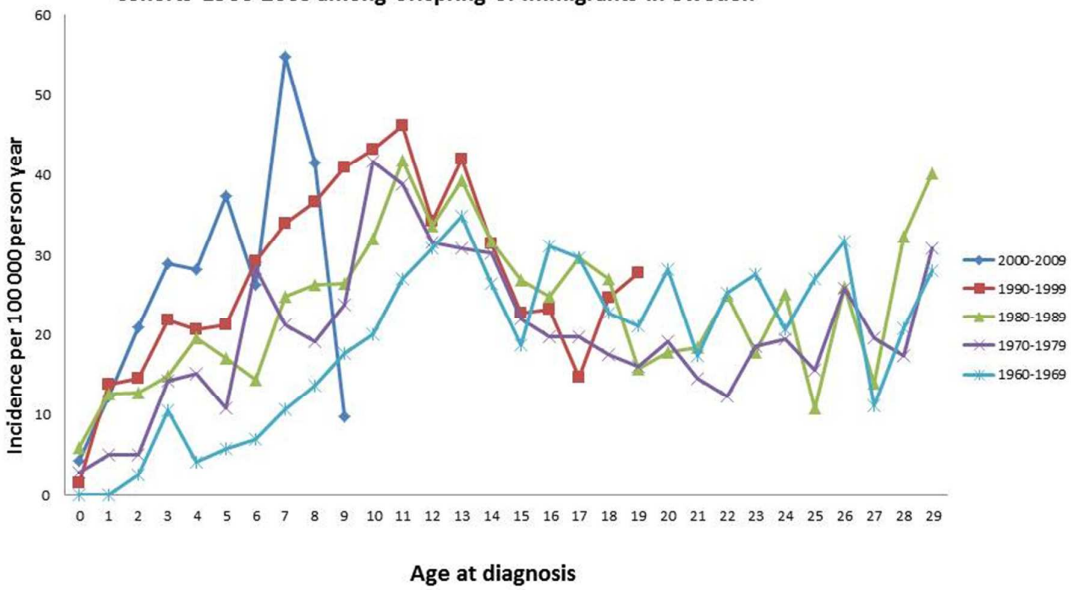

Table 1: Incidence rate ratio (IRR) and 95% confidence interval (CI) of type 1 diabetes among children aged (0-14) and young adults aged (15-30) by sex and parental country of birth, Sweden, 1969–2009.

	Male (0-14)				Female (0-14)			
Parental immigration Status	**Cases**	**PYRs**	**IRR* (95% CI)**	**IRR† (95% CI)**	**Cases**	**PYRs**	**IRR* (95% CI)**	**IRR† (95% CI)**
Mother foreign born	871	3810384	0.76 (0.71-0.81)	0.69 (0.64-0.74)	808	3610118	0.79 (0.73-0.85)	0.71 (0.66-0.77)
Father foreign born	858	3948653	0.72 (0.67-0.77)	0.65 (0.61-0.70)	833	3764091	0.78 (0.73-0.84)	0.70 (0.65-0.75)
Both parents foreign born	443	2249700	0.66 (0.60-0.73)	0.58 (0.52-0.64)	435	2134846	0.73 (0.66-0.80)	0.62 (0.56-0.69)
Both parents born in Sweden	8334	26670322	1	1	7417	25249558	1	1
	Male (15-30)				**Female (15-30)**			
Mother foreign born	624	2791560	0.82 (0.75-0.89)	0.79 (0.73-0.86)	510	2635294	0.82 (0.75-0.90)	0.85 (0.77-0.93)
Father foreign born	618	2636310	0.86 (0.79-0.93)	0.83 (0.76-0.90)	442	2504279	0.75 (0.68-0.82)	0.79 (0.72-0.87)
Both parents foreign born	270	1287893	0.76 (0.68-0.86)	0.72 (0.64-0.82)	204	1215563	0.71 (0.62-0.81)	0.75 (0.65-0.86)

Tables

Both parents born in Sweden	8024	29689985	1	1	6627	28192526	1	1

* Adjusted for age in five years categories.
† Mutually adjusted for age, parental education and calendar years of follow-up.

Table 2: Incidence rate ratio (IRR) and 95% confidence interval (CI) of type 1 diabetes among male and female ages 0-30 years by parental country of birth and sex Sweden, 1969-2009.

	IRR* (95 % CI)											
	Male						Female					
Parental country of birth	cases	Offspring of Mother	cases	Offspring of Father	Cases	Offspring of both Parents	cases	Offspring of Mother	cases	Offspring of Father	Cases	Offspring of both Parents
Sweden	16358	1	16358	1	16358	1	14044	1	14044	1	14044	1
Africa	92	**1.42 (1.15-1.75)**	148	**1.19 (1.01-1.41)**	78	1.12 (0.90-1.41)	86	**1.33 (1.10-1.65)**	129	**1.33 (1.12-1.59)**	75	**1.32 (1.05-1.66)**
Northern Africa	21	1.18 (0.77-1.81)	55	1.06 (0.81-1.40)	16	0.86 (0.53- 1.40)	26	1.27 (0.86-1.86)	50	1.18 (0.89-1.55)	19	1.25 (0.80- 1.96)
Western Africa	4	-	17	0.89 (0.55-1.42)	2	-	5	0.76 (0.32-1.83)	12	0.99 (0.56-1.74)	4	-
Eastern Africa	66	**1.51 (1.18-1.92)**	70	**1.46 (1.15-1.85)**	58	**1.45 (1.12-1.88)**	51	**1.47 (1.11-1.93)**	62	**1.61 (1.25-2.10)**	47	**1.44 (1.08-1.92)**
Asia	133	**0.37 (0.31-0.44)**	155	**0.40 (0.34-0.47)**	107	**0.36 (0.30-0.44)**	137	**0.48 (0.40-0.56)**	155	**0.49 (0.42-0.57)**	108	**0.45 (0.37-0.54)**
Europe												
Finland	692	0.98 (0.91-1.10)	523	0.99 (0.90-1.08)	273	0.96 (0.85-1.08)	587	0.96 (0.89-1.05)	442	0.97 (0.88-1.06)	232	0.93 (0.82-1.06)
North Europe (excl. Finland)	240	0.88 (0.77-1.00)	258	0.89 (0.78-1.00)	46	0.89 (0.67-1.19)	235	0.99 (0.87-1.12)	231	0.91 (0.80-1.04)	38	0.82 (0.60-1.13)
S.E.W. Europe†	284	**0.55 (0.49-0.62)**	319	**0.53 (0.47-0.59)**	110	**0.39 (0.33-0.47)**	227	**0.53 (0.46-0.60)**	264	**0.52 (0.46-0.58)**	95	**0.41 (0.33-0.50)**
Latin America	39	**0.56 (0.41-0.77)**	51	**0.65 (0.49-0.87)**	17	**0.39 (0.24-0.63)**	29	**0.51 (0.35-0.75)**	23	**0.33 (0.21-0.51)**	14	**0.41 (0.24-0.69)**
North America	13	**0.50 (0.29-0.86)**	20	**0.55 (0.36-0.86)**	0	-	15	0.78 (0.47-1.30)	31	1.02 (0.72-1.46)	0	-
Oceania	2	-	2	-	0	-	2	-	0	-	0	-
Mixed‡	0	-	0	-	84	**0.64 (0.52-0.79)**	0	-	0	-	82	**0.75 (0.61-0.94)**

* Adjusted for age, parental education and calendar years of follow-up.
† South, East and West Europe
‡ Both parents are not from the same country or region.
IRRs significantly different from 1 are bolded.

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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

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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

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ABSTRACT

Objective: To investigate the trends and the risk of developing type 1 diabetes in offspring of Swedes and immigrants by specific parental migration background, age, sex and birth cohort.

Design: Registry-based cohort study.

Setting: Using Swedish nation-wide data we analyzed the risk of developing type 1 diabetes in 3,457,486 female and 3,641,304 male offspring between 0-30 years of age, born to native Swedes or immigrants, and born and living in Sweden between 1969 and 2009. We estimated Incidence rate ratios (IRRs) with 95% confidence intervals using Poisson regression models. We further calculated age-standardized rates (ASRs) of type 1 diabetes, using the world population as standard.

Results: We observed a trend of increasing ASRs among offspring below 15 years of age born to native Swedes and a less evident increase among offspring of immigrants. We further observed a shift towards younger age at diagnosis in younger birth cohorts in both groups of offspring.

Compared with offspring of Swedes, children (0 to 14 years) and young adults (15 to 30 years) with one parent born abroad had an overall 30% and 15% to 20% lower IRR, respectively, after multivariable adjustment . The reduction in IRR was even greater among offspring of immigrants if both parents were born abroad. Analysis by specific parental region of birth revealed a 45% to 60% higher IRR among male and female offspring aged 0–30 years of Eastern Africa.

Conclusions: Parental country of birth and early exposures to environmental factors play an important role in the etiology of type 1 diabetes.

Key words

Type 1 diabetes, Birth Cohort, Incidence, Migration, Sweden

Article summary

Article focus

- The primary aim of the present study was to investigate if the risk of type 1 diabetes differs between offspring of Swedes and offspring of foreign born parents assuming that offspring of foreign born parents have similar environmental exposures as offspring of Swedes.

- The secondary aim was to investigate if age at onset of type 1 diabetes varies with ethnic background and between birth cohorts.

Key messages

- The observed increasing trend of type 1 diabetes and shift towards younger age at diagnosis in individuals younger than 15 years of age, suggests an important role of early exposures to environmental factors for the etiology of type 1 diabetes.

- The reduced Incidence rate ratio (IRR) among children (0 to 14 years) and young adults (15 to 30 years) with one foreign born parent, and even greater reduction if both parents were born abroad, also indicate the importance of parental country of birth in the etiology of type 1 diabetes.

Strengths and limitation of this study

- Study strengths include the nation-wide cohort design, nearly complete follow-up of type 1 diabetes occurrence over 40 years and avoiding misclassification bias through using unique Personal Identification Number (PIN) assigned to all Swedish citizens.

- A limitation with our study is the lack of specific ICD codes for type 1 diabetes in the earlier versions of ICD (i.e. 8th and 9th version of ICD). However, the prevalence of T2DM is low in Sweden and most likely the majority of diabetes cases diagnosed before 30 years of age are coded as type 1 diabetes.

INTRODUCTION

The epidemic of type 1 diabetes is accelerating in many parts of the world with large impact on the affected individual's life and also with great health economic consequences [1]. There is a wide variation in the incidence of type 1 diabetes between countries, ranging from 0.1 per 100 000 person years in China and

Venezuela to more than 40 per 100 000 person years in Sweden and Finland, respectively [2-4].

The concordance rate of type 1 diabetes among monozygotic twins has been estimated to 27% [5]. Thus, in the etiology of type 1 diabetes, there is considerable room for influence of environmental factors acting on genetic predisposition. Investigating the occurrence of type 1 diabetes in immigrants and their offspring offers a unique possibility to explore and delineate the gene-environment interaction for the development of type 1 diabetes.

