



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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-003418
Article Type:	Research
Date Submitted by the Author:	19-Jun-2013
Complete List of Authors:	Hussen, Hozan; Karolinska Institutet, Department of Environmental Medicine, Division of Epidemiology, Unit of Cardiovascular Epidemiology Persson, Martina; Karolinska University Hospital, Department of Medicine, Clinical Epidemiology Unit Moradi, Tahereh; Karolinska Institutet, Department of Environmental Medicine, Division of Epidemiology, Unit of Cardiovascular Epidemiology
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Epidemiology
Keywords:	Type 1 Diabetes, Birth Cohort, Incidence, Migration, Sweden

SCHOLARONE™
Manuscripts

1
2
3 **The trends and the risk of type 1 diabetes over the past 40 years: an analysis**
4 **by birth cohorts and by parental migration background in Sweden**
5
6
7
8

9 Hozan Ismael Hussen^{*1}, Martina Persson², Tahereh Moradi^{1,3}
10
11

12
13
14 ¹Department of Environmental Medicine, Division of Epidemiology, Unit of
15 Cardiovascular Epidemiology, Karolinska Institutet, Stockholm, Sweden.
16
17

18 ²Department of Medicine, Clinical Epidemiology Unit, Karolinska University Hospital,
19 Stockholm, Sweden.
20
21

22 ³Centre for Epidemiology and Social Medicine, Health Care Services, Stockholm
23 County Council, Sweden
24
25
26
27

28
29 ***Corresponding author:**
30

31 Hozan Ismael Hussen, MD
32

33 Department of Environmental Medicine, Division of Epidemiology,
34

35 Unit of Cardiovascular Epidemiology, Karolinska Institutet
36
37

38 Nobels väg 13, Box 210,
39

40 SE-171 77 Stockholm, Sweden
41

42 Phone: +46-8-524 800 55
43

44 Fax: +46-8-31 39 36
45

46 E-mail: hozan.hussen@ki.se
47
48
49

50
51 **Word count**
52

53 Main text 3079
54
55
56
57
58
59
60

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

1
2
3 heterogeneous population, there is a need to explore if the risk of type 1 diabetes
4 varies by specific parental country or region of birth.
5
6

7 In the present study, we used Swedish nation-wide data collected over 40 years to
8 investigate the trend and the risk of developing type 1 diabetes in offspring of
9 immigrants by specific paternal and maternal migration background and by birth
10 cohorts. Since the incidence of type 1 diabetes varies with sex and age [9, 10], the
11 analyses were stratified by offspring sex and age.
12
13
14
15
16
17
18
19

20 **METHODS**

21 *Database*

22 We used information from a newly established, nationwide dataset – The Migration
23 and Health Cohort (M&H Co.) [11], where data from national, longitudinal clinical,
24 health and socio - demographic registries have been compiled. This database was
25 built by individual record-linkage between more than fifteen Swedish national
26 registries to facilitate studies on diabetes, injuries, cancer, cardiovascular and
27 psychiatric diseases among immigrants and their descendants in Sweden. The
28 linkage was done using the Personal Identification Number (PIN), which is uniquely
29 assigned to each individual that have resided in Sweden for longer than one year
30 since 1947 [12]. The data used in this study are part of the M&H Co., including: 1)
31 The Swedish Total Population Register, which covers the entire population
32 registration in Sweden and is updated on a daily basis. The registry contains
33 information on demographic variables, such as date and place of birth and data on
34 emigration and immigration [13]. 2) The Cause of Death Register, which contains
35 information on the date of death, the main and contributing causes of death [14]. 3)
36 The National Patient Register, including the Inpatient Register which was established
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 in 1964 and with national coverage since 1987. Since 2001, the Patient Register
4 includes information on all outpatient visits to specialist care and day visits to
5 hospitals. The Patient Register contains data on the main diagnosis and up to eight
6 secondary diagnoses [15, 16]. 4) The Multi-Generation Register contains links
7 between children and their parents via PINs for all Swedish inhabitants born after
8 1931 who were alive in 1960 [17]. 5) The National Population and Housing Censuses
9 and longitudinal integration database for health insurance and labor market studies
10 (LISA), contains data on socio-economic, occupational and demographic variables
11 [18, 19].

12
13
14 The linkages between the registers have been completed by Statistics Sweden and
15 the National Board of Health and Welfare. To ensure confidentiality, the PINs have
16 been replaced by person-unique serial numbers and a key code is kept at Statistics
17 Sweden. The study was approved by one of the Regional Ethical Committees in
18 Stockholm, Sweden (Dnr. 2009/2033-32).

19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

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 \pm 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

1
2
3 diabetes (Table 2). The increased risk of type 1 diabetes was more prominent among
4 individuals whose mothers or fathers were born in Eastern Africa. With a few
5 exceptions, male and female offspring of mothers or fathers born in Asia, Europe
6 (except Northern Europe), Latin America and Northern America (except female
7 offspring to fathers from Northern America) had between 35% to 65% lower IRR than
8 male and female offspring of Swedish-born parents (Table 2). These reductions in
9 risks became even more prominent when we confined the analyses to parents born
10 in the same region (Table 2). Offspring of Finnish immigrants and rest of Northern
11 Europe had almost similar risks compared with offspring of Swedes (Table 2).
12
13
14
15
16
17
18
19
20
21
22
23
24

25 **DISCUSSION**

26
27 In this nation-wide cohort study of Sweden-born children and young adults, we
28 observed a continuing increase of type 1 diabetes in individuals younger than 15
29 years of age over the past decades. This increase was, however, less evident among
30 offspring of immigrants than in offspring of native Swedes. In contrast, no change in
31 trend was observed among young individuals between 15 to 30 years of age, and
32 regardless of parental country of birth.
33
34
35
36
37
38
39

40 An interesting finding in the present study was an almost identical pattern with a shift
41 towards lower age at onset of type 1 diabetes by younger birth cohorts in both
42 offspring of foreign born parents and Swedes.
43
44
45
46

47 Over the past decades, a rapid rise in the incidence of type 1 diabetes has been
48 demonstrated [21, 22]. The finding of an increased incidence rate of type 1 diabetes
49 between 1969 and 2009 among individuals below 15 years of age, and a decreasing
50 or steady incidence rate among young adults, is in line with previous studies from
51 Sweden [6] and other parts of the world [7]. The finding of an almost identical pattern
52
53
54
55
56
57
58
59
60

1
2
3 with a shift towards lower age at onset of type 1 diabetes in both offspring of foreign
4 born parents and Swedes indicates the exposure to similar environmental factors in
5 both groups. It has been hypothesized that this developments is due to increased
6 exposures in early life to factors that initiate and/ or accelerate beta cell destruction,
7 including viral infections, rapid postnatal growth and nutritional factors [23, 24].
8

9
10 We further found that offspring with one or two parents born abroad had a reduced
11 risk of type 1 diabetes compared with offspring to Sweden-born parents. The
12 reduction in risk was similar between sexes and was more apparent among
13 individuals where both parents were foreign born. Stratification by specific parental
14 region/country of birth, however, revealed that this reduction was confined to
15 offspring of immigrants from Asia, Latin and North America, South-, West- and East
16 Europe. In contrast, the IRR for type 1 diabetes was increased in individuals with
17 African parents, particularly so if the parents were born in Eastern or Northern Africa.
18 The primary strength of our study is the nation-wide cohort design with nearly
19 complete follow-up of type 1 diabetes occurrence over several decades. Using a
20 unique PIN assigned to all Swedish citizens, we were able to correctly assess
21 exposure (parental country of birth) and thus avoiding misclassification bias.
22

23
24 The observed increased risk among offspring of Africans in this study is also
25 observed in Swedish residents born in Africa [8, 25]. It is unclear if these findings
26 reflect a high risk of type 1 diabetes in the countries of origin, thus rating Eastern and
27 Northern Africa as the areas with the highest incidence of type 1 diabetes in the
28 world.
29

30
31 The reported low number of type 1 diabetes diagnoses in Africa [26] is most likely to
32 be underestimated due to lack of diagnostic measures [27], and high mortality
33 among uncontrolled type 1 diabetes cases as a result of limited access to insulin
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50

1
2
3 treatment [28]. Moreover, priorities are mostly given to the high burden of
4
5 communicable diseases in African countries [29], especially in busy emergency
6
7 hospitals. As a consequence, children with diabetic ketoacidosis at the time of
8
9 diagnosis [30] could be misdiagnosed as cerebral malaria or meningitis [31] which
10
11 would also lead to an underestimation of type 1 diabetes cases. The observed higher
12
13 risk in African offspring in the present study and the increased risk of type 1 diabetes
14
15 in Swedish residents born in Africa [8] might be due to genetic propensity interacting
16
17 with environmental factors in the new home country.
18
19

20
21 Offspring of Swedish residents born in Asia, Latin and North America, South-, West-
22
23 and East Europe retained the low risk profile we recently observed in young
24
25 immigrants in Sweden born in these areas [8]. This risk reduction was independent of
26
27 maternal or paternal birth region but was stronger if both parents were born in the
28
29 same region.
30

31
32 The importance of parental country of birth for the risk of developing type 1 diabetes
33
34 has also been observed in other studies [32-35] and may indicate the role of genetic
35
36 factors [36, 37]. Children of Sardinian heritage (a high risk area), born and living in
37
38 Lazio (a low risk area) retained the high risk profile of Sardinia [38]. The risk for type
39
40 1 diabetes in children of Yugoslavian, Italian and Greek heritage in Germany was
41
42 closer to the reported incidence in those countries than in Germany [39] However,
43
44 the importance of life style or environmental factors interacting with genetic factors
45
46 cannot be ruled out [40] as studies of immigration from regions with low to high
47
48 incidence of type 1 diabetes have been associated with increased incidence of type 1
49
50 diabetes [33] .
51
52

53
54 We lacked specific ICD codes for type 1 diabetes in the earlier versions of ICD (i.e.
55
56 8th and 9th version of ICD). However, the prevalence of type 2 diabetes is low in
57
58
59
60

1
2
3 Sweden [41, 42] and most likely the majority of cases of diabetes diagnosed before
4
5 30 years are type 1 diabetes. Moreover, the results of the analysis limited to only
6
7 cases of type 1 diabetes according to ICD 10 for the years 1997 and forward were
8
9 similar to the results for the entire period of the study.
10

11
12 Our findings of a lower IRR of type 1 diabetes among children and young adults with
13
14 one or two foreign born parents, with the notable exception of offspring of African
15
16 immigrants, and the shifting of age of diagnosis towards younger age in both
17
18 offspring of Swedes and of immigrants highlight the important role of environmental
19
20 factors and its interaction with genetic background in the etiology of type 1 diabetes.
21

22
23 Further studies of exploring early exposures to environmental factors and studies on
24
25 offspring of immigrants from African countries, in particular from Eastern Africa, might
26
27 improve our understanding on the etiology of the disease.
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Acknowledgements

This work was supported by grants from The Ministry of Higher Education and Scientific Research-Kurdistan Regional Government/Iraq, and the Department of Environmental Medicine, Karolinska institutet, Stockholm, Sweden.

The authors thank Professor Sven Cnattingius, for his critical review of the manuscript.

The authors appreciate the help from Statistics Sweden and the National Board of Health and Welfare, which provided them with data

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.