Over the past decades, a rapid rise in the incidence of type 1 diabetes among individuals below 15 years of age has been reported and also with a shift towards younger age at onset [6, 7]. These studies, however, have not distinguished between individuals born to parents with different migration background. If offspring of immigrants, with varying genetic background, experience the same change in age at onset as observed in offspring of natives, the importance of early environmental exposures for the development of type 1 diabetes would be further supported. We recently reported a decreased risk of type 1 diabetes among the majority of immigrants in Sweden compared with native Swedes. We also observed a tendency towards a convergence of risks for type 1 diabetes between offspring of immigrants as one group and native Swedes [8]. Since immigrants and their offspring are a heterogeneous population, there is a need to explore if the risk of type 1 diabetes varies by specific parental country or region of birth.

In the present study, we used Swedish nation-wide data collected over 40 years to investigate the trend and the risk of developing type 1 diabetes in offspring of immigrants by specific paternal and maternal migration background and by birth

cohorts. Since the incidence of type 1 diabetes varies with sex and age [9, 10], the analyses were stratified by offspring sex and age.

METHODS

Database

We used information from a newly established, nationwide dataset – The Migration and Health Cohort (M&H Co.) [11], where data from national, longitudinal clinical, health and socio - demographic registries have been compiled. This database was built by individual record-linkage between more than fifteen Swedish national registries to facilitate studies on diabetes, injuries, cancer, cardiovascular and psychiatric diseases among immigrants and their descendants in Sweden. The linkage was done using the Personal Identification Number (PIN), which is uniquely assigned to each individual that have resided in Sweden for longer than one year since 1947 [12]. The data used in this study are part of the M&H Co., including: 1) The Swedish Total Population Register, which covers the entire population registration in Sweden and is updated on a daily basis. The register contains information on demographic variables, such as date and place of birth and data on emigration and immigration [13]. 2) The Cause of Death Register, which contains information on the date of death, the main and contributing causes of death [14]. 3) The National Patient Register, including the Inpatient Register. It was established in 1964 but with national coverage since 1987 covering 85-95% of all diagnostic data [15]. Since 2001, the Patient Register includes information on all registered outpatient visits to specialist care and day visits to hospitals and covers about 80% of all visits to the specialized outpatient care [16]. The Patient Register contains data on the main diagnosis and up to eight secondary diagnoses [15, 16]. 4) The Multi-

Generation Register contains links between children and their parents via PINs for all Swedish inhabitants born after 1931 who were alive in 1960 [17]. 5) The National Population and Housing Censuses and longitudinal integration database for health insurance and labor market studies (LISA), contains data on socio-economic, occupational and demographic variables [18, 19].

The linkages between the registers have been completed by Statistics Sweden and the National Board of Health and Welfare. To ensure confidentiality, the PINs have been replaced by person-unique serial numbers and a key code is kept at Statistics Sweden. The study was approved by one of the Regional Ethical Committees in Stockholm, Sweden (Dnr. 2009/2033-32).

Study cohort

The study population comprised 3,794,477 (51.4%) males and 3,593,765 (48.6%) females between 0 to 30 years of age, born and living in Sweden any time between January 1st, 1969 and December 31st, 2009. We excluded individuals whose parents had unknown information on country of birth and all individuals who had a history of type 1 diabetes, before entry into the cohort. The final cohort included 7,098,790 individuals (3,641,304 (51.3%) males and 3,457,486 (48.7%) females) aged 0-30 years and born in Sweden.

Follow-up

The cohort members were followed from date of birth or January 1st, 1969, whichever occurred last, until the date of diagnosis of type 1 diabetes according to the Swedish versions of International Classification of Disease (ICD-8: 250, 1969-1986; ICD-9: 250, 1987-1996; ICD-10: E10, 1997 and onwards), emigration, death or end of

follow-up (December 31st, 2009), whichever occurred first. Every individual in the cohort were followed for maximum 30 years of age.

Since earlier versions of ICD (i.e. 8th and 9th version of ICD) could not disentangle between different types of diabetes, we have performed sensitivity analysis using ICD-10 only where we could identify type I diabetes (see method for details).

Classification of offspring based on parental country of birth

The cohort was divided into four groups according to parental country of birth: individuals with mothers born outside Sweden (father could be born in Sweden, abroad or unknown) (n= 345,827); individuals with fathers born outside Sweden (mother could be born in Sweden, abroad or unknown) (n= 317,397); individuals with both parents born outside of Sweden (n= 435,045) and individuals with both parents born in Sweden (n= 6,000,521). We also classified parental country of birth into 6 continents: Africa (North, South, East, West and Middle 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) Northern America, and Oceania (Australia/New Zealand, Melanesia, and Micronesia/Polynesia). Based on the findings from our previous study among immigrant individuals [8], we categorized Africa into North, East and West Africa; Europe into Finland, North Europe without Finland, and South-, East-, and West Europe (the latter three as one group). For the trend and the birth cohort analyses, we pooled all offspring of immigrants into one group.

Statistical analysis

We estimated Incidence rate ratios (IRRs) with 95% confidence intervals (CIs) using Poisson regression models. The analyses were adjusted for age at follow-up (in 5 years intervals 0-4, 5-9, 10-14, 15-19, 20-24, and 25-30 years), calendar years of follow-up (four categories: 1969-1978, 1979-1988, 1989-1998 and 1999-2009) and education of the mother or father (classified into four levels: 0-9 years, 10-12 years, 13 years or more and unknown). All analyses were performed for females and males separately. In addition, analyses were made separately for children (0-14 years) and young adults (15-30 years) where we did not distinguish specific parental region or country of birth. In further analyses, children and young adults (0-30 years) were pooled together as one category to allow reasonable statistical power for analyses by specific maternal and paternal regions or country of birth to test the hypothesis that the mother's and the father's background would affect the offspring's risk of type 1 diabetes differently. We also analyzed risk of type 1 diabetes in children with both mother and father born in the same country/region. Those with parents from different regions or from Sweden were categorized as a mixed group.

Since we had no specific ICD codes before 1997 to distinguish between type 1 and type 2 diabetes, we repeated the analysis and confined our cohort to individuals living in Sweden between 1997 and 2009 where we could strictly identify type 1 diabetes according to ICD-10.

For the trend analysis, we further calculated age-standardized rates (ASRs), by parental migration background for both children (0–14 years) and young adults (15–30 years), by dividing number of new cases with the estimated numbers of person-years at risk in 5-years age categories using the world population as standard [20]. ASRs were directly calculated to ensure comparability and to adjust for differences in

age in the study population, in each of the age groups 0–4, 5–9, 10–14, 15–19, 20–24, and 25–30 years. We reported ASR in unit of per 100,000 person years.

The Joint point regression analyses were performed to evaluate trends of type 1 diabetes in both offspring to immigrants and offspring to Swedes and in both age groups [21, 22]. Annual percent change (APC) was estimated, 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. We used Statistical Analysis System (SAS) version 9.3 for all the analysis.

RESULTS

On average, the age of onset of type 1 diabetes was similar in offspring of immigrants as in offspring of Swedes (mean ± SD; offspring of immigrants 14.31±7.70, offspring of swedes 15.47± 7.99).

Over the study period (1969 -2009), we observed a significant increasing trend for incidence of type 1 diabetes based on joint point regression analyses among offspring below 15 years of age born to native Swedes and to immigrants (offspring to Swedes: APC= 3.9, p values<0.001 and offspring to immigrants: APC= 2.2, p values<0.001 Figure 1). In contrast, no increase or a slight decreasing trend was observed among young individuals between 15 to 30 years of age regardless of parental migration background (offspring to Swedes: APC= -0.0, p= 0.9 and offspring to immigrants: APC= -0.7, p value= 0.08 , Figure 2).

The birth cohort analysis revealed a shift towards lower age at onset in individuals below 15 years of age in both offspring of Swedes and in offspring of immigrants (Figures 3a and 3b).

Compared with offspring of Swedish-born parents, boys and girls (0 to 14 years) with a foreign-born mother or father had about 30% lower IRR in the multivariable analyses adjusted for age, calendar period and parental education. Among boys and girls with both parents born abroad, corresponding risk reductions were about a 40% (Table 1). The results from the sensitivity analysis, where we repeated the analysis and confined our cohort to individuals born in Sweden between 1997 and 2009, were similar to the results of the entire cohort (Supplementary Table 1S).

Compared with young adults (15 to 30 years) of Swedish-born parents, young adults with only one parent born abroad had about 15% to 20% lower IRR of type 1 diabetes and among young adults with both parents born abroad, the risks were reduced by 25% to 30% (Table 1).

Next, we investigated risks of type 1 diabetes by parental region of birth. Compared with young offspring (0-30 years) of Swedish-born parents, male and female offspring of mothers or fathers born in Africa had about 20% to 40% higher IRR of type 1 diabetes (Table 2). The increased risk of type 1 diabetes was more prominent among individuals whose mothers or fathers were born in Eastern Africa. With a few exceptions, male and female offspring of mothers or fathers born in Asia, Europe (except Northern Europe), Latin America and Northern America (except female offspring to fathers from Northern America) had between 35% to 65% lower IRR than male and female offspring of Swedish-born parents (Table 2). These reductions in risks became even more prominent when we confined the analyses to parents born in the same region (Table 2). Offspring of Finnish immigrants and rest of Northern Europe had almost similar risks compared with offspring of Swedes (Table 2).

The results from the sensitivity analysis, where we repeated the analysis and confined our cohort to individuals born in Sweden between 1997 and 2009 (limited to

children ages 0 to 13) , were similar to the results of the entire cohort for the same age category (Supplementary Tables 2Sa and 2Sb).

DISCUSSION

In this nation-wide cohort study of Sweden-born children and young adults, we observed a continuing increase of type 1 diabetes in individuals younger than 15 years of age over the past decades. This increase was, however, less evident among offspring of immigrants than in offspring of native Swedes. In contrast, no change in trend was observed among young individuals between 15 to 30 years of age, and regardless of parental country of birth.

An interesting finding in the present study was an almost identical pattern with a shift towards lower age at onset of type 1 diabetes by younger birth cohorts in both offspring of foreign born parents and Swedes.

Over the past decades, a rapid rise in the incidence of type 1 diabetes has been demonstrated [23, 24]. The finding of an increased incidence rate of type 1 diabetes between 1969 and 2009 among individuals below 15 years of age, and a decreasing or steady incidence rate among young adults, is in line with previous studies from Sweden [6] and other parts of the world [7]. The observed increasing trend over time in our study might be due to the quality of National patient Register over time and not covering all of Sweden for the entire period of our study. This register became nation-wide in 1987. However, the sharpest increase in incidence observed in our study among individuals below 15 years of age is after around 1997 when the Inpatient Register had full coverage and when the ICD-10 were able to disentangle different types of diabetes.

The finding of an almost identical pattern with a shift towards lower age at onset of type 1 diabetes in both offspring of foreign born parents and Swedes indicates the exposure to similar environmental factors in both groups. It has been hypothesized that this developments is due to increased exposures in early life to factors that initiate and/ or accelerate beta cell destruction, including viral infections, rapid postnatal growth and nutritional factors [25, 26]. In addition, perinatal factors such as blood-group incompatibility, high maternal age, preeclampsia and caesarean section delivery have been shown to be associated with increased incidence of childhood type 1 diabetes [27]. Similar findings of a shift towards younger age at diagnosis and a declining incidence of type 1 diabetes among young adults aged 15 to 34 years were also observed in other studies from Sweden, using the two nation-wide prospectively collected research register, the Swedish Childhood Diabetes Register and the Diabetes Incidence Study in Sweden [10, 28]. The shift towards younger age at diagnosis may be due to risk factors accelerating the disease process.

We further found that offspring with one or two parents born abroad had a reduced risk of type 1 diabetes compared with offspring to Sweden-born parents. The reduction in risk was similar between sexes and was more apparent among individuals where both parents were foreign born. Stratification by specific parental region/country of birth, however, revealed that this reduction was confined to offspring of immigrants from Asia, Latin and North America, South-, West- and East Europe. In contrast, the IRR for type 1 diabetes was increased in individuals with African parents, particularly so if the parents were born in Eastern or Northern Africa. The observed increased risk among offspring of Africans in this study, in line with a previous Swedish register study [29] is also observed in Swedish residents born in Africa [8, 29]. It is unclear if these findings reflect a high risk of type 1 diabetes in the

countries of origin, thus rating Eastern and Northern Africa as the areas with the highest incidence of type 1 diabetes in the world. At the same time we should keep in mind that the population of immigrants in Sweden may not represent the population of countries of origin.

The reported low number of type 1 diabetes diagnoses in Africa [30] is most likely to be underestimated due to lack of diagnostic measures [31], and high mortality among uncontrolled type 1 diabetes cases as a result of limited access to insulin treatment [32]. Moreover, priorities are mostly given to the high burden of communicable diseases in African countries [33], especially in busy emergency hospitals. As a consequence, children with diabetic ketoacidosis at the time of diagnosis [34] could be misdiagnosed as cerebral malaria or meningitis [35] which would also lead to an underestimation of type 1 diabetes cases. The observed higher risk in African offspring in the present study and the increased risk of type 1 diabetes in Swedish residents born in Africa [8] might be due to genetic propensity interacting with environmental factors in the new home country.

Offspring of Swedish residents born in Asia, Latin and North America, South-, West- and East Europe retained the low risk profile were recently observed in young immigrants in Sweden born in these areas [8]. This risk reduction was independent of maternal or paternal birth region but was stronger if both parents were born in the same region.

The importance of parental country of birth for the risk of developing type 1 diabetes has also been observed in other studies [36-39] and may indicate the role of genetic factors [40, 41]. Children of Sardinian heritage (a high risk area), born and living in Lazio (a low risk area) retained the high risk profile of Sardinia [42]. The risk for type 1 diabetes in children of Yugoslavian, Italian and Greek heritage in Germany was

closer to the reported incidence in those countries than in Germany [43] However, the importance of life style or environmental factors interacting with genetic factors cannot be ruled out [44] as studies of immigration from regions with low to high incidence of type 1 diabetes have been associated with increased incidence of type 1 diabetes [37] .

The primary strength of our study is the nation-wide cohort design with nearly complete follow-up of type 1 diabetes occurrence over several decades. Using a unique PIN assigned to all Swedish citizens, we were able to correctly assess exposure (parental country of birth) and thus avoiding misclassification bias.

We lacked specific ICD codes for type 1 diabetes in the earlier versions of ICD before 1997 (i.e. 8th and 9th version of ICD). However, the results of the sensitivity analysis limited to only cases of type 1 diabetes according to ICD 10 for the years 1997 and forward were similar to the results for the entire period of the study. But, in this sensitivity analysis, we were only able to verify the results for children born between 1997 and 2009 (0 to 13 years old). Whereas, for the age groups over 15 years when type 1 diabetes is more likely to be mixed with type 2 diabetes, we had no data. However, the prevalence of type 2 diabetes is low in Sweden [45, 46] and other northern European countries and most likely the majority of cases of diabetes diagnosed before 30 years are true type 1 diabetes. While this may not be applicable for offspring born to parents from other parts of the world with known high prevalence of type 2 diabetes which may have led to overestimation of the true type 1 diabetes.

Our findings of a lower IRR of type 1 diabetes among children and young adults with one or two foreign born parents, with the notable exception of offspring of African immigrants, and the shifting of age at diagnosis towards younger age in both

offspring of Swedes and of immigrants highlight the important role of environmental factors and its interaction with genetic background in the etiology of type 1 diabetes.

In order to further clarify potential pathophysiological mechanisms for the development of type1 diabetes, further studies are needed with data on important exposures such as viral infections in early life, nutritional habits and weight gain in infancy. Moreover, studies on offspring of immigrants from African countries, in particular from Eastern Africa, might improve our understanding on the etiology of the disease.

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Competing interests

No potential conflicts of interest relevant to this article were reported.

Contributors

H.I.H. designed the research, drafted the manuscript, analyzed data, and interpreted results.

M.P. designed the research, interpreted the results critically reviewed and edited the manuscript.

T.M. designed the research, interpreted the results, critically reviewed and edited the manuscript, handled research data and funding, and supervised.

Data sharing

no additional data available.

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Figure legends

Figure 1 – Age-standardized type 1 diabetes incidence rate per 100,000 person-years (ASR) among offspring of Swedes of immigrants in the age group (0-14), 1969-2009, Sweden

Figure 2 - Age-standardized type 1 diabetes incidence rate per 100,000 person-years (ASR) among offspring of Swedes of immigrants in the age group (15-30), 1969-2009, Sweden

Figure 3a – Incidence of type 1 diabetes by age at diagnosis (0-30 years) and birth cohorts 1960-2009 among offspring of Swedes in Sweden

Figure 3b - – Incidence of type 1 diabetes by age at diagnosis (0-30 years) and birth cohorts 1960-2009 among offspring of Immigrants in Sweden

Figures

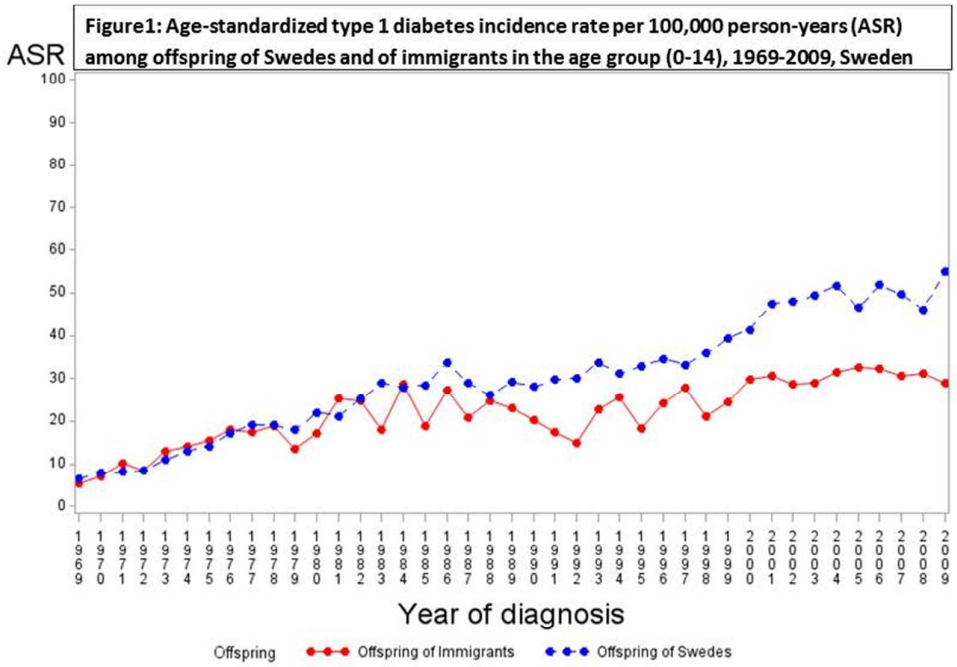

Figure 2: Age-standardized type 1 diabetes incidence rate per 100,000 person-years (ASR) among offspring of Swedes and of immigrants in the age group (15-30), 1969-2009, Sweden

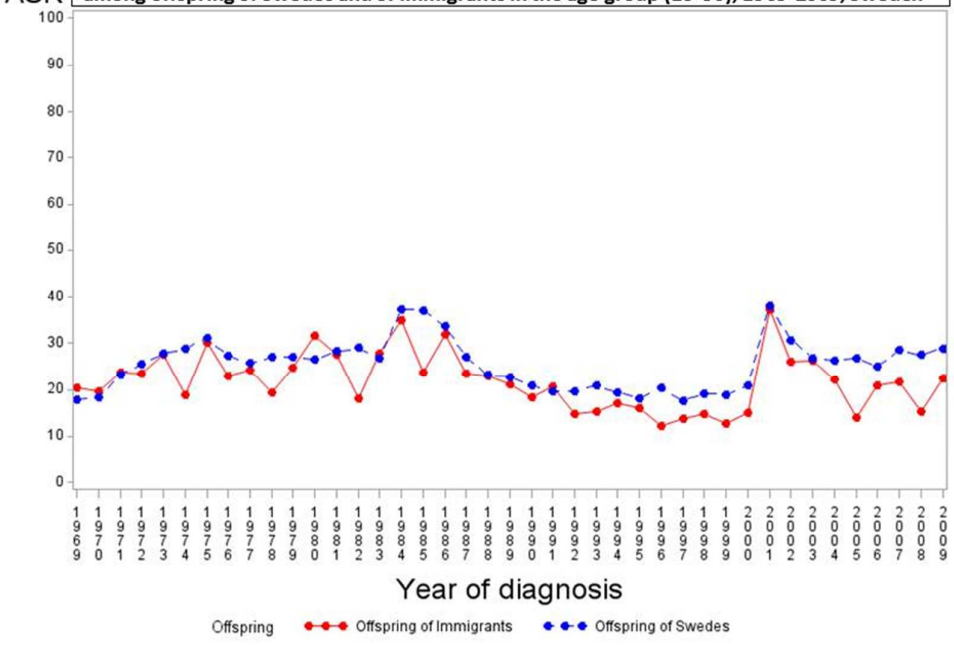

Figure 3.A. : Incidence of type 1 diabetes by age at diagnosis (0-30 years) and birth cohorts 1960-2009 among offspring of Swedes in Sweden

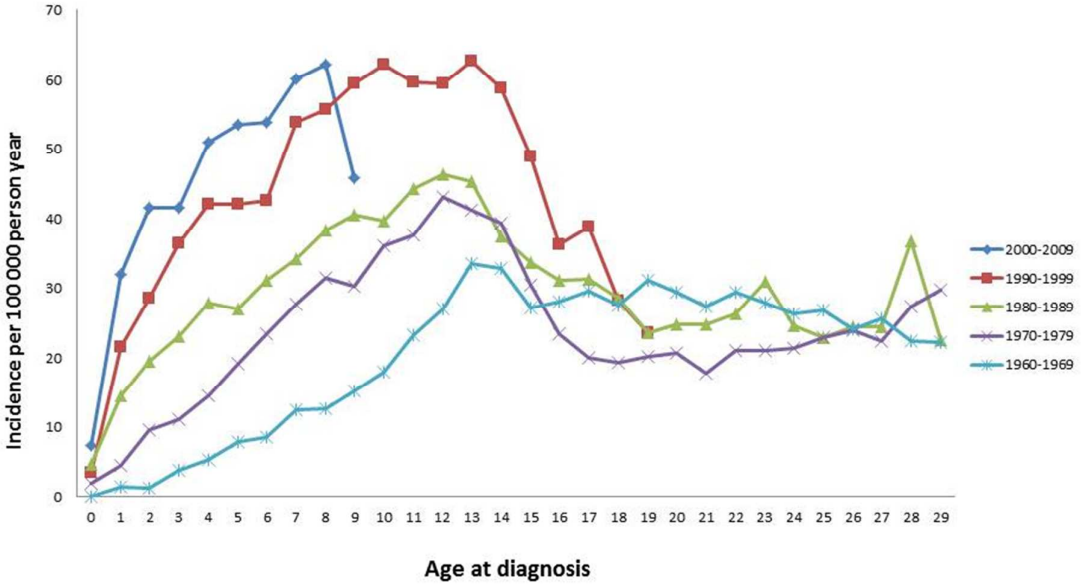

Figure 3.B: Incidence of type 1 diabetes by age at diagnosis (0-30 years) and birth cohorts 1960-2009 among offspring of Immigrants in Sweden