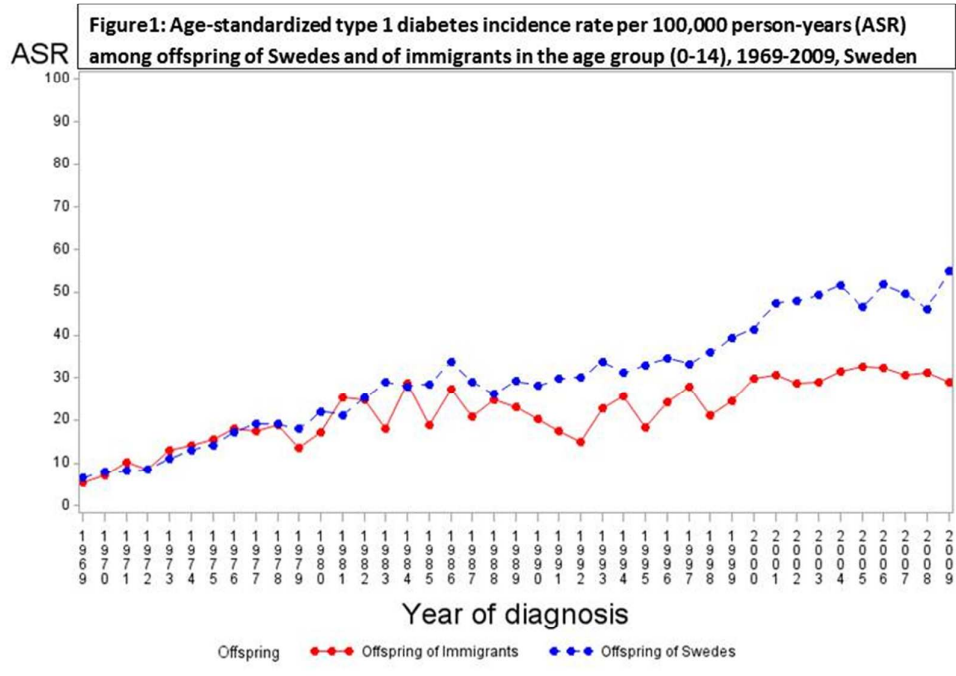
REFERENCES

1. Dabelea, D., *The accelerating epidemic of childhood diabetes*. Lancet, 2009. **373**(9680): p. 1999-2000.
2. Berhan, Y., et al., *Thirty years of prospective nationwide incidence of childhood type 1 diabetes: the accelerating increase by time tends to level off in Sweden*. Diabetes, 2011. **60**(2): p. 577-81.
3. Kondrashova, A., et al., *A six-fold gradient in the incidence of type 1 diabetes at the eastern border of Finland*. Ann Med, 2005. **37**(1): p. 67-72.
4. Pitkaniemi, J., et al., *Increasing incidence of Type 1 diabetes--role for genes?* BMC Genet, 2004. **5**: p. 5.
5. Hyttinen, V., et al., *Genetic liability of type 1 diabetes and the onset age among 22,650 young Finnish twin pairs: a nationwide follow-up study*. Diabetes, 2003. **52**(4): p. 1052-5.
6. Pundziute-Lycka, A., et al., *The incidence of Type I diabetes has not increased but shifted to a younger age at diagnosis in the 0-34 years group in Sweden 1983-1998*. Diabetologia, 2002. **45**(6): p. 783-91.
7. Weets, I., et al., *The incidence of type 1 diabetes in the age group 0-39 years has not increased in Antwerp (Belgium) between 1989 and 2000: evidence for earlier disease manifestation*. Diabetes Care, 2002. **25**(5): p. 840-6.
8. Hussen, H.I., et al., *Type I diabetes among children and young adults: the role of country of birth, socioeconomic position and sex*. Pediatr Diabetes, 2012.
9. Karvonen, M., et al., *Sex difference in the incidence of insulin-dependent diabetes mellitus: an analysis of the recent epidemiological data*. World Health Organization DIAMOND Project Group. Diabetes Metab Rev, 1997. **13**(4): p. 275-91.
10. Ostman, J., et al., *Gender differences and temporal variation in the incidence of type 1 diabetes: results of 8012 cases in the nationwide Diabetes Incidence Study in Sweden 1983-2002*. J Intern Med, 2008. **263**(4): p. 386-94.
11. Beiki, O., B. Stegmayr, and T. Moradi, *Country reports: Sweden*, in *Migration-sensitive Cancer Registration in Europe* O. Razum, et al., Editors. 2011, Lang p. 106-123.
12. Ludvigsson, J.F., et al., *The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research*. Eur J Epidemiol, 2009. **24**(11): p. 659-67.
13. Johannesson, I., *The total population register of statistics Sweden. New possibilities and better quality*. Statistics Sweden: Örebro. 2002.
14. Socialstyrelsen, *Causes of death, The National Board of Health and Welfare, CENTRE FOR EPIDEMIOLOGY*. Official Statistics of Sweden, 2007.
15. Socialstyrelsen. *Kvalitet och innehåll i patientregistret*. 2009 [cited 2010 08-05]; Available from: www.socialstyrelsen.se, The National Board of Health and Welfare.
16. Ludvigsson, J.F., et al., *External review and validation of the Swedish national inpatient register*. BMC Public Health, 2011. **11**: p. 450.
17. *The Multi-Generation Registry. Bakgrundsfakta till befolknings-ochvålfärdsstatistik*. Statistiska Centralbyrån: Örebro; 2001.
18. Statistics_Sweden. *Folk- och bostadsräkningar, FoB*. 2010 [cited 2010 02-25]; Available from: www.scb.se.
19. Socialstyrelsen. *Longitudinal integration database for health insurance and labour market studies (LISA by Swedish acronym)*. 2010 [cited 2010 08-10]; Available from: www.socialstyrelsen.se.
20. Omar B. Ahmad, C.B.-P., Alan D. Lopez, Christopher JL Murray, Rafael Lozano, Mie Inoue, *AGE STANDARDIZATION OF RATES: A NEW WHO STANDARD*. GPE Discussion Paper Series: No.31, EIP/GPE/EBD, World Health Organization 2001.

- 1
 - 2
 - 3
 - 4
 - 5
 - 6
 - 7
 - 8
 - 9
 - 10
 - 11
 - 12
 - 13
 - 14
 - 15
 - 16
 - 17
 - 18
 - 19
 - 20
 - 21
 - 22
 - 23
 - 24
 - 25
 - 26
 - 27
 - 28
 - 29
 - 30
 - 31
 - 32
 - 33
 - 34
 - 35
 - 36
 - 37
 - 38
 - 39
 - 40
 - 41
 - 42
 - 43
 - 44
 - 45
 - 46
 - 47
 - 48
 - 49
 - 50
 - 51
 - 52
 - 53
 - 54
 - 55
 - 56
 - 57
 - 58
 - 59
 - 60
21. Green, A. and C.C. Patterson, *Trends in the incidence of childhood-onset diabetes in Europe 1989-1998*. Diabetologia, 2001. **44 Suppl 3**: p. B3-8.
22. *Incidence and trends of childhood Type 1 diabetes worldwide 1990-1999*. Diabetic Medicine, 2006. **23**(8): p. 857-866.
23. Dahlquist, G., *Can we slow the rising incidence of childhood-onset autoimmune diabetes? The overload hypothesis*. Diabetologia, 2006. **49**(1): p. 20-4.
24. Haynes, A., et al., *Perinatal risk factors for childhood Type 1 diabetes in Western Australia--a population-based study (1980-2002)*. Diabet Med, 2007. **24**(5): p. 564-70.
25. Hjern, A., U. Soderstrom, and J. Aman, *East Africans in Sweden have a high risk for type 1 diabetes*. Diabetes Care, 2012. **35**(3): p. 597-8.
26. Karvonen, M., et al., *Incidence of childhood type 1 diabetes worldwide. Diabetes Mondiale (DiaMond) Project Group*. Diabetes Care, 2000. **23**(10): p. 1516-26.
27. Hall, V., et al., *Diabetes in Sub Saharan Africa 1999-2011: epidemiology and public health implications. A systematic review*. BMC Public Health, 2011. **11**: p. 564.
28. <http://www.idf.org/diabetesatlas/5e/africa>.
29. Majaliwa, E.S., et al., *Type 1 diabetes mellitus in the African population: epidemiology and management challenges*. Acta Biomed, 2008. **79**(3): p. 255-9.
30. Monabeka, H.G., A. Mbika-Cardorelle, and G. Moyon, *[Ketoacidosis in children and teenagers in Congo]*. Sante, 2003. **13**(3): p. 139-41.
31. Rwiza, H.T., A.B. Swai, and D.G. McLarty, *Failure to diagnose diabetic ketoacidosis in Tanzania*. Diabet Med, 1986. **3**(2): p. 181-3.
32. Hjern, A. and U. Soderstrom, *Parental country of birth is a major determinant of childhood type 1 diabetes in Sweden*. Pediatr Diabetes, 2008. **9**(1): p. 35-9.
33. Cataldo, F., *Early onset of Type 1 diabetes mellitus in immigrant children from developing countries to Western Europe: the role of environmental factors?* J Endocrinol Invest, 2005. **28**(6): p. 574-5.
34. Soderstrom, U., J. Aman, and A. Hjern, *Being born in Sweden increases the risk for type 1 diabetes - a study of migration of children to Sweden as a natural experiment*. Acta Paediatr, 2012. **101**(1): p. 73-7.
35. Podar, T., et al., *Risk of childhood type 1 diabetes for Russians in Estonia and Siberia*. Int J Epidemiol, 1993. **22**(2): p. 262-7.
36. Patrick, S.L., et al., *IDDM incidence in a multiracial population. The Hawaii IDDM Registry, 1980-1990*. Diabetes Care, 1997. **20**(6): p. 983-7.
37. Ji, J., et al., *Ethnic differences in incidence of type 1 diabetes among second-generation immigrants and adoptees from abroad*. J Clin Endocrinol Metab, 2010. **95**(2): p. 847-50.
38. Muntoni, S., et al., *Incidence of insulin-dependent diabetes mellitus among Sardinian-heritage children born in Lazio region, Italy*. Lancet, 1997. **349**(9046): p. 160-2.
39. Neu, A., et al., *Diabetes incidence in children of different nationalities: an epidemiological approach to the pathogenesis of diabetes*. Diabetologia, 2001. **44 Suppl 3**: p. B21-6.
40. Zung, A., et al., *Type 1 diabetes in Jewish Ethiopian immigrants in Israel: HLA class II immunogenetics and contribution of new environment*. Hum Immunol, 2004. **65**(12): p. 1463-8.
41. Arnqvist, H.J., et al., *Difficulties in classifying diabetes at presentation in the young adult*. Diabet Med, 1993. **10**(7): p. 606-13.
42. Lynch, K.F., et al., *Context and disease when disease risk is low: the case of type 1 diabetes in Sweden*. J Epidemiol Community Health, 2010. **64**(9): p. 789-95.

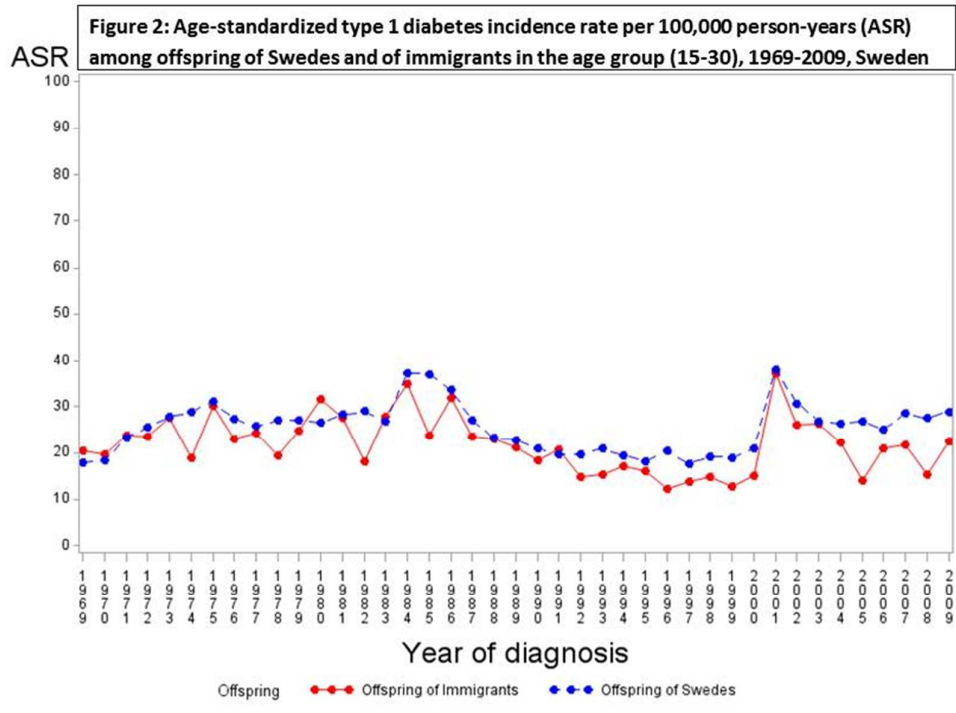
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figures