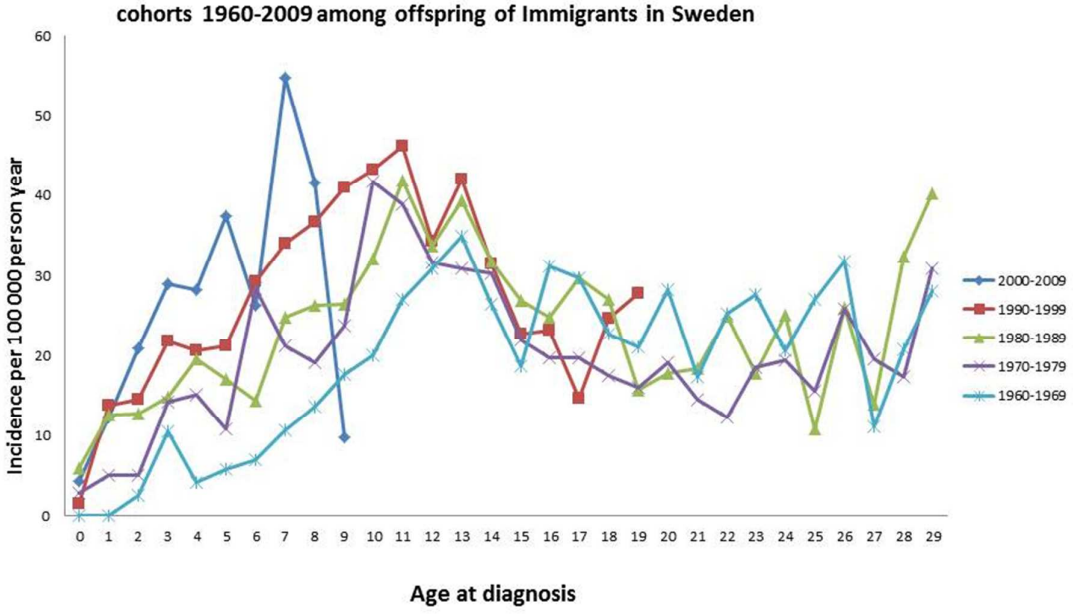

Table 1: Incidence rate ratio (IRR) and 95% confidence interval (CI) of type 1 diabetes among children aged (0-14) and young adults aged (15-30) by sex and parental country of birth, Sweden, 1969–2009.

	Male (0-14)				Female (0-14)			
Parental immigration Status	**Cases**	**PYRs**	**IRR* (95% CI)**	**IRR† (95% CI)**	**Cases**	**PYRs**	**IRR* (95% CI)**	**IRR† (95% CI)**
Mother foreign born	871	3810384	0.76 (0.71-0.81)	0.69 (0.64-0.74)	808	3610118	0.79 (0.73-0.85)	0.71 (0.66-0.77)

Father foreign born	858	3948653	0.72 (0.67-0.77)	0.65 (0.61-0.70)	833	3764091	0.78 (0.73-0.84)	0.70 (0.65-0.75)
Both parents foreign born	443	2249700	0.66 (0.60-0.73)	0.58 (0.52-0.64)	435	2134846	0.73 (0.66-0.80)	0.62 (0.56-0.69)
Both parents born in Sweden	8334	26670322	1	1	7417	25249558	1	1
Male (15-30)					**Female (15-30)**			
Mother foreign born	624	2791560	0.82 (0.75-0.89)	0.79 (0.73-0.86)	510	2635294	0.82 (0.75-0.90)	0.85 (0.77-0.93)
Father foreign born	618	2636310	0.86 (0.79-0.93)	0.83 (0.76-0.90)	442	2504279	0.75 (0.68-0.82)	0.79 (0.72-0.87)
Both parents foreign born	270	1287893	0.76 (0.68-0.86)	0.72 (0.64-0.82)	204	1215563	0.71 (0.62-0.81)	0.75 (0.65-0.86)
Both parents born in Sweden	8024	29689985	1	1	6627	28192526	1	1
* Adjusted for age in five years categories. † Mutually adjusted for age, parental education and calendar years of follow-up.								

Table 2: Incidence rate ratio (IRR) and 95% confidence interval (CI) of type 1 diabetes among male and female ages 0-30 years by parental country of birth and sex Sweden, 1969-2009.

	IRR* (95 % CI)											
	Male						Female					
Parental country of birth	cases	Offspring of Mother	cases	Offspring of Father	Cases	Offspring of both Parents	cases	Offspring of Mother	cases	Offspring of Father	Cases	Offspring of both Parents
Sweden	16358	1	16358	1	16358	1	14044	1	14044	1	14044	1
Africa	92	**1.42 (1.15-1.75)**	148	**1.19 (1.01-1.41)**	78	1.12 (0.90-1.41)	86	**1.33 (1.10-1.65)**	129	**1.33 (1.12-1.59)**	75	**1.32 (1.05-1.66)**
Northern Africa	21	1.18 (0.77-1.81)	55	1.06 (0.81-1.40)	16	0.86 (0.53- 1.40)	26	1.27 (0.86-1.86)	50	1.18 (0.89-1.55)	19	1.25 (0.80- 1.96)
Western Africa	4	-	17	0.89 (0.55-1.42)	2	-	5	0.76 (0.32-1.83)	12	0.99 (0.56-1.74)	4	-
Eastern Africa	66	**1.51 (1.18-1.92)**	70	**1.46 (1.15-1.85)**	58	**1.45 (1.12-1.88)**	51	**1.47 (1.11-1.93)**	62	**1.61 (1.25-2.10)**	47	**1.44 (1.08-1.92)**
Asia	133	**0.37 (0.31-0.44)**	155	**0.40 (0.34-0.47)**	107	**0.36 (0.30-0.44)**	137	**0.48 (0.40-0.56)**	155	**0.49 (0.42-0.57)**	108	**0.45 (0.37-0.54)**
Europe												
Finland	692	0.98 (0.91-1.10)	523	0.99 (0.90-1.08)	273	0.96 (0.85-1.08)	587	0.96 (0.89-1.05)	442	0.97 (0.88-1.06)	232	0.93 (0.82-1.06)
North Europe (excl. Finland)	240	0.88 (0.77-1.00)	258	0.89 (0.78-1.00)	46	0.89 (0.67-1.19)	235	0.99 (0.87-1.12)	231	0.91 (0.80-1.04)	38	0.82 (0.60-1.13)
S.E.W. Europe†	284	**0.55 (0.49-0.62)**	319	**0.53 (0.47-0.59)**	110	**0.39 (0.33-0.47)**	227	**0.53 (0.46-0.60)**	264	**0.52 (0.46-0.58)**	95	**0.41 (0.33-0.50)**
Latin America	39	**0.56 (0.41-0.77)**	51	**0.65 (0.49-0.87)**	17	**0.39 (0.24-0.63)**	29	**0.51 (0.35-0.75)**	23	**0.33 (0.21-0.51)**	14	**0.41 (0.24-0.69)**
North America	13	**0.50 (0.29-0.86)**	20	**0.55 (0.36-0.86)**	0	-	15	0.78 (0.47-1.30)	31	1.02 (0.72-1.46)	0	-
Oceania	2	-	2	-	0	-	2	-	0	-	0	-
Mixed‡	0	-	0	-	84	**0.64 (0.52-0.79)**	0	-	0	-	82	**0.75 (0.61-0.94)**

* Adjusted for age, parental education and calendar years of follow-up.

† South, East and West Europe

‡ Both parents are not from the same country or region.

IRRs significantly different from 1 are bolded.

Supplementary tables

Table 1S: Incidence rate ratio (IRR) and 95% confidence interval (CI) of type 1 diabetes among children aged (0-13) by sex and parental country of birth, Sweden, 1997–2009.

	Male (0-13)				Female (0-13)			
Parental migration Status	**Cases**	**PYRs**	**IRR* (95% CI)**	**IRR† (95% CI)**	**Cases**	**PYRs**	**IRR* (95% CI)**	**IRR† (95% CI)**
Mother foreign born	388	1291769	0.57 (0.52-0.64)	0.58 (0.52-0.64)	371	1225944	0.60 (0.54-0.66)	0.59 (0.53-0.66)
Father foreign born	413	1348032	0.58 (0.53-0.65)	0.59 (0.53-0.65)	392	1285912	0.60 (0.54-0.66)	0.60 (0.54-0.66)
Both parents foreign born	221	869641	0.49 (0.43-0.56)	0.50 (0.43-0.57)	223	826716	0.54 (0.47-0.61)	0.53 (0.46-0.61)
Both parents born in Sweden	3710	6742640	1	1	3427	6380947	1	1

* Adjusted for age in four years categories.

† Mutually adjusted for age, parental education and calendar years of follow-up.

Table 2Sa: Incidence rate ratio (IRR) and 95% confidence interval (CI) of type 1 diabetes among male and female ages 0-13 years by parental country of birth and sex, Sweden, 1997-2009.

	IRR* (95 % CI)											
	Male						Female					
Parental country of birth	cases	Offspring of Mother	cases	Offspring of Father	Cases	Offspring of both Parents	cases	Offspring of Mother	cases	Offspring of Father	Cases	Offspring of both Parents
Sweden	3710	1	3710	1	3710	1	3427	1	3427	1	3427	1
Africa	70	**1.27 (1.00-1.61)**	92	**1.23 (1.00-1.51)**	64	1.10 (0.86-1.41)	63	1.12 (0.87-1.44)	81	1.19 (0.95-1.48)	58	1.07 (0.82-1.39)
Northern Africa	15	1.32 (0.79-2.19)	25	1.04 (0.70-1.54)	12	1.07 (0.61-1.89)	19	1.52 (0.97-2.39)	26	1.40 (0.95-2.05)	13	1.27 (0.74-2.20)
Western Africa	2	-	8	1.05 (0.53-2.11)	2	-	3	-	4	-	3	-
Eastern Africa	53	1.29 (0.98-1.69)	57	**1.32 (1.02-1.72)**	49	1.26 (0.95-1.68)	39	1.02 (0.74-1.40)	47	1.18 (0.89-1.58)	38	1.04 (0.76-1.44)
Asia	95	**0.41 (0.33-0.50)**	102	**0.43 (0.35-0.52)**	79	**0.39 (0.31-0.49)**	86	**0.40 (0.32-0.50)**	94	**0.43 (0.35-0.52)**	68	**0.35 (0.28-0.45)**
Europé												
Finland	87	1.05 (0.85-1.30)	79	1.09 (0.87-1.36)	20	1.27 (0.82-1.97)	83	1.07 (0.86-1.33)	68	0.99 (0.77-1.25)	17	1.15 (0.71-1.85)
North Europe (excl. Finland)	37	0.89 (0.65-1.24)	45	0.86 (0.64-1.16)	3	-	34	0.88 (0.63-1.23)	41	0.86 (0.63-1.17)	2	-
S.E.W. Europe†	73	**0.47 (0.37-0.59)**	69	**0.42 (0.33-0.54)**	23	**0.23 (0.15-0.35)**	80	**0.56 (0.45-0.70)**	86	**0.56 (0.45-0.69)**	46	**0.49 (0.37-0.66)**
Latin America	23	**0.63 (0.42-0.95)**	20	**0.62 (0.40-0.96)**	6	**0.28 (0.13-0.62)**	19	**0.58 (0.37-0.91)**	11	**0.33 (0.18-0.60)**	8	**0.41 (0.20-0.81)**
North America	3	-	4	-	0	-	6	1.04 (0.47-2.32)	11	1.02 (0.57-1.85)	0	-
Oceania	-	-	2	-	0	-	0	-	0	-	0	-
Mixed‡					17	**0.47 (0.29-0.76)**					17	**0.51 (0.32-0.82)**

* Adjusted for age, parental education and calendar years of follow-up.
† South, East and West Europe
‡ Both parents are not from the same country or region.
IRRs significantly different from 1 are bolded.

Table 2Sb: Incidence rate ratio (IRR) and 95% confidence interval (CI) of type 1 diabetes among male and female ages 0-13 years by parental country of birth and sex, Sweden, 1969-2009.

	IRR* (95 % CI)											
	Male						Female					
Parental country of birth	cases	Offspring of Mother	cases	Offspring of Father	Cases	Offspring of both Parents	cases	Offspring of Mother	cases	Offspring of Father	Cases	Offspring of both Parents
Sweden	6620	1	6620	1	6620	1	6319	1	6319	1	6319	1
Africa	76	**1.34 (1.07-1.68)**	111	**1.24 (1.03-1.50)**	68	1.12 (0.88-1.42)	70	1.16 (0.92-1.47)	96	1.15 (0.94-1.41)	62	1.08 (0.84-1.39)
Northern Africa	15	1.12 (0.67-1.86)	36	1.07 (0.77-1.49)	12	0.88 (0.50-1.55)	21	1.38 (0.90-2.12)	34	1.09 (0.78-1.53)	14	1.08 (0.64-1.82)
Western Africa	3	-	11	0.92 (0.51-1.66)	2	-	4	-	6	0.63 (0.28-1.40)	3	-
Eastern Africa	58	**1.42 (1.10-1.85)**	62	**1.42 (1.10-1.82)**	52	**1.36 (1.04-1.79)**	42	1.12 (0.82-1.51)	52	1.29 (0.98-1.70)	40	1.12 (0.82-1.52)
Asia	103	**0.39 (0.32-0.48)**	115	**0.42 (0.35-0.50)**	84	**0.37 (0.30-0.46)**	98	**0.38 (0.31-0.46)**	113	**0.43 (0.36-0.52)**	77	**0.35 (0.28-0.44)**
Europe												
Finland	274	1.08 (0.95-1.22)	224	1.09 (0.95-1.25)	112	1.20 (0.99-1.45)	279	1.10 (0.98-1.25)	232	1.13 (0.99-1.28)	119	**1.23 (1.03-1.48)**
North Europe (excl. Finland)	85	0.88 (0.71-1.09)	84	0.75 (0.61-0.93)	8	0.52 (0.26-1.05)	89	0.99 (0.80-1.22)	103	0.93 (0.76-1.13)	11	0.69 (0.38-1.25)
S.E.W. Europe†	134	**0.53 (0.44-0.63)**	133	**0.46 (0.38-0.54)**	45	**0.30 (0.22-0.40)**	130	**0.53 (0.45-0.64)**	146	**0.52 (0.44-0.61)**	59	**0.41 (0.32-0.53)**
Latin America	27	**0.56 (0.39-0.82)**	30	**0.64 (0.45-0.92)**	9	**0.30 (0.16-0.58)**	23	**0.52 (0.35-0.78)**	15	**0.30 (0.18-0.51)**	11	**0.40 (0.22-0.72)**
North America	4	-	8	**0.44 (0.22-0.88)**	0	-	8	0.82 (0.41-1.65)	15	0.87 (0.52-1.44)	0	-
Oceania	1	-	2	-	0	-	1	-	0	-	0	-
Mixed‡					26	**0.53 (0.36-0.78)**					23	**0.49 (0.33-0.75)**

* Adjusted for age, parental education and calendar years of follow-up.
† South, East and West Europe
‡ Both parents are not from the same country or region.
IRRs significantly different from 1 are bolded.

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

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ABSTRACT

Objective: To investigate the trends and the risk of developing type 1 diabetes in offspring of Swedes and immigrants by specific parental migration background, age, sex and birth cohort.

Design: Registry-based cohort study.

Setting: Using Swedish nation-wide data we analyzed the risk of developing type 1 diabetes in 3,457,486 female and 3,641,304 male offspring between 0-30 years of age, born to native Swedes or immigrants, and born and living in Sweden between 1969 and 2009. We estimated Incidence rate ratios (IRRs) with 95% confidence intervals using Poisson regression models. We further calculated age-standardized rates (ASRs) of type 1 diabetes, using the world population as standard.

Results: We observed a trend of increasing ASRs among offspring below 15 years of age born to native Swedes and a less evident increase among offspring of immigrants. We further observed a shift towards younger age at diagnosis in younger birth cohorts in both groups of offspring.

Compared with offspring of Swedes, children (0 to 14 years) and young adults (15 to 30 years) with one parent born abroad had an overall 30% and 15% to 20% lower IRR, respectively, after multivariable adjustment . The reduction in IRR was even greater among offspring of immigrants if both parents were born abroad. Analysis by specific parental region of birth revealed a 45% to 60% higher IRR among male and female offspring aged 0–30 years of Eastern Africa.

Conclusions: Parental country of birth and early exposures to environmental factors play an important role in the etiology of type 1 diabetes.

Key words

Type 1 diabetes, Birth Cohort, Incidence, Migration, Sweden

INTRODUCTION

The epidemic of type 1 diabetes is accelerating in many parts of the world with large impact on the affected individual's life and also with great health economic consequences [1]. There is a wide variation in the incidence of type 1 diabetes between countries, ranging from 0.1 per 100 000 person years in China and Venezuela to more than 40 per 100 000 person years in Sweden and Finland, respectively [2-4].

The concordance rate of type 1 diabetes among monozygotic twins has been estimated to 27% [5]. Thus, in the etiology of type 1 diabetes, there is considerable room for influence of environmental factors acting on genetic predisposition. Investigating the occurrence of type 1 diabetes in immigrants and their offspring offers a unique possibility to explore and delineate the gene-environment interaction for the development of type 1 diabetes.

Over the past decades, a rapid rise in the incidence of type 1 diabetes among individuals below 15 years of age has been reported and also with a shift towards younger age at onset [6, 7]. These studies, however, have not distinguished between individuals born to parents with different migration background. If offspring of immigrants, with varying genetic background, experience the same change in age at onset as observed in offspring of natives, the importance of early environmental exposures for the development of type 1 diabetes would be further supported. We recently reported a decreased risk of type 1 diabetes among the majority of immigrants in Sweden compared with native Swedes. We also observed a tendency towards a convergence of risks for type 1 diabetes between offspring of immigrants as one group and native Swedes [8]. Since immigrants and their offspring are a

heterogeneous population, there is a need to explore if the risk of type 1 diabetes varies by specific parental country or region of birth.

In the present study, we used Swedish nation-wide data collected over 40 years to investigate the trend and the risk of developing type 1 diabetes in offspring of immigrants by specific paternal and maternal migration background and by birth cohorts. Since the incidence of type 1 diabetes varies with sex and age [9, 10], the analyses were stratified by offspring sex and age.

METHODS

Database

We used information from a newly established, nationwide dataset – The Migration and Health Cohort (M&H Co.) [11], where data from national, longitudinal clinical, health and socio - demographic registries have been compiled. This database was built by individual record-linkage between more than fifteen Swedish national registries to facilitate studies on diabetes, injuries, cancer, cardiovascular and psychiatric diseases among immigrants and their descendants in Sweden. The linkage was done using the Personal Identification Number (PIN), which is uniquely assigned to each individual that have resided in Sweden for longer than one year since 1947 [12]. The data used in this study are part of the M&H Co., including: 1) The Swedish Total Population Register, which covers the entire population registration in Sweden and is updated on a daily basis. The register contains information on demographic variables, such as date and place of birth and data on emigration and immigration [13]. 2) The Cause of Death Register, which contains information on the date of death, the main and contributing causes of death [14]. 3) The National Patient Register, including the Inpatient Register. It was established in

1964 but with national coverage since 1987 covering 85-95% of all diagnostic data [15]. Since 2001, the Patient Register includes information on all registered outpatient visits to specialist care and day visits to hospitals and covers about 80% of all visits to the specialized outpatient care [16]. The Patient Register contains data on the main diagnosis and up to eight secondary diagnoses [15, 16]. 4) The Multi-Generation Register contains links between children and their parents via PINs for all Swedish inhabitants born after 1931 who were alive in 1960 [17]. 5) The National Population and Housing Censuses and longitudinal integration database for health insurance and labor market studies (LISA), contains data on socio-economic, occupational and demographic variables [18, 19].

The linkages between the registers have been completed by Statistics Sweden and the National Board of Health and Welfare. To ensure confidentiality, the PINs have been replaced by person-unique serial numbers and a key code is kept at Statistics Sweden. The study was approved by one of the Regional Ethical Committees in Stockholm, Sweden (Dnr. 2009/2033-32).

Study cohort

The study population comprised 3,794,477 (51.4%) males and 3,593,765 (48.6%) females between 0 to 30 years of age, born and living in Sweden any time between January 1st, 1969 and December 31st, 2009. We excluded individuals whose parents had unknown information on country of birth and all individuals who had a history of type 1 diabetes, before entry into the cohort. The final cohort included 7,098,790 individuals (3,641,304 (51.3%) males and 3,457,486 (48.7%) females) aged 0-30 years and born in Sweden.

Follow-up

The cohort members were followed from date of birth or January 1st, 1969, whichever occurred last, until the date of diagnosis of type 1 diabetes according to the Swedish versions of International Classification of Disease (ICD-8: 250, 1969-1986; ICD-9: 250, 1987-1996; ICD-10: E10, 1997 and onwards), emigration, death or end of follow-up (December 31st, 2009), whichever occurred first. Every individual in the cohort were followed for maximum 30 years of age.

Since earlier versions of ICD (i.e. 8th and 9th version of ICD) could not disentangle between different types of diabetes, we have performed sensitivity analysis using ICD-10 only where we could identify type I diabetes (see method for details).