ew only

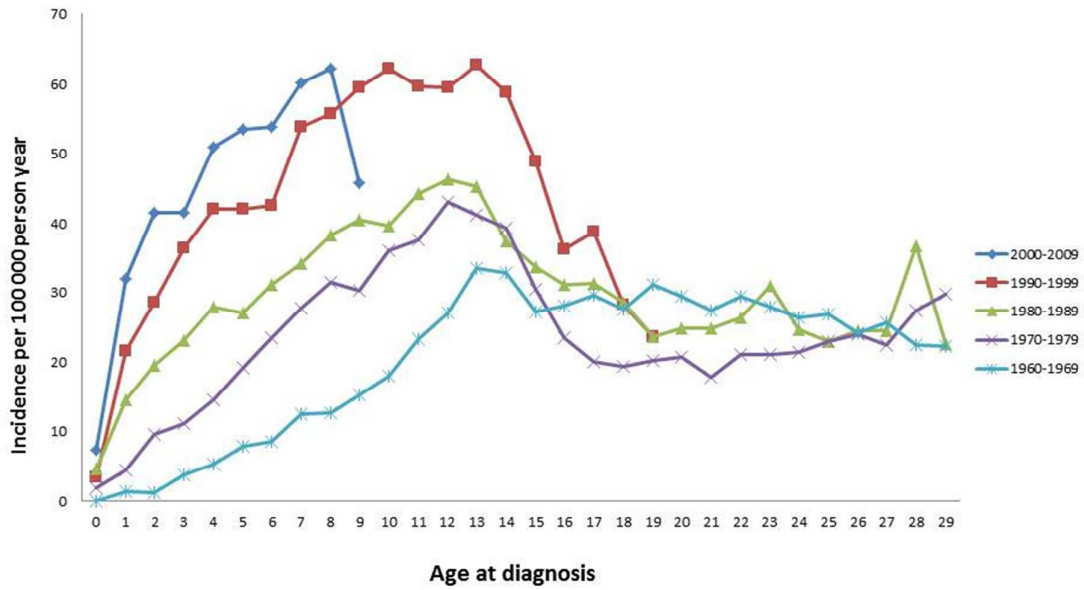
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



view only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

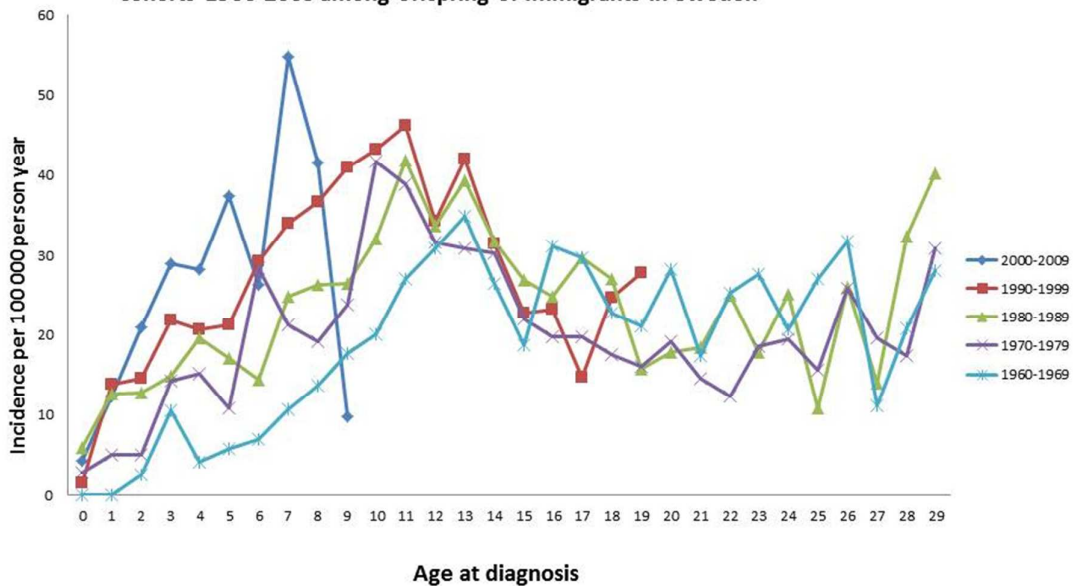
Figure 3.A. : Incidence of type 1 diabetes by age at diagnosis (0-30 years) and birth cohorts 1960-2009 among offspring of Swedes in Sweden



view only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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



view only

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.								

For peer review only

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.

Parental country of birth	IRR* (95 % CI)											
	Male						Female					
	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.

IRR 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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-003418.R1
Article Type:	Research
Date Submitted by the Author:	05-Sep-2013
Complete List of Authors:	Hussen, Hozan; Karolinska Institutet, Department of Environmental Medicine, Division of Epidemiology, Unit of Cardiovascular Epidemiology Persson, Martina; Karolinska University Hospital, Department of Medicine, Clinical Epidemiology Unit Moradi, Tahereh; Karolinska Institutet, Department of Environmental Medicine, Division of Epidemiology, Unit of Cardiovascular Epidemiology
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Epidemiology
Keywords:	Type 1 diabetes, Birth Cohort, Incidence, Migration, Sweden

SCHOLARONE™
Manuscripts

1
2
3 **The trends and the risk of type 1 diabetes over the past 40 years: an analysis**
4 **by birth cohorts and by parental migration background in Sweden**
5
6
7
8

9 Hozan Ismael Hussen^{*1}, Martina Persson², Tahereh Moradi^{1,3}
10
11

12
13
14 ¹Department of Environmental Medicine, Division of Epidemiology, Unit of
15 Cardiovascular Epidemiology, Karolinska Institutet, Stockholm, Sweden.
16
17

18 ²Department of Medicine, Clinical Epidemiology Unit, Karolinska University Hospital,
19 Stockholm, Sweden.
20
21

22 ³Centre for Epidemiology and Social Medicine, Health Care Services, Stockholm
23 County Council, Sweden
24
25
26
27

28
29 ***Corresponding author:**
30

31 Hozan Ismael Hussen, MD
32

33 Department of Environmental Medicine, Division of Epidemiology,
34

35 Unit of Cardiovascular Epidemiology, Karolinska Institutet
36
37

38 Nobels väg 13, Box 210,
39

40 SE-171 77 Stockholm, Sweden
41

42 Phone: +46-8-524 800 55
43

44 Fax: +46-8-31 39 36
45

46 E-mail: hozan.hussen@ki.se
47
48
49

50
51 **Word count**
52

53 Main text 3737
54
55
56
57
58
59
60

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

1
2
3 Venezuela to more than 40 per 100 000 person years in Sweden and Finland,
4
5 respectively [2-4].
6

7
8 The concordance rate of type 1 diabetes among monozygotic twins has been
9
10 estimated to 27% [5]. Thus, in the etiology of type 1 diabetes, there is considerable
11
12 room for influence of environmental factors acting on genetic predisposition.
13
14 Investigating the occurrence of type 1 diabetes in immigrants and their offspring
15
16 offers a unique possibility to explore and delineate the gene-environment interaction
17
18 for the development of type 1 diabetes.
19

20
21 Over the past decades, a rapid rise in the incidence of type 1 diabetes among
22
23 individuals below 15 years of age has been reported and also with a shift towards
24
25 younger age at onset [6, 7]. These studies, however, have not distinguished between
26
27 individuals born to parents with different migration background. If offspring of
28
29 immigrants, with varying genetic background, experience the same change in age at
30
31 onset as observed in offspring of natives, the importance of early environmental
32
33 exposures for the development of type 1 diabetes would be further supported. We
34
35 recently reported a decreased risk of type 1 diabetes among the majority of
36
37 immigrants in Sweden compared with native Swedes. We also observed a tendency
38
39 towards a convergence of risks for type 1 diabetes between offspring of immigrants
40
41 as one group and native Swedes [8]. Since immigrants and their offspring are a
42
43 heterogeneous population, there is a need to explore if the risk of type 1 diabetes
44
45 varies by specific parental country or region of birth.
46
47
48

49
50 In the present study, we used Swedish nation-wide data collected over 40 years to
51
52 investigate the trend and the risk of developing type 1 diabetes in offspring of
53
54 immigrants by specific paternal and maternal migration background and by birth
55
56
57
58
59
60

1
2
3 cohorts. Since the incidence of type 1 diabetes varies with sex and age [9, 10], the
4
5 analyses were stratified by offspring sex and age.
6
7

8 9 **METHODS**

10 *Database*

11
12 We used information from a newly established, nationwide dataset – The Migration
13
14 and Health Cohort (M&H Co.) [11], where data from national, longitudinal clinical,
15
16 health and socio - demographic registries have been compiled. This database was
17
18 built by individual record-linkage between more than fifteen Swedish national
19
20 registries to facilitate studies on diabetes, injuries, cancer, cardiovascular and
21
22 psychiatric diseases among immigrants and their descendants in Sweden. The
23
24 linkage was done using the Personal Identification Number (PIN), which is uniquely
25
26 assigned to each individual that have resided in Sweden for longer than one year
27
28 since 1947 [12]. The data used in this study are part of the M&H Co., including: 1)
29
30 The Swedish Total Population Register, which covers the entire population
31
32 registration in Sweden and is updated on a daily basis. The register contains
33
34 information on demographic variables, such as date and place of birth and data on
35
36 emigration and immigration [13]. 2) The Cause of Death Register, which contains
37
38 information on the date of death, the main and contributing causes of death [14]. 3)
39
40 The National Patient Register, including the Inpatient Register. It was established in
41
42 1964 but with national coverage since 1987 covering 85-95% of all diagnostic data
43
44 [15]. Since 2001, the Patient Register includes information on all registered
45
46 outpatient visits to specialist care and day visits to hospitals and covers about 80% of
47
48 all visits to the specialized outpatient care [16]. The Patient Register contains data on
49
50 the main diagnosis and up to eight secondary diagnoses [15, 16]. 4) The Multi-
51
52
53
54
55
56
57
58
59
60

1
2
3 Generation Register contains links between children and their parents via PINs for all
4
5 Swedish inhabitants born after 1931 who were alive in 1960 [17]. 5) The National
6
7 Population and Housing Censuses and longitudinal integration database for health
8
9 insurance and labor market studies (LISA), contains data on socio-economic,
10
11 occupational and demographic variables [18, 19].
12

13
14 The linkages between the registers have been completed by Statistics Sweden and
15
16 the National Board of Health and Welfare. To ensure confidentiality, the PINs have
17
18 been replaced by person-unique serial numbers and a key code is kept at Statistics
19
20 Sweden. The study was approved by one of the Regional Ethical Committees in
21
22 Stockholm, Sweden (Dnr. 2009/2033-32).
23

24 25 26 27 *Study cohort*

28
29 The study population comprised 3,794,477 (51.4%) males and 3,593,765 (48.6%)
30
31 females between 0 to 30 years of age, born and living in Sweden any time between
32
33 January 1st, 1969 and December 31st, 2009. We excluded individuals whose parents
34
35 had unknown information on country of birth and all individuals who had a history of
36
37 type 1 diabetes, before entry into the cohort. The final cohort included 7,098,790
38
39 individuals (3,641,304 (51.3%) males and 3,457,486 (48.7%) females) aged 0-30
40
41 years and born in Sweden.
42
43
44

45 46 47 *Follow-up*

48
49 The cohort members were followed from date of birth or January 1st, 1969, whichever
50
51 occurred last, until the date of diagnosis of type 1 diabetes according to the Swedish
52
53 versions of International Classification of Disease (ICD-8: 250, 1969-1986; ICD-9:
54
55 250, 1987-1996; ICD-10: E10, 1997 and onwards), emigration, death or end of
56
57
58
59
60

1
2
3 follow-up (December 31st, 2009), whichever occurred first. Every individual in the
4
5 cohort were followed for maximum 30 years of age.
6

7 Since earlier versions of ICD (i.e. 8th and 9th version of ICD) could not disentangle
8
9 between different types of diabetes, we have performed sensitivity analysis using
10
11 ICD-10 only where we could identify type I diabetes (see method for details).
12
13

14 15 16 *Classification of offspring based on parental country of birth*

17
18 The cohort was divided into four groups according to parental country of birth:
19
20 individuals with mothers born outside Sweden (father could be born in Sweden,
21
22 abroad or unknown) (n= 345,827); individuals with fathers born outside Sweden
23
24 (mother could be born in Sweden, abroad or unknown) (n= 317,397); individuals with
25
26 both parents born outside of Sweden (n= 435,045) and individuals with both parents
27
28 born in Sweden (n= 6,000,521). We also classified parental country of birth into 6
29
30 continents: Africa (North, South, East, West and Middle Africa), Asia (East, West,
31
32 South-Central, and South-East Asia), Europe (North, South, East, and West Europe),
33
34 Latin America (Caribbean, Central America and South America) Northern America,
35
36 and Oceania (Australia/New Zealand, Melanesia, and Micronesia/Polynesia). Based
37
38 on the findings from our previous study among immigrant individuals [8], we
39
40 categorized Africa into North, East and West Africa; Europe into Finland, North
41
42 Europe without Finland, and South-, East-, and West Europe (the latter three as one
43
44 group). For the trend and the birth cohort analyses, we pooled all offspring of
45
46 immigrants into one group.
47
48
49
50