Classification of offspring based on parental country of birth

The cohort was divided into four groups according to parental country of birth: individuals with mothers born outside Sweden (father could be born in Sweden, abroad or unknown) (n= 345,827); individuals with fathers born outside Sweden (mother could be born in Sweden, abroad or unknown) (n= 317,397); individuals with both parents born outside of Sweden (n= 435,045) and individuals with both parents born in Sweden (n= 6,000,521). We also classified parental country of birth into 6 continents: Africa (North, South, East, West and Middle 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) Northern America, and Oceania (Australia/New Zealand, Melanesia, and Micronesia/Polynesia). Based on the findings from our previous study among immigrant individuals [8], we categorized Africa into North, East and West Africa; Europe into Finland, North Europe without Finland, and South-, East-, and West Europe (the latter three as one

group). For the trend and the birth cohort analyses, we pooled all offspring of immigrants into one group.

Statistical analysis

We estimated Incidence rate ratios (IRRs) with 95% confidence intervals (CIs) using Poisson regression models. The analyses were adjusted for age at follow-up (in 5 years intervals 0-4, 5-9, 10-14, 15-19, 20-24, and 25-30 years), calendar years of follow-up (four categories: 1969-1978, 1979-1988, 1989-1998 and 1999-2009) and education of the mother or father (classified into four levels: 0-9 years, 10-12 years, 13 years or more and unknown). All analyses were performed for females and males separately. In addition, analyses were made separately for children (0-14 years) and young adults (15-30 years) where we did not distinguish specific parental region or country of birth. In further analyses, children and young adults (0-30 years) were pooled together as one category to allow reasonable statistical power for analyses by specific maternal and paternal regions or country of birth to test the hypothesis that the mother's and the father's background would affect the offspring's risk of type 1 diabetes differently. We also analyzed risk of type 1 diabetes in children with both mother and father born in the same country/region. Those with parents from different regions or from Sweden were categorized as a mixed group.

Since we had no specific ICD codes before 1997 to distinguish between type 1 and type 2 diabetes, we repeated the analysis and confined our cohort to individuals living in Sweden between 1997 and 2009 where we could strictly identify type 1 diabetes according to ICD-10.

For the trend analysis, we further calculated age-standardized rates (ASRs), by parental migration background for both children (0–14 years) and young adults (15–

30 years), by dividing number of new cases with the estimated numbers of person-years at risk in 5-years age categories using the world population as standard [20]. ASRs were directly calculated to ensure comparability and to adjust for differences in age in the study population, in each of the age groups 0–4, 5–9, 10–14, 15–19, 20–24, and 25–30 years. We reported ASR in unit of per 100,000 person years.

The Joint point regression analyses were performed to evaluate trends of type 1 diabetes in both offspring to immigrants and offspring to Swedes and in both age groups [21, 22]. Annual percent change (APC) was estimated, 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. We used Statistical Analysis System (SAS) version 9.3 for all the analysis.

RESULTS

On average, the age of onset of type 1 diabetes was similar in offspring of immigrants as in offspring of Swedes (mean ± SD; offspring of immigrants 14.31±7.70, offspring of swedes 15.47± 7.99).

Over the study period (1969 -2009), we observed a significant increasing trend for incidence of type 1 diabetes based on joint point regression analyses among offspring below 15 years of age born to native Swedes and to immigrants (offspring to Swedes: APC= 3.9, p values<0.001 and offspring to immigrants: APC= 2.2, p values<0.001 Figure 1). In contrast, no increase or a slight decreasing trend was observed among young individuals between 15 to 30 years of age regardless of parental migration background (offspring to Swedes: APC= -0.0, p= 0.9 and offspring to immigrants: APC= -0.7, p value= 0.08 , Figure 2).

The birth cohort analysis revealed a shift towards lower age at onset in individuals below 15 years of age in both offspring of Swedes and in offspring of immigrants (Figures 3a and 3b).

Compared with offspring of Swedish-born parents, boys and girls (0 to 14 years) with a foreign-born mother or father had about 30% lower IRR in the multivariable analyses adjusted for age, calendar period and parental education. Among boys and girls with both parents born abroad, corresponding risk reductions were about a 40% (Table 1). The results from the sensitivity analysis, where we repeated the analysis and confined our cohort to individuals born in Sweden between 1997 and 2009, were similar to the results of the entire cohort (Supplementary Table 1S).

Compared with young adults (15 to 30 years) of Swedish-born parents, young adults with only one parent born abroad had about 15% to 20% lower IRR of type 1 diabetes and among young adults with both parents born abroad, the risks were reduced by 25% to 30% (Table 1).

Next, we investigated risks of type 1 diabetes by parental region of birth. Compared with young offspring (0-30 years) of Swedish-born parents, male and female offspring of mothers or fathers born in Africa had about 20% to 40% higher IRR of type 1 diabetes (Table 2). The increased risk of type 1 diabetes was more prominent among individuals whose mothers or fathers were born in Eastern Africa. With a few exceptions, male and female offspring of mothers or fathers born in Asia, Europe (except Northern Europe), Latin America and Northern America (except female offspring to fathers from Northern America) had between 35% to 65% lower IRR than male and female offspring of Swedish-born parents (Table 2). These reductions in risks became even more prominent when we confined the analyses to parents born

in the same region (Table 2). Offspring of Finnish immigrants and rest of Northern Europe had almost similar risks compared with offspring of Swedes (Table 2).

The results from the sensitivity analysis, where we repeated the analysis and confined our cohort to individuals born in Sweden between 1997 and 2009 (limited to children ages 0 to 13) , were similar to the results of the entire cohort for the same age category (Supplementary Tables 2Sa and 2Sb).

DISCUSSION

In this nation-wide cohort study of Sweden-born children and young adults, we observed a continuing increase of type 1 diabetes in individuals younger than 15 years of age over the past decades. This increase was, however, less evident among offspring of immigrants than in offspring of native Swedes. In contrast, no change in trend was observed among young individuals between 15 to 30 years of age, and regardless of parental country of birth.

An interesting finding in the present study was an almost identical pattern with a shift towards lower age at onset of type 1 diabetes by younger birth cohorts in both offspring of foreign born parents and Swedes.

Over the past decades, a rapid rise in the incidence of type 1 diabetes has been demonstrated [23, 24]. The finding of an increased incidence rate of type 1 diabetes between 1969 and 2009 among individuals below 15 years of age, and a decreasing or steady incidence rate among young adults, is in line with previous studies from Sweden [6] and other parts of the world [7]. The observed increasing trend over time in our study might be due to the quality of National patient Register over time and not covering all of Sweden for the entire period of our study. This register became nation-wide in 1987. However, the sharpest increase in incidence observed in our study

among individuals below 15 years of age is after around 1997 when the Inpatient Register had full coverage and when the ICD-10 were able to disentangle different types of diabetes.

The finding of an almost identical pattern with a shift towards lower age at onset of type 1 diabetes in both offspring of foreign born parents and Swedes indicates the exposure to similar environmental factors in both groups. It has been hypothesized that this developments is due to increased exposures in early life to factors that initiate and/ or accelerate beta cell destruction, including viral infections, rapid postnatal growth and nutritional factors [25, 26]. In addition, perinatal factors such as blood-group incompatibility, high maternal age, preeclampsia and caesarean section delivery have been shown to be associated with increased incidence of childhood type 1 diabetes [27]. Similar findings of a shift towards younger age at diagnosis and a declining incidence of type 1 diabetes among young adults aged 15 to 34 years were also observed in other studies from Sweden, using the two nation-wide prospectively collected research register, the Swedish Childhood Diabetes Register and the Diabetes Incidence Study in Sweden [10, 28]. The shift towards younger age at diagnosis may be due to risk factors accelerating the disease process.

We further found that offspring with one or two parents born abroad had a reduced risk of type 1 diabetes compared with offspring to Sweden-born parents. The reduction in risk was similar between sexes and was more apparent among individuals where both parents were foreign born. Stratification by specific parental region/country of birth, however, revealed that this reduction was confined to offspring of immigrants from Asia, Latin and North America, South-, West- and East Europe. In contrast, the IRR for type 1 diabetes was increased in individuals with

African parents, particularly so if the parents were born in Eastern or Northern Africa. The observed increased risk among offspring of Africans in this study, in line with a previous Swedish register study [29] is also observed in Swedish residents born in Africa [8, 29]. It is unclear if these findings reflect a high risk of type 1 diabetes in the countries of origin, thus rating Eastern and Northern Africa as the areas with the highest incidence of type 1 diabetes in the world. At the same time we should keep in mind that the population of immigrants in Sweden may not represent the population of countries of origin.

The reported low number of type 1 diabetes diagnoses in Africa [30] is most likely to be underestimated due to lack of diagnostic measures [31], and high mortality among uncontrolled type 1 diabetes cases as a result of limited access to insulin treatment [32]. Moreover, priorities are mostly given to the high burden of communicable diseases in African countries [33], especially in busy emergency hospitals. As a consequence, children with diabetic ketoacidosis at the time of diagnosis [34] could be misdiagnosed as cerebral malaria or meningitis [35] which would also lead to an underestimation of type 1 diabetes cases. The observed higher risk in African offspring in the present study and the increased risk of type 1 diabetes in Swedish residents born in Africa [8] might be due to genetic propensity interacting with environmental factors in the new home country.

Offspring of Swedish residents born in Asia, Latin and North America, South-, West- and East Europe retained the low risk profile were recently observed in young immigrants in Sweden born in these areas [8]. This risk reduction was independent of maternal or paternal birth region but was stronger if both parents were born in the same region.

The importance of parental country of birth for the risk of developing type 1 diabetes has also been observed in other studies [36-39] and may indicate the role of genetic factors [40, 41]. Children of Sardinian heritage (a high risk area), born and living in Lazio (a low risk area) retained the high risk profile of Sardinia [42]. The risk for type 1 diabetes in children of Yugoslavian, Italian and Greek heritage in Germany was closer to the reported incidence in those countries than in Germany [43] However, the importance of life style or environmental factors interacting with genetic factors cannot be ruled out [44] as studies of immigration from regions with low to high incidence of type 1 diabetes have been associated with increased incidence of type 1 diabetes [37] .

The primary strength of our study is the nation-wide cohort design with nearly complete follow-up of type 1 diabetes occurrence over several decades. Using a unique PIN assigned to all Swedish citizens, we were able to correctly assess exposure (parental country of birth) and thus avoiding misclassification bias.

We lacked specific ICD codes for type 1 diabetes in the earlier versions of ICD before 1997 (i.e. 8th and 9th version of ICD). However, the results of the sensitivity analysis limited to only cases of type 1 diabetes according to ICD 10 for the years 1997 and forward were similar to the results for the entire period of the study. But, in this sensitivity analysis, we were only able to verify the results for children born between 1997 and 2009 (0 to 13 years old). Whereas, for the age groups over 15 years when type 1 diabetes is more likely to be mixed with type 2 diabetes, we had no data. However, the prevalence of type 2 diabetes is low in Sweden [45, 46] and other northern European countries and most likely the majority of cases of diabetes diagnosed before 30 years are true type 1 diabetes. While this may not be applicable

for offspring born to parents from other parts of the world with known high prevalence of type 2 diabetes which may have led to overestimation of the true type 1 diabetes.

Our findings of a lower IRR of type 1 diabetes among children and young adults with one or two foreign born parents, with the notable exception of offspring of African immigrants, and the shifting of age at diagnosis towards younger age in both offspring of Swedes and of immigrants highlight the important role of environmental factors and its interaction with genetic background in the etiology of type 1 diabetes.