51 52 53 *Statistical analysis*

54
55
56
57
58
59
60

1
2
3 We estimated Incidence rate ratios (IRRs) with 95% confidence intervals (CIs) using
4
5 Poisson regression models. The analyses were adjusted for age at follow-up (in 5
6
7 years intervals 0-4, 5-9, 10-14, 15-19, 20-24, and 25-30 years), calendar years of
8
9 follow-up (four categories: 1969-1978, 1979-1988, 1989-1998 and 1999-2009) and
10
11 education of the mother or father (classified into four levels: 0-9 years, 10-12 years,
12
13 13 years or more and unknown). All analyses were performed for females and males
14
15 separately. In addition, analyses were made separately for children (0-14 years) and
16
17 young adults (15-30 years) where we did not distinguish specific parental region or
18
19 country of birth. In further analyses, children and young adults (0-30 years) were
20
21 pooled together as one category to allow reasonable statistical power for analyses by
22
23 specific maternal and paternal regions or country of birth to test the hypothesis that
24
25 the mother's and the father's background would affect the offspring's risk of type 1
26
27 diabetes differently. We also analyzed risk of type 1 diabetes in children with both
28
29 mother and father born in the same country/region. Those with parents from different
30
31 regions or from Sweden were categorized as a mixed group.
32
33
34
35

36 Since we had no specific ICD codes before 1997 to distinguish between type 1 and
37
38 type 2 diabetes, we repeated the analysis and confined our cohort to individuals
39
40 living in Sweden between 1997 and 2009 where we could strictly identify type 1
41
42 diabetes according to ICD-10.
43
44

45 For the trend analysis, we further calculated age-standardized rates (ASRs), by
46
47 parental migration background for both children (0-14 years) and young adults (15-
48
49 30 years), by dividing number of new cases with the estimated numbers of person-
50
51 years at risk in 5-years age categories using the world population as standard [20].
52
53 ASRs were directly calculated to ensure comparability and to adjust for differences in
54
55
56
57
58
59
60

1
2
3 age in the study population, in each of the age groups 0–4, 5–9, 10–14, 15–19, 20–
4
5 24, and 25–30 years. We reported ASR in unit of per 100,000 person years.
6

7
8 The Joint point regression analyses were performed to evaluate trends of type 1
9
10 diabetes in both offspring to immigrants and offspring to Swedes and in both age
11
12 groups [21, 22]. Annual percent change (APC) was estimated, to describe and test
13
14 the statistical significance of the trends. The null hypothesis in this analysis is that the
15
16 trend in incidence rates is the same over time. We used Statistical Analysis System
17
18 (SAS) version 9.3 for all the analysis.
19
20

21 22 23 **RESULTS**

24
25 On average, the age of onset of type 1 diabetes was similar in offspring of immigrants
26
27 as in offspring of Swedes (mean \pm SD; offspring of immigrants 14.31 \pm 7.70, offspring
28
29 of swedes 15.47 \pm 7.99).
30

31
32 Over the study period (1969 -2009), we observed a significant increasing trend for
33
34 incidence of type 1 diabetes based on joint point regression analyses among
35
36 offspring below 15 years of age born to native Swedes and to immigrants (offspring
37
38 to Swedes: APC= 3.9, p values<0.001 and offspring to immigrants: APC= 2.2, p
39
40 values<0.001 Figure 1). In contrast, no increase or a slight decreasing trend was
41
42 observed among young individuals between 15 to 30 years of age regardless of
43
44 parental migration background (offspring to Swedes: APC= -0.0, p= 0.9 and offspring
45
46 to immigrants: APC= -0.7, p value= 0.08 , Figure 2).
47
48

49
50 The birth cohort analysis revealed a shift towards lower age at onset in individuals
51
52 below 15 years of age in both offspring of Swedes and in offspring of immigrants
53
54 (Figures 3a and 3b).
55
56
57
58
59
60

1
2
3 Compared with offspring of Swedish-born parents, boys and girls (0 to 14 years) with
4 a foreign-born mother or father had about 30% lower IRR in the multivariable
5 analyses adjusted for age, calendar period and parental education. Among boys and
6 girls with both parents born abroad, corresponding risk reductions were about a 40%
7 (Table 1). The results from the sensitivity analysis, where we repeated the analysis
8 and confined our cohort to individuals born in Sweden between 1997 and 2009, were
9 similar to the results of the entire cohort (Supplementary Table 1S).

10
11
12 Compared with young adults (15 to 30 years) of Swedish-born parents, young adults
13 with only one parent born abroad had about 15% to 20% lower IRR of type 1
14 diabetes and among young adults with both parents born abroad, the risks were
15 reduced by 25% to 30% (Table 1).

16
17
18 Next, we investigated risks of type 1 diabetes by parental region of birth. Compared
19 with young offspring (0-30 years) of Swedish-born parents, male and female offspring
20 of mothers or fathers born in Africa had about 20% to 40% higher IRR of type 1
21 diabetes (Table 2). The increased risk of type 1 diabetes was more prominent among
22 individuals whose mothers or fathers were born in Eastern Africa. With a few
23 exceptions, male and female offspring of mothers or fathers born in Asia, Europe
24 (except Northern Europe), Latin America and Northern America (except female
25 offspring to fathers from Northern America) had between 35% to 65% lower IRR than
26 male and female offspring of Swedish-born parents (Table 2). These reductions in
27 risks became even more prominent when we confined the analyses to parents born
28 in the same region (Table 2). Offspring of Finnish immigrants and rest of Northern
29 Europe had almost similar risks compared with offspring of Swedes (Table 2).

30
31
32 The results from the sensitivity analysis, where we repeated the analysis and
33 confined our cohort to individuals born in Sweden between 1997 and 2009 (limited to
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 children ages 0 to 13) , were similar to the results of the entire cohort for the same
4
5 age category (Supplementary Tables 2Sa and 2Sb).
6
7

8 9 **DISCUSSION**

10
11 In this nation-wide cohort study of Sweden-born children and young adults, we
12
13 observed a continuing increase of type 1 diabetes in individuals younger than 15
14
15 years of age over the past decades. This increase was, however, less evident among
16
17 offspring of immigrants than in offspring of native Swedes. In contrast, no change in
18
19 trend was observed among young individuals between 15 to 30 years of age, and
20
21 regardless of parental country of birth.
22
23

24
25 An interesting finding in the present study was an almost identical pattern with a shift
26
27 towards lower age at onset of type 1 diabetes by younger birth cohorts in both
28
29 offspring of foreign born parents and Swedes.
30

31
32 Over the past decades, a rapid rise in the incidence of type 1 diabetes has been
33
34 demonstrated [23, 24]. The finding of an increased incidence rate of type 1 diabetes
35
36 between 1969 and 2009 among individuals below 15 years of age, and a decreasing
37
38 or steady incidence rate among young adults, is in line with previous studies from
39
40 Sweden [6] and other parts of the world [7]. The observed increasing trend over time
41
42 in our study might be due to the quality of National patient Register over time and not
43
44 covering all of Sweden for the entire period of our study. This register became nation-
45
46 wide in 1987. However, the sharpest increase in incidence observed in our study
47
48 among individuals below 15 years of age is after around 1997 when the Inpatient
49
50 Register had full coverage and when the ICD-10 were able to disentangle different
51
52 types of diabetes.
53
54
55
56
57
58
59
60

1
2
3 The finding of an almost identical pattern with a shift towards lower age at onset of
4 type 1 diabetes in both offspring of foreign born parents and Swedes indicates the
5 exposure to similar environmental factors in both groups. It has been hypothesized
6 that this developments is due to increased exposures in early life to factors that
7 initiate and/ or accelerate beta cell destruction, including viral infections, rapid
8 postnatal growth and nutritional factors [25, 26]. In addition, perinatal factors such as
9 blood-group incompatibility, high maternal age, preeclampsia and caesarean section
10 delivery have been shown to be associated with increased incidence of childhood
11 type 1 diabetes [27]. Similar findings of a shift towards younger age at diagnosis and
12 a declining incidence of type 1 diabetes among young adults aged 15 to 34 years
13 were also observed in other studies from Sweden, using the two nation-wide
14 prospectively collected research register, the Swedish Childhood Diabetes Register
15 and the Diabetes Incidence Study in Sweden [10, 28]. The shift towards younger age
16 at diagnosis may be due to risk factors accelerating the disease process.

17
18 We further found that offspring with one or two parents born abroad had a reduced
19 risk of type 1 diabetes compared with offspring to Sweden-born parents. The
20 reduction in risk was similar between sexes and was more apparent among
21 individuals where both parents were foreign born. Stratification by specific parental
22 region/country of birth, however, revealed that this reduction was confined to
23 offspring of immigrants from Asia, Latin and North America, South-, West- and East
24 Europe. In contrast, the IRR for type 1 diabetes was increased in individuals with
25 African parents, particularly so if the parents were born in Eastern or Northern Africa.
26 The observed increased risk among offspring of Africans in this study, in line with a
27 previous Swedish register study [29] is also observed in Swedish residents born in
28 Africa [8, 29]. It is unclear if these findings reflect a high risk of type 1 diabetes in the

1
2
3 countries of origin, thus rating Eastern and Northern Africa as the areas with the
4 highest incidence of type 1 diabetes in the world. At the same time we should keep in
5 mind that the population of immigrants in Sweden may not represent the population
6 of countries of origin.
7
8
9

10
11 The reported low number of type 1 diabetes diagnoses in Africa [30] is most likely to
12 be underestimated due to lack of diagnostic measures [31], and high mortality
13 among uncontrolled type 1 diabetes cases as a result of limited access to insulin
14 treatment [32]. Moreover, priorities are mostly given to the high burden of
15 communicable diseases in African countries [33], especially in busy emergency
16 hospitals. As a consequence, children with diabetic ketoacidosis at the time of
17 diagnosis [34] could be misdiagnosed as cerebral malaria or meningitis [35] which
18 would also lead to an underestimation of type 1 diabetes cases. The observed higher
19 risk in African offspring in the present study and the increased risk of type 1 diabetes
20 in Swedish residents born in Africa [8] might be due to genetic propensity interacting
21 with environmental factors in the new home country.
22
23
24
25
26
27
28
29
30
31
32
33
34
35

36 Offspring of Swedish residents born in Asia, Latin and North America, South-, West-
37 and East Europe retained the low risk profile were recently observed in young
38 immigrants in Sweden born in these areas [8]. This risk reduction was independent of
39 maternal or paternal birth region but was stronger if both parents were born in the
40 same region.
41
42
43
44
45
46

47 The importance of parental country of birth for the risk of developing type 1 diabetes
48 has also been observed in other studies [36-39] and may indicate the role of genetic
49 factors [40, 41]. Children of Sardinian heritage (a high risk area), born and living in
50 Lazio (a low risk area) retained the high risk profile of Sardinia [42]. The risk for type
51 1 diabetes in children of Yugoslavian, Italian and Greek heritage in Germany was
52
53
54
55
56
57
58
59
60

1
2
3 closer to the reported incidence in those countries than in Germany [43] However,
4 the importance of life style or environmental factors interacting with genetic factors
5 cannot be ruled out [44] as studies of immigration from regions with low to high
6 incidence of type 1 diabetes have been associated with increased incidence of type 1
7 diabetes [37] .
8
9

10
11
12
13
14 The primary strength of our study is the nation-wide cohort design with nearly
15 complete follow-up of type 1 diabetes occurrence over several decades. Using a
16 unique PIN assigned to all Swedish citizens, we were able to correctly assess
17 exposure (parental country of birth) and thus avoiding misclassification bias.
18
19
20

21
22 We lacked specific ICD codes for type 1 diabetes in the earlier versions of ICD before
23 1997 (i.e. 8th and 9th version of ICD). However, the results of the sensitivity analysis
24 limited to only cases of type 1 diabetes according to ICD 10 for the years 1997 and
25 forward were similar to the results for the entire period of the study. But, in this
26 sensitivity analysis, we were only able to verify the results for children born between
27 1997 and 2009 (0 to 13 years old). Whereas, for the age groups over 15 years when
28 type 1 diabetes is more likely to be mixed with type 2 diabetes, we had no data.
29 However, the prevalence of type 2 diabetes is low in Sweden [45, 46] and other
30 northern European countries and most likely the majority of cases of diabetes
31 diagnosed before 30 years are true type 1 diabetes. While this may not be applicable
32 for offspring born to parents from other parts of the world with known high prevalence
33 of type 2 diabetes which may have led to overestimation of the true type 1 diabetes.
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48

49 Our findings of a lower IRR of type 1 diabetes among children and young adults with
50 one or two foreign born parents, with the notable exception of offspring of African
51 immigrants, and the shifting of age at diagnosis towards younger age in both
52
53
54
55
56
57
58
59
60

1
2
3 offspring of Swedes and of immigrants highlight the important role of environmental
4 factors and its interaction with genetic background in the etiology of type 1 diabetes.
5
6

7 In order to further clarify potential pathophysiological mechanisms for the
8 development of type1 diabetes, further studies are needed with data on important
9 exposures such as viral infections in early life, nutritional habits and weight gain in
10 infancy. Moreover, studies on offspring of immigrants from African countries, in
11 particular from Eastern Africa, might improve our understanding on the etiology of the
12 disease.
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

47 **Acknowledgements**

48
49 This work was supported by grants from The Ministry of Higher Education and
50 Scientific Research-Kurdistan Regional Government/Iraq, and the Department of
51 Environmental Medicine, Karolinska institutet, Stockholm, Sweden.
52
53
54
55
56
57
58
59
60

1
2
3 The authors thank Professor Sven Cnattingius, for his critical review of the
4
5 manuscript.
6
7

8
9
10 The authors appreciate the help from Statistics Sweden and the National Board of
11
12 Health and Welfare, which provided them with data
13

14 15 16 **Competing interests**

17
18 No potential conflicts of interest relevant to this article were reported.
19
20

21 22 23 **Contributors**

24
25 H.I.H. designed the research, drafted the manuscript, analyzed data, and interpreted
26
27 results.
28

29
30 M.P. designed the research, interpreted the results critically reviewed and edited the
31
32 manuscript.
33

34
35 T.M. designed the research, interpreted the results, critically reviewed and edited the
36
37 manuscript, handled research data and funding, and supervised.
38
39

40 41 **Data sharing**

42
43 no additional data available.
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

REFERENCES

1. Dabelea, D., *The accelerating epidemic of childhood diabetes*. Lancet, 2009. **373**(9680): p. 1999-2000.
2. Berhan, Y., et al., *Thirty years of prospective nationwide incidence of childhood type 1 diabetes: the accelerating increase by time tends to level off in Sweden*. Diabetes, 2011. **60**(2): p. 577-81.
3. Kondrashova, A., et al., *A six-fold gradient in the incidence of type 1 diabetes at the eastern border of Finland*. Ann Med, 2005. **37**(1): p. 67-72.
4. Pitkaniemi, J., et al., *Increasing incidence of Type 1 diabetes--role for genes?* BMC Genet, 2004. **5**: p. 5.
5. Hyttinen, V., et al., *Genetic liability of type 1 diabetes and the onset age among 22,650 young Finnish twin pairs: a nationwide follow-up study*. Diabetes, 2003. **52**(4): p. 1052-5.
6. Pundziute-Lycka, A., et al., *The incidence of Type I diabetes has not increased but shifted to a younger age at diagnosis in the 0-34 years group in Sweden 1983-1998*. Diabetologia, 2002. **45**(6): p. 783-91.
7. Weets, I., et al., *The incidence of type 1 diabetes in the age group 0-39 years has not increased in Antwerp (Belgium) between 1989 and 2000: evidence for earlier disease manifestation*. Diabetes Care, 2002. **25**(5): p. 840-6.
8. Hussen, H.I., et al., *Type I diabetes among children and young adults: the role of country of birth, socioeconomic position and sex*. Pediatr Diabetes, 2012.
9. Karvonen, M., et al., *Sex difference in the incidence of insulin-dependent diabetes mellitus: an analysis of the recent epidemiological data*. World Health Organization DIAMOND Project Group. Diabetes Metab Rev, 1997. **13**(4): p. 275-91.
10. Ostman, J., et al., *Gender differences and temporal variation in the incidence of type 1 diabetes: results of 8012 cases in the nationwide Diabetes Incidence Study in Sweden 1983-2002*. J Intern Med, 2008. **263**(4): p. 386-94.
11. Beiki, O., B. Stegmayr, and T. Moradi, *Country reports: Sweden*, in *Migration-sensitive Cancer Registration in Europe* O. Razum, et al., Editors. 2011, Lang p. 106-123.
12. Ludvigsson, J.F., et al., *The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research*. Eur J Epidemiol, 2009. **24**(11): p. 659-67.
13. Johannesson, I., *The total population register of statistics Sweden. New possibilities and better quality*. Statistics Sweden: Örebro. 2002.
14. Socialstyrelsen, *Causes of death, The National Board of Health and Welfare, CENTRE FOR EPIDEMIOLOGY*. Official Statistics of Sweden, 2007.
15. Ludvigsson, J.F., et al., *External review and validation of the Swedish national inpatient register*. BMC Public Health, 2011. **11**: p. 450.
16. Socialstyrelsen. *Kvalitet och innehåll i patientregistret*. 2009 [cited 2010 08-05]; Available from: www.socialstyrelsen.se, The National Board of Health and Welfare.
17. *The Multi-Generation Registry. Bakgrundsfakta till befolknings-och välfärdstatistik*. Statistiska Centralbyrån: Örebro; 2001.
18. Statistics_Sweden. *Folk- och bostadsräkningar, FoB*. 2010 [cited 2010 02-25]; Available from: www.scb.se.
19. Socialstyrelsen. *Longitudinal integration database for health insurance and labour market studies (LISA by Swedish acronym)*. 2010 [cited 2010 08-10]; Available from: www.socialstyrelsen.se.
20. Omar B. Ahmad, C.B.-P., Alan D. Lopez, Christopher JL Murray, Rafael Lozano, Mie Inoue, *AGE STANDARDIZATION OF RATES: A NEW WHO STANDARD*. GPE Discussion Paper Series: No.31, EIP/GPE/EBD, World Health Organization 2001.
21. *Statistical Research and Applications Branch NCI. Joinpoint regression program*. 2008. **Version 3.3.1**.

- 1
 - 2
 - 3
 - 4
 - 5
 - 6
 - 7
 - 8
 - 9
 - 10
 - 11
 - 12
 - 13
 - 14
 - 15
 - 16
 - 17
 - 18
 - 19
 - 20
 - 21
 - 22
 - 23
 - 24
 - 25
 - 26
 - 27
 - 28
 - 29
 - 30
 - 31
 - 32
 - 33
 - 34
 - 35
 - 36
 - 37
 - 38
 - 39
 - 40
 - 41
 - 42
 - 43
 - 44
 - 45
 - 46
 - 47
 - 48
 - 49
 - 50
 - 51
 - 52
 - 53
 - 54
 - 55
 - 56
 - 57
 - 58
 - 59
 - 60
22. Kim, H.J., et al., *Permutation tests for joinpoint regression with applications to cancer rates*. Stat Med, 2000. **19**(3): p. 335-51.
23. Green, A. and C.C. Patterson, *Trends in the incidence of childhood-onset diabetes in Europe 1989-1998*. Diabetologia, 2001. **44 Suppl 3**: p. B3-8.
24. *Incidence and trends of childhood Type 1 diabetes worldwide 1990-1999*. Diabetic Medicine, 2006. **23**(8): p. 857-866.
25. Dahlquist, G., *Can we slow the rising incidence of childhood-onset autoimmune diabetes? The overload hypothesis*. Diabetologia, 2006. **49**(1): p. 20-4.
26. Haynes, A., et al., *Perinatal risk factors for childhood Type 1 diabetes in Western Australia--a population-based study (1980-2002)*. Diabet Med, 2007. **24**(5): p. 564-70.
27. Dahlquist, G.G., C. Patterson, and G. Soltesz, *Perinatal risk factors for childhood type 1 diabetes in Europe. The EURODIAB Substudy 2 Study Group*. Diabetes Care, 1999. **22**(10): p. 1698-702.
28. Dahlquist, G.G., L. Nystrom, and C.C. Patterson, *Incidence of type 1 diabetes in Sweden among individuals aged 0-34 years, 1983-2007: an analysis of time trends*. Diabetes Care, 2011. **34**(8): p. 1754-9.
29. Hjern, A., U. Soderstrom, and J. Aman, *East Africans in Sweden have a high risk for type 1 diabetes*. Diabetes Care, 2012. **35**(3): p. 597-8.
30. Karvonen, M., et al., *Incidence of childhood type 1 diabetes worldwide. Diabetes Mondiale (DiaMond) Project Group*. Diabetes Care, 2000. **23**(10): p. 1516-26.
31. Hall, V., et al., *Diabetes in Sub Saharan Africa 1999-2011: epidemiology and public health implications. A systematic review*. BMC Public Health, 2011. **11**: p. 564.
32. <http://www.idf.org/diabetesatlas/5e/africa>.
33. Majaliwa, E.S., et al., *Type 1 diabetes mellitus in the African population: epidemiology and management challenges*. Acta Biomed, 2008. **79**(3): p. 255-9.
34. Monabeka, H.G., A. Mbika-Cardorelle, and G. Moyon, *[Ketoacidosis in children and teenagers in Congo]*. Sante, 2003. **13**(3): p. 139-41.
35. Rwiza, H.T., A.B. Swai, and D.G. McLarty, *Failure to diagnose diabetic ketoacidosis in Tanzania*. Diabet Med, 1986. **3**(2): p. 181-3.
36. Hjern, A. and U. Soderstrom, *Parental country of birth is a major determinant of childhood type 1 diabetes in Sweden*. Pediatr Diabetes, 2008. **9**(1): p. 35-9.
37. Cataldo, F., *Early onset of Type 1 diabetes mellitus in immigrant children from developing countries to Western Europe: the role of environmental factors?* J Endocrinol Invest, 2005. **28**(6): p. 574-5.
38. Soderstrom, U., J. Aman, and A. Hjern, *Being born in Sweden increases the risk for type 1 diabetes - a study of migration of children to Sweden as a natural experiment*. Acta Paediatr, 2012. **101**(1): p. 73-7.
39. Podar, T., et al., *Risk of childhood type 1 diabetes for Russians in Estonia and Siberia*. Int J Epidemiol, 1993. **22**(2): p. 262-7.
40. Patrick, S.L., et al., *IDDM incidence in a multiracial population. The Hawaii IDDM Registry, 1980-1990*. Diabetes Care, 1997. **20**(6): p. 983-7.
41. Ji, J., et al., *Ethnic differences in incidence of type 1 diabetes among second-generation immigrants and adoptees from abroad*. J Clin Endocrinol Metab, 2010. **95**(2): p. 847-50.
42. Muntoni, S., et al., *Incidence of insulin-dependent diabetes mellitus among Sardinian-heritage children born in Lazio region, Italy*. Lancet, 1997. **349**(9046): p. 160-2.
43. Neu, A., et al., *Diabetes incidence in children of different nationalities: an epidemiological approach to the pathogenesis of diabetes*. Diabetologia, 2001. **44 Suppl 3**: p. B21-6.
44. Zung, A., et al., *Type 1 diabetes in Jewish Ethiopian immigrants in Israel: HLA class II immunogenetics and contribution of new environment*. Hum Immunol, 2004. **65**(12): p. 1463-8.
45. Arnqvist, H.J., et al., *Difficulties in classifying diabetes at presentation in the young adult*. Diabet Med, 1993. **10**(7): p. 606-13.

- 1
2
3 46. Lynch, K.F., et al., *Context and disease when disease risk is low: the case of type 1 diabetes in*
4 *Sweden*. J Epidemiol Community Health, 2010. **64**(9): p. 789-95.
5
6
7
8
9

10 Figure legends

11
12 Figure 1 – Age-standardized type 1 diabetes incidence rate per 100,000 person-
13 years (ASR) among offspring of Swedes of immigrants in the age group (0-14), 1969-
14 2009, Sweden
15

16
17 Figure 2 - Age-standardized type 1 diabetes incidence rate per 100,000 person-years
18 (ASR) among offspring of Swedes of immigrants in the age group (15-30), 1969-
19 2009, Sweden
20

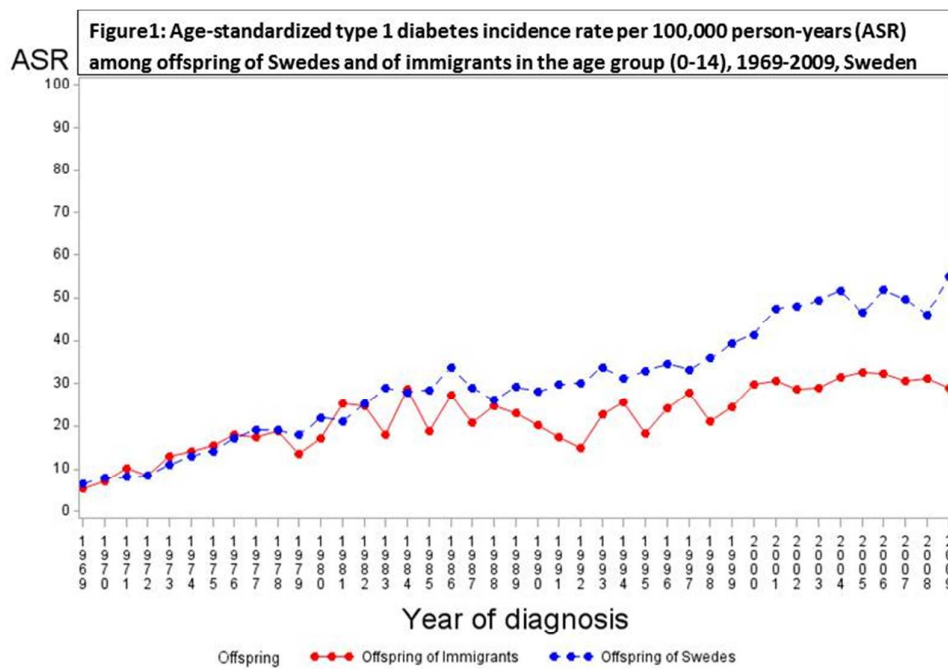
21
22 Figure 3a – Incidence of type 1 diabetes by age at diagnosis (0-30 years) and birth
23 cohorts 1960-2009 among offspring of Swedes in Sweden
24