In order to further clarify potential pathophysiological mechanisms for the development of type1 diabetes, further studies are needed with data on important exposures such as viral infections in early life, nutritional habits and weight gain in infancy. Moreover, studies on offspring of immigrants from African countries, in particular from Eastern Africa, might improve our understanding on the etiology of the disease.

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Competing interests

No potential conflicts of interest relevant to this article were reported.

Contributors

H.I.H. designed the research, drafted the manuscript, analyzed data, and interpreted results.

M.P. designed the research, interpreted the results critically reviewed and edited the manuscript.

T.M. designed the research, interpreted the results, critically reviewed and edited the manuscript, handled research data and funding, and supervised.

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Figures

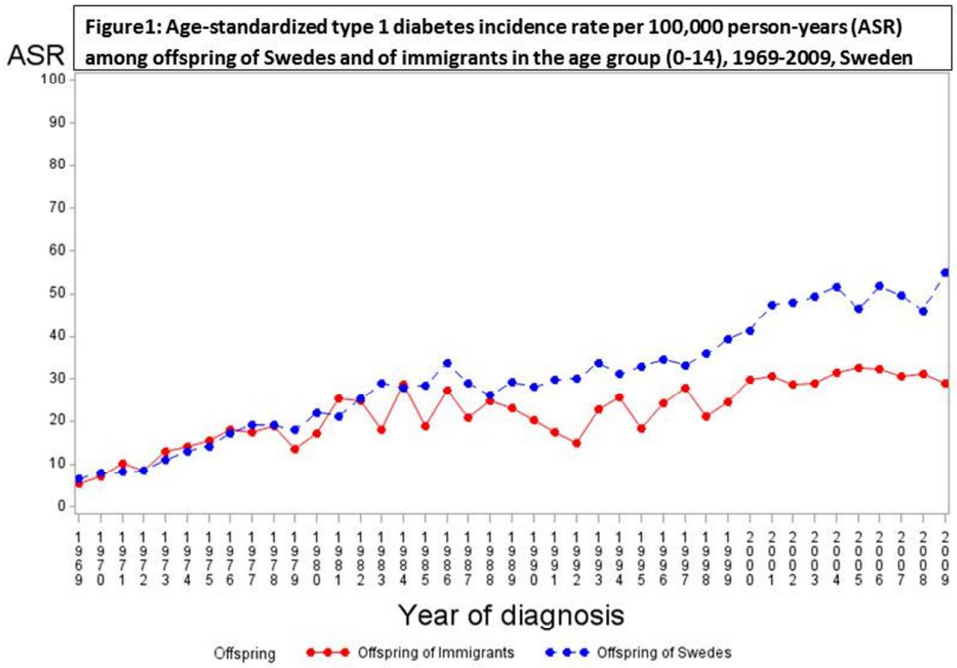


Figure 2: Age-standardized type 1 diabetes incidence rate per 100,000 person-years (ASR) among offspring of Swedes and of immigrants in the age group (15-30), 1969-2009, Sweden

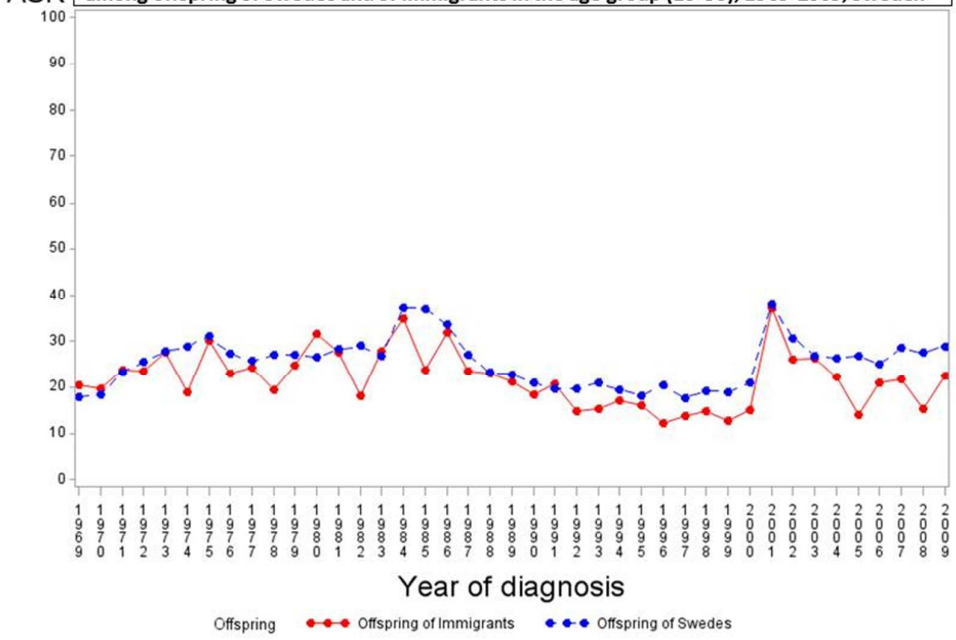


Figure 3.A. : Incidence of type 1 diabetes by age at diagnosis (0-30 years) and birth cohorts 1960-2009 among offspring of Swedes in Sweden

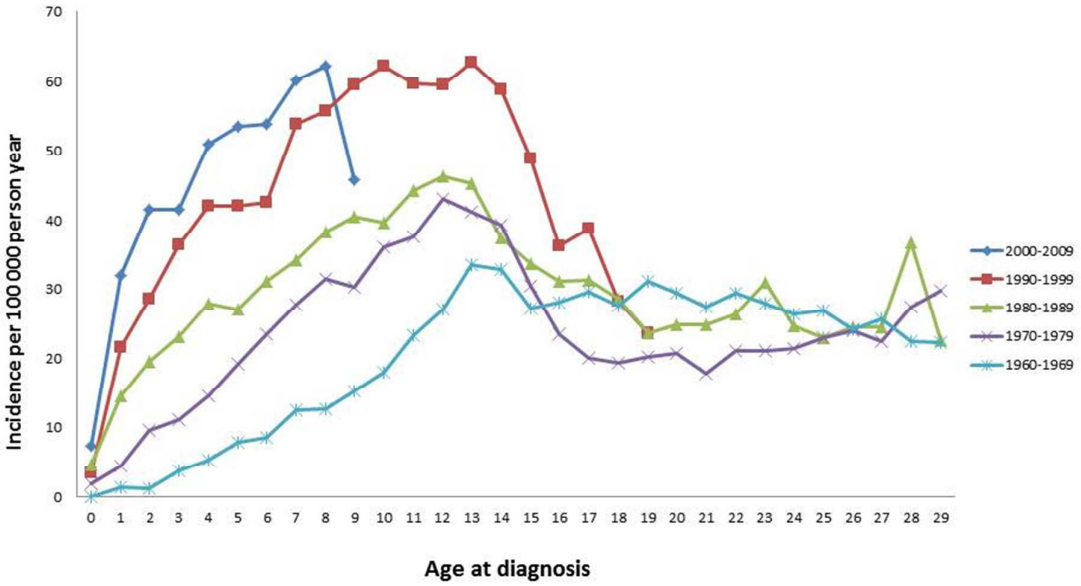


Figure 3.B: Incidence of type 1 diabetes by age at diagnosis (0-30 years) and birth cohorts 1960-2009 among offspring of Immigrants in Sweden

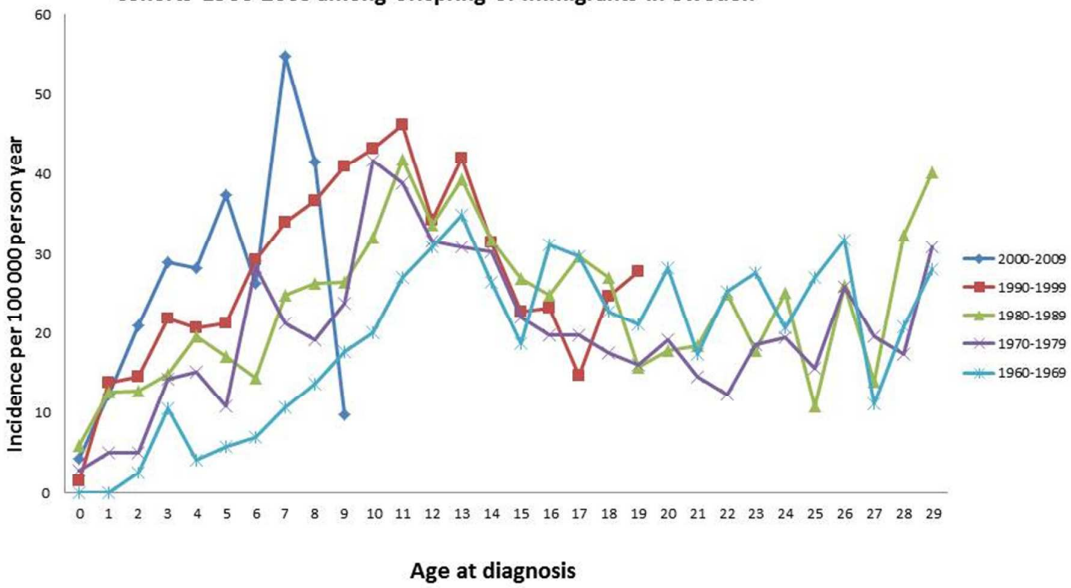


Table 1: Incidence rate ratio (IRR) and 95% confidence interval (CI) of type 1 diabetes among children aged (0-14) and young adults aged (15-30) by sex and parental country of birth, Sweden, 1969–2009.

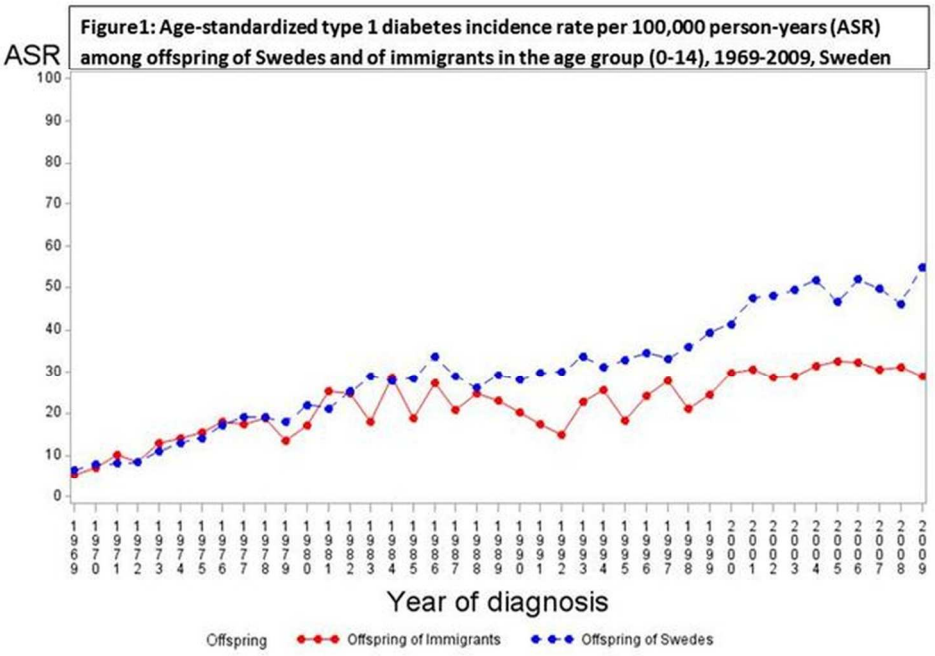
	Male (0-14)				Female (0-14)			
Parental immigration Status	**Cases**	**PYRs**	**IRR* (95% CI)**	**IRR† (95% CI)**	**Cases**	**PYRs**	**IRR* (95% CI)**	**IRR† (95% CI)**
Mother foreign born	871	3810384	0.76 (0.71-0.81)	0.69 (0.64-0.74)	808	3610118	0.79 (0.73-0.85)	0.71 (0.66-0.77)
Father foreign born	858	3948653	0.72 (0.67-0.77)	0.65 (0.61-0.70)	833	3764091	0.78 (0.73-0.84)	0.70 (0.65-0.75)
Both parents foreign born	443	2249700	0.66 (0.60-0.73)	0.58 (0.52-0.64)	435	2134846	0.73 (0.66-0.80)	0.62 (0.56-0.69)
Both parents born in Sweden	8334	26670322	1	1	7417	25249558	1	1
	Male (15-30)				**Female (15-30)**			
Mother foreign born	624	2791560	0.82 (0.75-0.89)	0.79 (0.73-0.86)	510	2635294	0.82 (0.75-0.90)	0.85 (0.77-0.93)
Father foreign born	618	2636310	0.86 (0.79-0.93)	0.83 (0.76-0.90)	442	2504279	0.75 (0.68-0.82)	0.79 (0.72-0.87)
Both parents foreign born	270	1287893	0.76 (0.68-0.86)	0.72 (0.64-0.82)	204	1215563	0.71 (0.62-0.81)	0.75 (0.65-0.86)
Both parents born in Sweden	8024	29689985	1	1	6627	28192526	1	1