25
26 Figure 3b - – Incidence of type 1 diabetes by age at diagnosis (0-30 years) and birth
27 cohorts 1960-2009 among offspring of Immigrants in Sweden
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

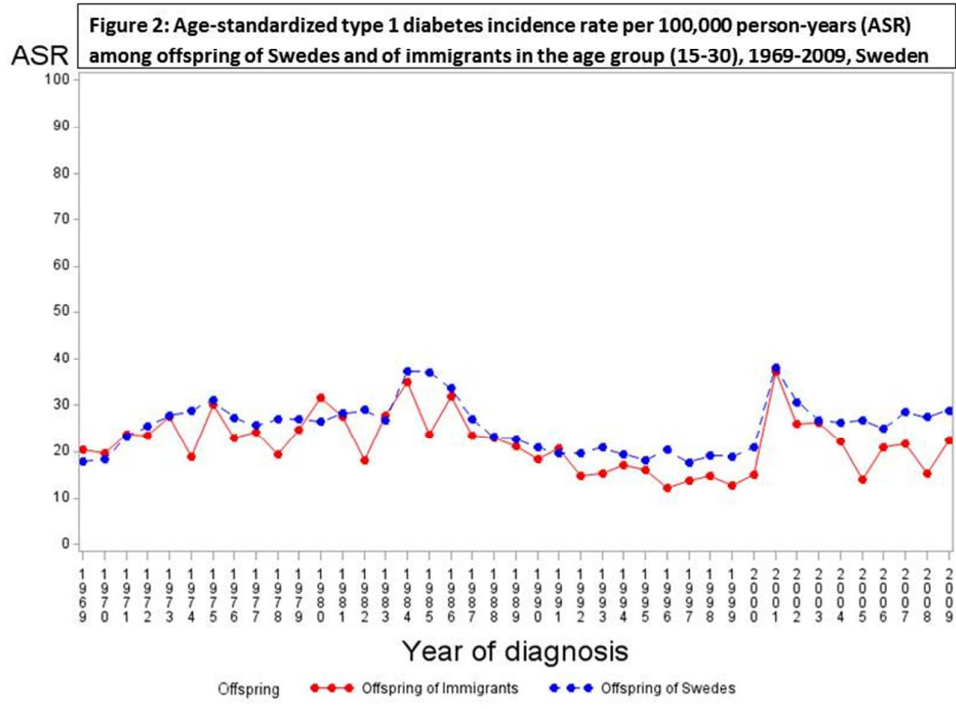
For peer review only

Figures



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

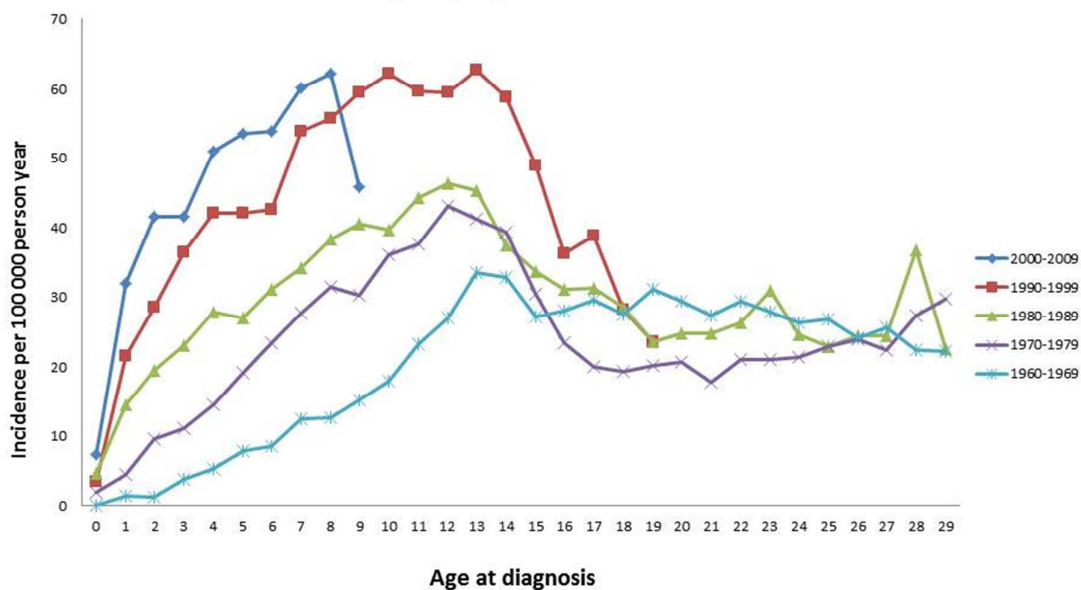
For peer review only



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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

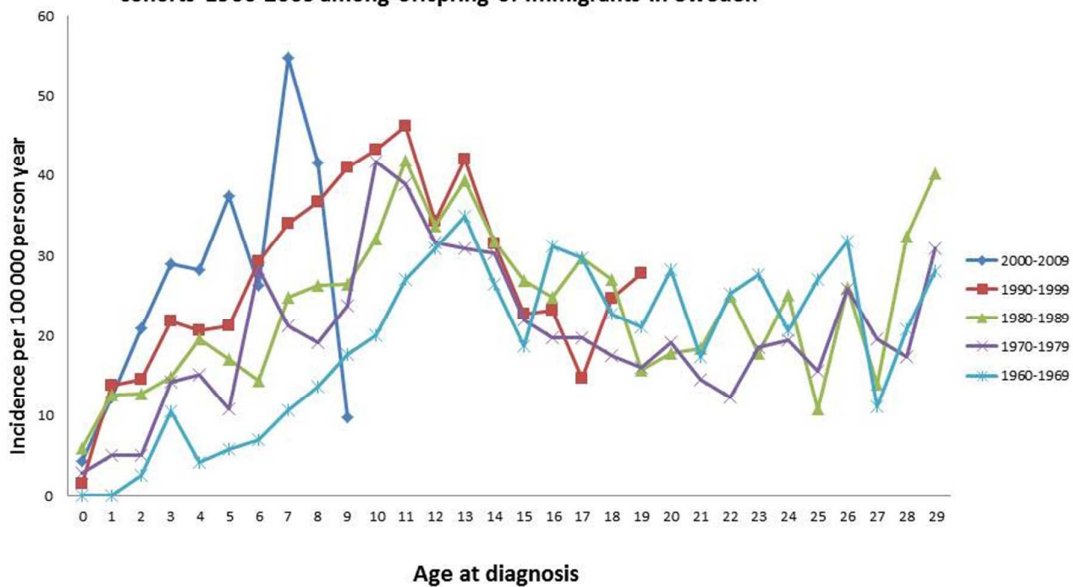


Table 1: Incidence rate ratio (IRR) and 95% confidence interval (CI) of type 1 diabetes among children aged (0-14) and young adults aged (15-30) by sex and parental country of birth, Sweden, 1969–2009.

Parental immigration Status	Male (0-14)				Female (0-14)			
	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)

For peer review only

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.

Parental country of birth	IRR* (95 % CI)											
	Male						Female					
	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.

IRR 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.

Parental Migration Status	Male (0-13)				Female (0-13)			
	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.

Parental country of birth	IRR* (95 % CI)											
	Male						Female					
	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)
Europe												
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.

Parental country of birth	IRR* (95 % CI)											
	Male						Female					
	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.

1
2
3 **The trends and the risk of type 1 diabetes over the past 40 years: an analysis**
4 **by birth cohorts and by parental migration background in Sweden**
5
6
7

8
9 Hozan Ismael Hussen^{*1}, Martina Persson², Tahereh Moradi^{1,3}
10
11

12
13
14 ¹Department of Environmental Medicine, Division of Epidemiology, Unit of
15 Cardiovascular Epidemiology, Karolinska Institutet, Stockholm, Sweden.
16

17
18 ²Department of Medicine, Clinical Epidemiology Unit, Karolinska University Hospital,
19 Stockholm, Sweden.
20

21
22 ³Centre for Epidemiology and Social Medicine, Health Care Services, Stockholm
23 County Council, Sweden
24
25
26
27

28
29 ***Corresponding author:**
30

31 Hozan Ismael Hussen, MD
32

33 Department of Environmental Medicine, Division of Epidemiology,
34

35 Unit of Cardiovascular Epidemiology, Karolinska Institutet
36

37 Nobels väg 13, Box 210,
38

39 SE-171 77 Stockholm, Sweden
40

41 Phone: +46-8-524 800 55
42

43 Fax: +46-8-31 39 36
44

45 E-mail: hozan.hussen@ki.se
46
47
48
49

50
51 **Word count**
52

53 Main text 3737
54
55
56
57
58
59
60

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

1
2
3 heterogeneous population, there is a need to explore if the risk of type 1 diabetes
4 varies by specific parental country or region of birth.
5
6

7
8 In the present study, we used Swedish nation-wide data collected over 40 years to
9 investigate the trend and the risk of developing type 1 diabetes in offspring of
10 immigrants by specific paternal and maternal migration background and by birth
11 cohorts. Since the incidence of type 1 diabetes varies with sex and age [9, 10], the
12 analyses were stratified by offspring sex and age.
13
14
15
16
17
18
19

20 **METHODS**

21 *Database*

22
23 We used information from a newly established, nationwide dataset – The Migration
24 and Health Cohort (M&H Co.) [11], where data from national, longitudinal clinical,
25 health and socio - demographic registries have been compiled. This database was
26 built by individual record-linkage between more than fifteen Swedish national
27 registries to facilitate studies on diabetes, injuries, cancer, cardiovascular and
28 psychiatric diseases among immigrants and their descendants in Sweden. The
29 linkage was done using the Personal Identification Number (PIN), which is uniquely
30 assigned to each individual that have resided in Sweden for longer than one year
31 since 1947 [12]. The data used in this study are part of the M&H Co., including: 1)
32 The Swedish Total Population Register, which covers the entire population
33 registration in Sweden and is updated on a daily basis. The register contains
34 information on demographic variables, such as date and place of birth and data on
35 emigration and immigration [13]. 2) The Cause of Death Register, which contains
36 information on the date of death, the main and contributing causes of death [14]. 3)
37 The National Patient Register, including the Inpatient Register. It was established in
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 1964 but with national coverage since 1987 covering 85-95% of all diagnostic data
4
5 [15]. Since 2001, the Patient Register includes information on all registered
6
7 outpatient visits to specialist care and day visits to hospitals and covers about 80% of
8
9 all visits to the specialized outpatient care [16]. The Patient Register contains data on
10
11 the main diagnosis and up to eight secondary diagnoses [15, 16]. 4) The Multi-
12
13 Generation Register contains links between children and their parents via PINs for all
14
15 Swedish inhabitants born after 1931 who were alive in 1960 [17]. 5) The National
16
17 Population and Housing Censuses and longitudinal integration database for health
18
19 insurance and labor market studies (LISA), contains data on socio-economic,
20
21 occupational and demographic variables [18, 19].
22
23

24
25 The linkages between the registers have been completed by Statistics Sweden and
26
27 the National Board of Health and Welfare. To ensure confidentiality, the PINs have
28
29 been replaced by person-unique serial numbers and a key code is kept at Statistics
30
31 Sweden. The study was approved by one of the Regional Ethical Committees in
32
33 Stockholm, Sweden (Dnr. 2009/2033-32).
34
35

36 37 38 *Study cohort*

39
40 The study population comprised 3,794,477 (51.4%) males and 3,593,765 (48.6%)
41
42 females between 0 to 30 years of age, born and living in Sweden any time between
43
44 January 1st, 1969 and December 31st, 2009. We excluded individuals whose parents
45
46 had unknown information on country of birth and all individuals who had a history of
47
48 type 1 diabetes, before entry into the cohort. The final cohort included 7,098,790
49
50 individuals (3,641,304 (51.3%) males and 3,457,486 (48.7%) females) aged 0-30
51
52 years and born in Sweden.
53
54
55
56
57
58
59
60

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

1
2
3 group). For the trend and the birth cohort analyses, we pooled all offspring of
4
5 immigrants into one group.
6
7

8 9 *Statistical analysis*

10
11 We estimated Incidence rate ratios (IRRs) with 95% confidence intervals (CIs) using
12
13 Poisson regression models. The analyses were adjusted for age at follow-up (in 5
14
15 years intervals 0-4, 5-9, 10-14, 15-19, 20-24, and 25-30 years), calendar years of
16
17 follow-up (four categories: 1969-1978, 1979-1988, 1989-1998 and 1999-2009) and
18
19 education of the mother or father (classified into four levels: 0-9 years, 10-12 years,
20
21 13 years or more and unknown). All analyses were performed for females and males
22
23 separately. In addition, analyses were made separately for children (0-14 years) and
24
25 young adults (15-30 years) where we did not distinguish specific parental region or
26
27 country of birth. In further analyses, children and young adults (0-30 years) were
28
29 pooled together as one category to allow reasonable statistical power for analyses by
30
31 specific maternal and paternal regions or country of birth to test the hypothesis that
32
33 the mother's and the father's background would affect the offspring's risk of type 1
34
35 diabetes differently. We also analyzed risk of type 1 diabetes in children with both
36
37 mother and father born in the same country/region. Those with parents from different
38
39 regions or from Sweden were categorized as a mixed group.
40
41
42
43
44

45 Since we had no specific ICD codes before 1997 to distinguish between type 1 and
46
47 type 2 diabetes, we repeated the analysis and confined our cohort to individuals
48
49 living in Sweden between 1997 and 2009 where we could strictly identify type 1
50
51 diabetes according to ICD-10.
52

53 For the trend analysis, we further calculated age-standardized rates (ASRs), by
54
55 parental migration background for both children (0-14 years) and young adults (15-
56
57
58
59
60

1
2
3 30 years), by dividing number of new cases with the estimated numbers of person-
4 years at risk in 5-years age categories using the world population as standard [20].
5
6
7 ASRs were directly calculated to ensure comparability and to adjust for differences in
8
9 age in the study population, in each of the age groups 0–4, 5–9, 10–14, 15–19, 20–
10
11 24, and 25–30 years. We reported ASR in unit of per 100,000 person years.
12
13
14 The Joint point regression analyses were performed to evaluate trends of type 1
15
16 diabetes in both offspring to immigrants and offspring to Swedes and in both age
17
18 groups [21, 22]. Annual percent change (APC) was estimated, to describe and test
19
20 the statistical significance of the trends. The null hypothesis in this analysis is that the
21
22 trend in incidence rates is the same over time. We used Statistical Analysis System
23
24 (SAS) version 9.3 for all the analysis.
25
26
27
28
29

30 RESULTS

31
32 On average, the age of onset of type 1 diabetes was similar in offspring of immigrants
33
34 as in offspring of Swedes (mean \pm SD; offspring of immigrants 14.31 \pm 7.70, offspring
35
36 of swedes 15.47 \pm 7.99).

37
38 Over the study period (1969 -2009), we observed a significant increasing trend for
39
40 incidence of type 1 diabetes based on joint point regression analyses among
41
42 offspring below 15 years of age born to native Swedes and to immigrants (offspring
43
44 to Swedes: APC= 3.9, p values<0.001 and offspring to immigrants: APC= 2.2, p
45
46 values<0.001 Figure 1). In contrast, no increase or a slight decreasing trend was
47
48 observed among young individuals between 15 to 30 years of age regardless of
49
50 parental migration background (offspring to Swedes: APC= -0.0, p= 0.9 and offspring
51
52 to immigrants: APC= -0.7, p value= 0.08 , Figure 2).
53
54
55
56
57
58
59
60

1
2
3 The birth cohort analysis revealed a shift towards lower age at onset in individuals
4 below 15 years of age in both offspring of Swedes and in offspring of immigrants
5 (Figures 3a and 3b).
6
7

8
9 Compared with offspring of Swedish-born parents, boys and girls (0 to 14 years) with
10 a foreign-born mother or father had about 30% lower IRR in the multivariable
11 analyses adjusted for age, calendar period and parental education. Among boys and
12 girls with both parents born abroad, corresponding risk reductions were about a 40%
13 (Table 1). The results from the sensitivity analysis, where we repeated the analysis
14 and confined our cohort to individuals born in Sweden between 1997 and 2009, were
15 similar to the results of the entire cohort (Supplementary Table 1S).
16
17
18
19
20
21
22
23
24

25 Compared with young adults (15 to 30 years) of Swedish-born parents, young adults
26 with only one parent born abroad had about 15% to 20% lower IRR of type 1
27 diabetes and among young adults with both parents born abroad, the risks were
28 reduced by 25% to 30% (Table 1).
29
30
31
32
33

34 Next, we investigated risks of type 1 diabetes by parental region of birth. Compared
35 with young offspring (0-30 years) of Swedish-born parents, male and female offspring
36 of mothers or fathers born in Africa had about 20% to 40% higher IRR of type 1
37 diabetes (Table 2). The increased risk of type 1 diabetes was more prominent among
38 individuals whose mothers or fathers were born in Eastern Africa. With a few
39 exceptions, male and female offspring of mothers or fathers born in Asia, Europe
40 (except Northern Europe), Latin America and Northern America (except female
41 offspring to fathers from Northern America) had between 35% to 65% lower IRR than
42 male and female offspring of Swedish-born parents (Table 2). These reductions in
43 risks became even more prominent when we confined the analyses to parents born
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 in the same region (Table 2). Offspring of Finnish immigrants and rest of Northern
4
5 Europe had almost similar risks compared with offspring of Swedes (Table 2).
6

7 The results from the sensitivity analysis, where we repeated the analysis and
8
9 confined our cohort to individuals born in Sweden between 1997 and 2009 (limited to
10
11 children ages 0 to 13) , were similar to the results of the entire cohort for the same
12
13 age category (Supplementary Tables 2Sa and 2Sb).
14
15

16 17 18 **DISCUSSION** 19

20 In this nation-wide cohort study of Sweden-born children and young adults, we
21
22 observed a continuing increase of type 1 diabetes in individuals younger than 15
23
24 years of age over the past decades. This increase was, however, less evident among
25
26 offspring of immigrants than in offspring of native Swedes. In contrast, no change in
27
28 trend was observed among young individuals between 15 to 30 years of age, and
29
30 regardless of parental country of birth.
31
32

33 An interesting finding in the present study was an almost identical pattern with a shift
34
35 towards lower age at onset of type 1 diabetes by younger birth cohorts in both
36
37 offspring of foreign born parents and Swedes.
38
39

40 Over the past decades, a rapid rise in the incidence of type 1 diabetes has been
41
42 demonstrated [23, 24]. The finding of an increased incidence rate of type 1 diabetes
43
44 between 1969 and 2009 among individuals below 15 years of age, and a decreasing
45
46 or steady incidence rate among young adults, is in line with previous studies from
47
48 Sweden [6] and other parts of the world [7]. The observed increasing trend over time
49
50 in our study might be due to the quality of National patient Register over time and not
51
52 covering all of Sweden for the entire period of our study. This register became nation-
53
54 wide in 1987. However, the sharpest increase in incidence observed in our study
55
56
57
58
59
60

1
2
3 among individuals below 15 years of age is after around 1997 when the Inpatient
4 Register had full coverage and when the ICD-10 were able to disentangle different
5 types of diabetes.
6
7
8

9
10 The finding of an almost identical pattern with a shift towards lower age at onset of
11 type 1 diabetes in both offspring of foreign born parents and Swedes indicates the
12 exposure to similar environmental factors in both groups. It has been hypothesized
13 that this developments is due to increased exposures in early life to factors that
14 initiate and/ or accelerate beta cell destruction, including viral infections, rapid
15 postnatal growth and nutritional factors [25, 26]. In addition, perinatal factors such as
16 blood-group incompatibility, high maternal age, preeclampsia and caesarean section
17 delivery have been shown to be associated with increased incidence of childhood
18 type 1 diabetes [27]. Similar findings of a shift towards younger age at diagnosis and
19 a declining incidence of type 1 diabetes among young adults aged 15 to 34 years
20 were also observed in other studies from Sweden, using the two nation-wide
21 prospectively collected research register, the Swedish Childhood Diabetes Register
22 and the Diabetes Incidence Study in Sweden [10, 28]. The shift towards younger age
23 at diagnosis may be due to risk factors accelerating the disease process.
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39

40 We further found that offspring with one or two parents born abroad had a reduced
41 risk of type 1 diabetes compared with offspring to Sweden-born parents. The
42 reduction in risk was similar between sexes and was more apparent among
43 individuals where both parents were foreign born. Stratification by specific parental
44 region/country of birth, however, revealed that this reduction was confined to
45 offspring of immigrants from Asia, Latin and North America, South-, West- and East
46 Europe. In contrast, the IRR for type 1 diabetes was increased in individuals with
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 African parents, particularly so if the parents were born in Eastern or Northern Africa.
4
5 The observed increased risk among offspring of Africans in this study, in line with a
6
7 previous Swedish register study [29] is also observed in Swedish residents born in
8
9 Africa [8, 29]. It is unclear if these findings reflect a high risk of type 1 diabetes in the
10
11 countries of origin, thus rating Eastern and Northern Africa as the areas with the
12
13 highest incidence of type 1 diabetes in the world. At the same time we should keep in
14
15 mind that the population of immigrants in Sweden may not represent the population
16
17 of countries of origin.
18
19

20
21 The reported low number of type 1 diabetes diagnoses in Africa [30] is most likely to
22
23 be underestimated due to lack of diagnostic measures [31], and high mortality
24
25 among uncontrolled type 1 diabetes cases as a result of limited access to insulin
26
27 treatment [32]. Moreover, priorities are mostly given to the high burden of
28
29 communicable diseases in African countries [33], especially in busy emergency
30
31 hospitals. As a consequence, children with diabetic ketoacidosis at the time of
32
33 diagnosis [34] could be misdiagnosed as cerebral malaria or meningitis [35] which
34
35 would also lead to an underestimation of type 1 diabetes cases. The observed higher
36
37 risk in African offspring in the present study and the increased risk of type 1 diabetes
38
39 in Swedish residents born in Africa [8] might be due to genetic propensity interacting
40
41 with environmental factors in the new home country.
42
43

44
45 Offspring of Swedish residents born in Asia, Latin and North America, South-, West-
46
47 and East Europe retained the low risk profile were recently observed in young
48
49 immigrants in Sweden born in these areas [8]. This risk reduction was independent of
50
51 maternal or paternal birth region but was stronger if both parents were born in the
52
53 same region.
54
55
56
57
58
59
60

1
2
3 The importance of parental country of birth for the risk of developing type 1 diabetes
4 has also been observed in other studies [36-39] and may indicate the role of genetic
5 factors [40, 41]. Children of Sardinian heritage (a high risk area), born and living in
6 Lazio (a low risk area) retained the high risk profile of Sardinia [42]. The risk for type
7 1 diabetes in children of Yugoslavian, Italian and Greek heritage in Germany was
8 closer to the reported incidence in those countries than in Germany [43]. However,
9 the importance of life style or environmental factors interacting with genetic factors
10 cannot be ruled out [44] as studies of immigration from regions with low to high
11 incidence of type 1 diabetes have been associated with increased incidence of type 1
12 diabetes [37].

13
14
15
16
17
18
19
20
21
22
23
24
25 The primary strength of our study is the nation-wide cohort design with nearly
26 complete follow-up of type 1 diabetes occurrence over several decades. Using a
27 unique PIN assigned to all Swedish citizens, we were able to correctly assess
28 exposure (parental country of birth) and thus avoiding misclassification bias.

29
30
31
32
33
34 We lacked specific ICD codes for type 1 diabetes in the earlier versions of ICD before
35 1997 (i.e. 8th and 9th version of ICD). However, the results of the sensitivity analysis
36 limited to only cases of type 1 diabetes according to ICD 10 for the years 1997 and
37 forward were similar to the results for the entire period of the study. But, in this
38 sensitivity analysis, we were only able to verify the results for children born between
39 1997 and 2009 (0 to 13 years old). Whereas, for the age groups over 15 years when
40 type 1 diabetes is more likely to be mixed with type 2 diabetes, we had no data.
41 However, the prevalence of type 2 diabetes is low in Sweden [45, 46] and other
42 northern European countries and most likely the majority of cases of diabetes
43 diagnosed before 30 years are true type 1 diabetes. While this may not be applicable
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 for offspring born to parents from other parts of the world with known high prevalence
4
5 of type 2 diabetes which may have led to overestimation of the true type 1 diabetes.
6

7
8 Our findings of a lower IRR of type 1 diabetes among children and young adults with
9
10 one or two foreign born parents, with the notable exception of offspring of African
11
12 immigrants, and the shifting of age at diagnosis towards younger age in both
13
14 offspring of Swedes and of immigrants highlight the important role of environmental
15
16 factors and its interaction with genetic background in the etiology of type 1 diabetes.
17

18 In order to further clarify potential pathophysiological mechanisms for the
19
20 development of type1 diabetes, further studies are needed with data on important
21
22 exposures such as viral infections in early life, nutritional habits and weight gain in
23
24 infancy. Moreover, studies on offspring of immigrants from African countries, in
25
26 particular from Eastern Africa, might improve our understanding on the etiology of the
27
28 disease.
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Acknowledgements

This work was supported by grants from The Ministry of Higher Education and Scientific Research-Kurdistan Regional Government/Iraq, and the Department of Environmental Medicine, Karolinska institutet, Stockholm, Sweden.