* Adjusted for age in five years categories.
† Mutually adjusted for age, parental education and calendar years of follow-up.

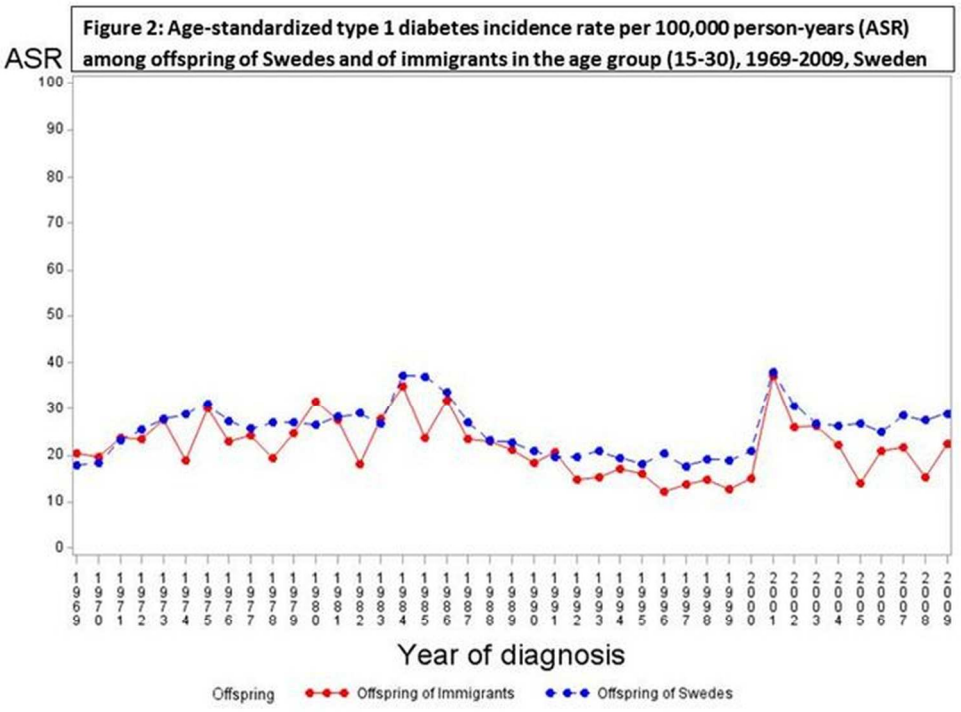
Table 2: Incidence rate ratio (IRR) and 95% confidence interval (CI) of type 1 diabetes among male and female ages 0-30 years by parental country of birth and sex Sweden, 1969-2009.

	IRR* (95 % CI)											
	Male						Female					
Parental country of birth	cases	Offspring of Mother	cases	Offspring of Father	Cases	Offspring of both Parents	cases	Offspring of Mother	cases	Offspring of Father	Cases	Offspring of both Parents
Sweden	16358	1	16358	1	16358	1	14044	1	14044	1	14044	1
Africa	92	**1.42 (1.15-1.75)**	148	**1.19 (1.01-1.41)**	78	1.12 (0.90-1.41)	86	**1.33 (1.10-1.65)**	129	**1.33 (1.12-1.59)**	75	**1.32 (1.05-1.66)**
Northern Africa	21	1.18 (0.77-1.81)	55	1.06 (0.81-1.40)	16	0.86 (0.53- 1.40)	26	1.27 (0.86-1.86)	50	1.18 (0.89-1.55)	19	1.25 (0.80- 1.96)
Western Africa	4	-	17	0.89 (0.55-1.42)	2	-	5	0.76 (0.32-1.83)	12	0.99 (0.56-1.74)	4	-
Eastern Africa	66	**1.51 (1.18-1.92)**	70	**1.46 (1.15-1.85)**	58	**1.45 (1.12-1.88)**	51	**1.47 (1.11-1.93)**	62	**1.61 (1.25-2.10)**	47	**1.44 (1.08-1.92)**
Asia	133	**0.37 (0.31-0.44)**	155	**0.40 (0.34-0.47)**	107	**0.36 (0.30-0.44)**	137	**0.48 (0.40-0.56)**	155	**0.49 (0.42-0.57)**	108	**0.45 (0.37-0.54)**
Europe												
Finland	692	0.98 (0.91-1.10)	523	0.99 (0.90-1.08)	273	0.96 (0.85-1.08)	587	0.96 (0.89-1.05)	442	0.97 (0.88-1.06)	232	0.93 (0.82-1.06)
North Europe (excl. Finland)	240	0.88 (0.77-1.00)	258	0.89 (0.78-1.00)	46	0.89 (0.67-1.19)	235	0.99 (0.87-1.12)	231	0.91 (0.80-1.04)	38	0.82 (0.60-1.13)
S.E.W. Europe†	284	**0.55 (0.49-0.62)**	319	**0.53 (0.47-0.59)**	110	**0.39 (0.33-0.47)**	227	**0.53 (0.46-0.60)**	264	**0.52 (0.46-0.58)**	95	**0.41 (0.33-0.50)**
Latin America	39	**0.56 (0.41-0.77)**	51	**0.65 (0.49-0.87)**	17	**0.39 (0.24-0.63)**	29	**0.51 (0.35-0.75)**	23	**0.33 (0.21-0.51)**	14	**0.41 (0.24-0.69)**
North America	13	**0.50 (0.29-0.86)**	20	**0.55 (0.36-0.86)**	0	-	15	0.78 (0.47-1.30)	31	1.02 (0.72-1.46)	0	-
Oceania	2	-	2	-	0	-	2	-	0	-	0	-
Mixed‡	0	-	0	-	84	**0.64 (0.52-0.79)**	0	-	0	-	82	**0.75 (0.61-0.94)**

* Adjusted for age, parental education and calendar years of follow-up.
† South, East and West Europe
‡ Both parents are not from the same country or region.
IRRs significantly different from 1 are bolded.

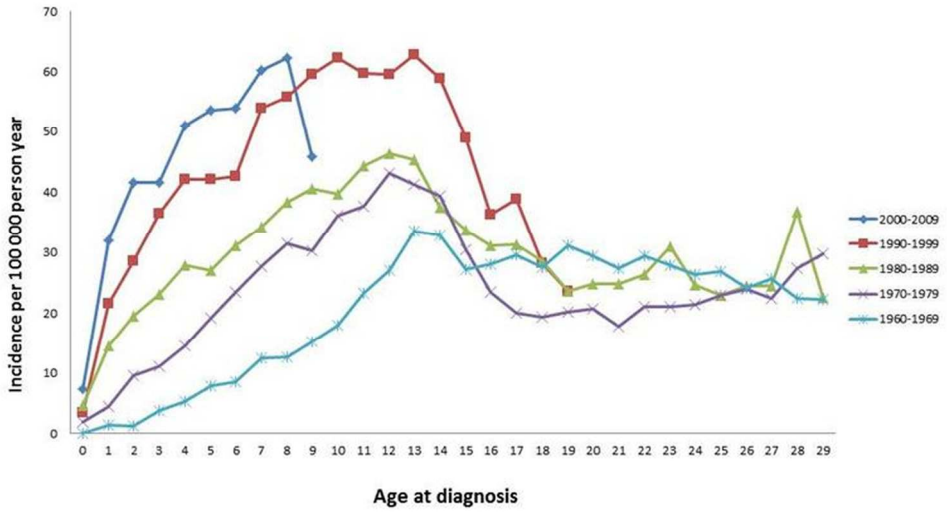


126x90mm (300 x 300 DPI)

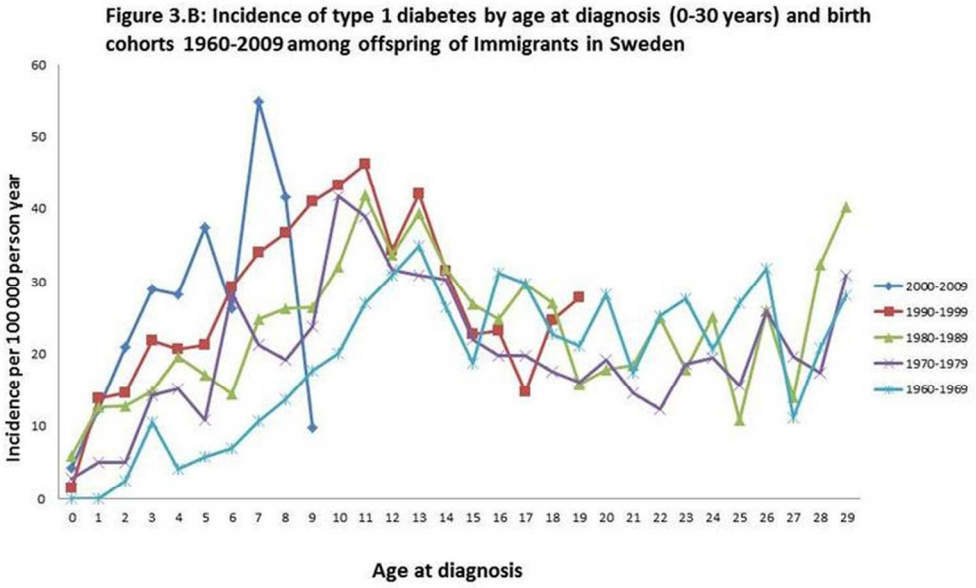


119x90mm (300 x 300 DPI)

Figure 3.A. : Incidence of type 1 diabetes by age at diagnosis (0-30 years) and birth cohorts 1960-2009 among offspring of Swedes in Sweden



142x90mm (300 x 300 DPI)



149x90mm (300 x 300 DPI)