The authors thank Professor Sven Cnattingius, for his critical review of the manuscript.

The authors appreciate the help from Statistics Sweden and the National Board of Health and Welfare, which provided them with data

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.

REFERENCES

1. Dabelea, D., *The accelerating epidemic of childhood diabetes*. Lancet, 2009. **373**(9680): p. 1999-2000.
2. Berhan, Y., et al., *Thirty years of prospective nationwide incidence of childhood type 1 diabetes: the accelerating increase by time tends to level off in Sweden*. Diabetes, 2011. **60**(2): p. 577-81.
3. Kondrashova, A., et al., *A six-fold gradient in the incidence of type 1 diabetes at the eastern border of Finland*. Ann Med, 2005. **37**(1): p. 67-72.
4. Pitkaniemi, J., et al., *Increasing incidence of Type 1 diabetes--role for genes?* BMC Genet, 2004. **5**: p. 5.
5. Hyttinen, V., et al., *Genetic liability of type 1 diabetes and the onset age among 22,650 young Finnish twin pairs: a nationwide follow-up study*. Diabetes, 2003. **52**(4): p. 1052-5.
6. Pundziute-Lycka, A., et al., *The incidence of Type I diabetes has not increased but shifted to a younger age at diagnosis in the 0-34 years group in Sweden 1983-1998*. Diabetologia, 2002. **45**(6): p. 783-91.
7. Weets, I., et al., *The incidence of type 1 diabetes in the age group 0-39 years has not increased in Antwerp (Belgium) between 1989 and 2000: evidence for earlier disease manifestation*. Diabetes Care, 2002. **25**(5): p. 840-6.
8. Hussen, H.I., et al., *Type I diabetes among children and young adults: the role of country of birth, socioeconomic position and sex*. Pediatr Diabetes, 2012.
9. Karvonen, M., et al., *Sex difference in the incidence of insulin-dependent diabetes mellitus: an analysis of the recent epidemiological data*. World Health Organization DIAMOND Project Group. Diabetes Metab Rev, 1997. **13**(4): p. 275-91.
10. Ostman, J., et al., *Gender differences and temporal variation in the incidence of type 1 diabetes: results of 8012 cases in the nationwide Diabetes Incidence Study in Sweden 1983-2002*. J Intern Med, 2008. **263**(4): p. 386-94.
11. Beiki, O., B. Stegmayr, and T. Moradi, *Country reports: Sweden*, in *Migration-sensitive Cancer Registration in Europe* O. Razum, et al., Editors. 2011, Lang p. 106-123.
12. Ludvigsson, J.F., et al., *The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research*. Eur J Epidemiol, 2009. **24**(11): p. 659-67.
13. Johannesson, I., *The total population register of statistics Sweden. New possibilities and better quality*. Statistics Sweden: Örebro. 2002.
14. Socialstyrelsen, *Causes of death, The National Board of Health and Welfare, CENTRE FOR EPIDEMIOLOGY*. Official Statistics of Sweden, 2007.
15. Ludvigsson, J.F., et al., *External review and validation of the Swedish national inpatient register*. BMC Public Health, 2011. **11**: p. 450.
16. Socialstyrelsen. *Kvalitet och innehåll i patientregistret*. 2009 [cited 2010 08-05]; Available from: www.socialstyrelsen.se, The National Board of Health and Welfare.
17. *The Multi-Generation Registry. Bakgrundsfakta till befolknings-och välfärdstatistik*. Statistiska Centralbyrån: Örebro; 2001.
18. Statistics_Sweden. *Folk- och bostadsräkningar, FoB*. 2010 [cited 2010 02-25]; Available from: www.scb.se.
19. Socialstyrelsen. *Longitudinal integration database for health insurance and labour market studies (LISA by Swedish acronym)*. 2010 [cited 2010 08-10]; Available from: www.socialstyrelsen.se.
20. Omar B. Ahmad, C.B.-P., Alan D. Lopez, Christopher JL Murray, Rafael Lozano, Mie Inoue, *AGE STANDARDIZATION OF RATES: A NEW WHO STANDARD*. GPE Discussion Paper Series: No.31, EIP/GPE/EBD, World Health Organization 2001.
21. *Statistical Research and Applications Branch NCI. Joinpoint regression program*. 2008. **Version 3.3.1**.

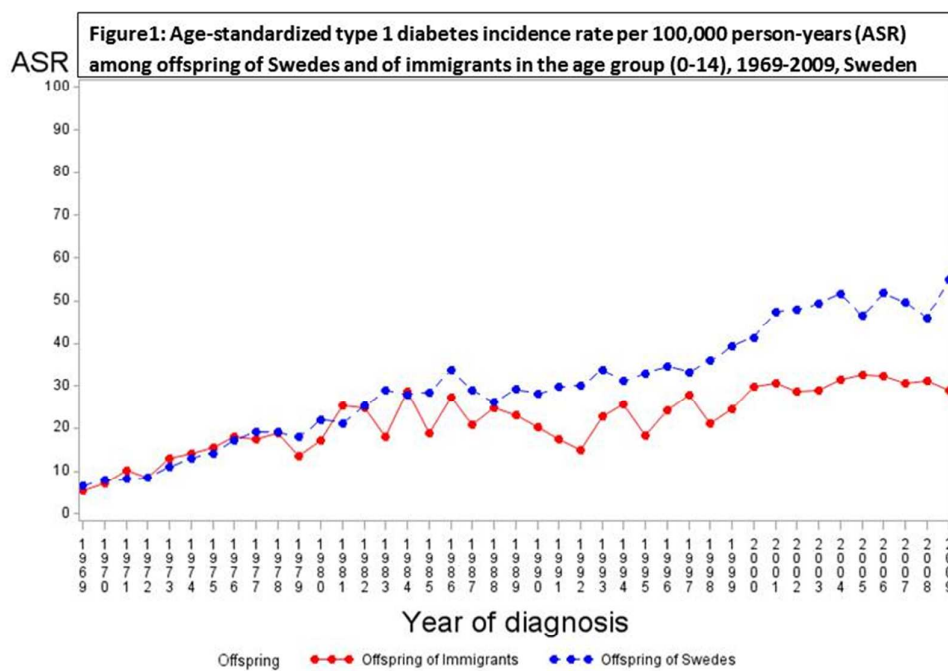
- 1
 - 2
 - 3
 - 4
 - 5
 - 6
 - 7
 - 8
 - 9
 - 10
 - 11
 - 12
 - 13
 - 14
 - 15
 - 16
 - 17
 - 18
 - 19
 - 20
 - 21
 - 22
 - 23
 - 24
 - 25
 - 26
 - 27
 - 28
 - 29
 - 30
 - 31
 - 32
 - 33
 - 34
 - 35
 - 36
 - 37
 - 38
 - 39
 - 40
 - 41
 - 42
 - 43
 - 44
 - 45
 - 46
 - 47
 - 48
 - 49
 - 50
 - 51
 - 52
 - 53
 - 54
 - 55
 - 56
 - 57
 - 58
 - 59
 - 60
22. Kim, H.J., et al., *Permutation tests for joinpoint regression with applications to cancer rates*. Stat Med, 2000. **19**(3): p. 335-51.
23. Green, A. and C.C. Patterson, *Trends in the incidence of childhood-onset diabetes in Europe 1989-1998*. Diabetologia, 2001. **44 Suppl 3**: p. B3-8.
24. *Incidence and trends of childhood Type 1 diabetes worldwide 1990-1999*. Diabetic Medicine, 2006. **23**(8): p. 857-866.
25. Dahlquist, G., *Can we slow the rising incidence of childhood-onset autoimmune diabetes? The overload hypothesis*. Diabetologia, 2006. **49**(1): p. 20-4.
26. Haynes, A., et al., *Perinatal risk factors for childhood Type 1 diabetes in Western Australia--a population-based study (1980-2002)*. Diabet Med, 2007. **24**(5): p. 564-70.
27. Dahlquist, G.G., C. Patterson, and G. Soltesz, *Perinatal risk factors for childhood type 1 diabetes in Europe. The EURODIAB Substudy 2 Study Group*. Diabetes Care, 1999. **22**(10): p. 1698-702.
28. Dahlquist, G.G., L. Nystrom, and C.C. Patterson, *Incidence of type 1 diabetes in Sweden among individuals aged 0-34 years, 1983-2007: an analysis of time trends*. Diabetes Care, 2011. **34**(8): p. 1754-9.
29. Hjern, A., U. Soderstrom, and J. Aman, *East Africans in Sweden have a high risk for type 1 diabetes*. Diabetes Care, 2012. **35**(3): p. 597-8.
30. Karvonen, M., et al., *Incidence of childhood type 1 diabetes worldwide. Diabetes Mondiale (DiaMond) Project Group*. Diabetes Care, 2000. **23**(10): p. 1516-26.
31. Hall, V., et al., *Diabetes in Sub Saharan Africa 1999-2011: epidemiology and public health implications. A systematic review*. BMC Public Health, 2011. **11**: p. 564.
32. <http://www.idf.org/diabetesatlas/5e/africa>.
33. Majaliwa, E.S., et al., *Type 1 diabetes mellitus in the African population: epidemiology and management challenges*. Acta Biomed, 2008. **79**(3): p. 255-9.
34. Monabeka, H.G., A. Mbika-Cardorelle, and G. Moyen, *[Ketoacidosis in children and teenagers in Congo]*. Sante, 2003. **13**(3): p. 139-41.
35. Rwiza, H.T., A.B. Swai, and D.G. McLarty, *Failure to diagnose diabetic ketoacidosis in Tanzania*. Diabet Med, 1986. **3**(2): p. 181-3.
36. Hjern, A. and U. Soderstrom, *Parental country of birth is a major determinant of childhood type 1 diabetes in Sweden*. Pediatr Diabetes, 2008. **9**(1): p. 35-9.
37. Cataldo, F., *Early onset of Type 1 diabetes mellitus in immigrant children from developing countries to Western Europe: the role of environmental factors?* J Endocrinol Invest, 2005. **28**(6): p. 574-5.
38. Soderstrom, U., J. Aman, and A. Hjern, *Being born in Sweden increases the risk for type 1 diabetes - a study of migration of children to Sweden as a natural experiment*. Acta Paediatr, 2012. **101**(1): p. 73-7.
39. Podar, T., et al., *Risk of childhood type 1 diabetes for Russians in Estonia and Siberia*. Int J Epidemiol, 1993. **22**(2): p. 262-7.
40. Patrick, S.L., et al., *IDDM incidence in a multiracial population. The Hawaii IDDM Registry, 1980-1990*. Diabetes Care, 1997. **20**(6): p. 983-7.
41. Ji, J., et al., *Ethnic differences in incidence of type 1 diabetes among second-generation immigrants and adoptees from abroad*. J Clin Endocrinol Metab, 2010. **95**(2): p. 847-50.
42. Muntoni, S., et al., *Incidence of insulin-dependent diabetes mellitus among Sardinian-heritage children born in Lazio region, Italy*. Lancet, 1997. **349**(9046): p. 160-2.
43. Neu, A., et al., *Diabetes incidence in children of different nationalities: an epidemiological approach to the pathogenesis of diabetes*. Diabetologia, 2001. **44 Suppl 3**: p. B21-6.
44. Zung, A., et al., *Type 1 diabetes in Jewish Ethiopian immigrants in Israel: HLA class II immunogenetics and contribution of new environment*. Hum Immunol, 2004. **65**(12): p. 1463-8.
45. Arnqvist, H.J., et al., *Difficulties in classifying diabetes at presentation in the young adult*. Diabet Med, 1993. **10**(7): p. 606-13.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

46. Lynch, K.F., et al., *Context and disease when disease risk is low: the case of type 1 diabetes in Sweden*. J Epidemiol Community Health, 2010. **64**(9): p. 789-95.

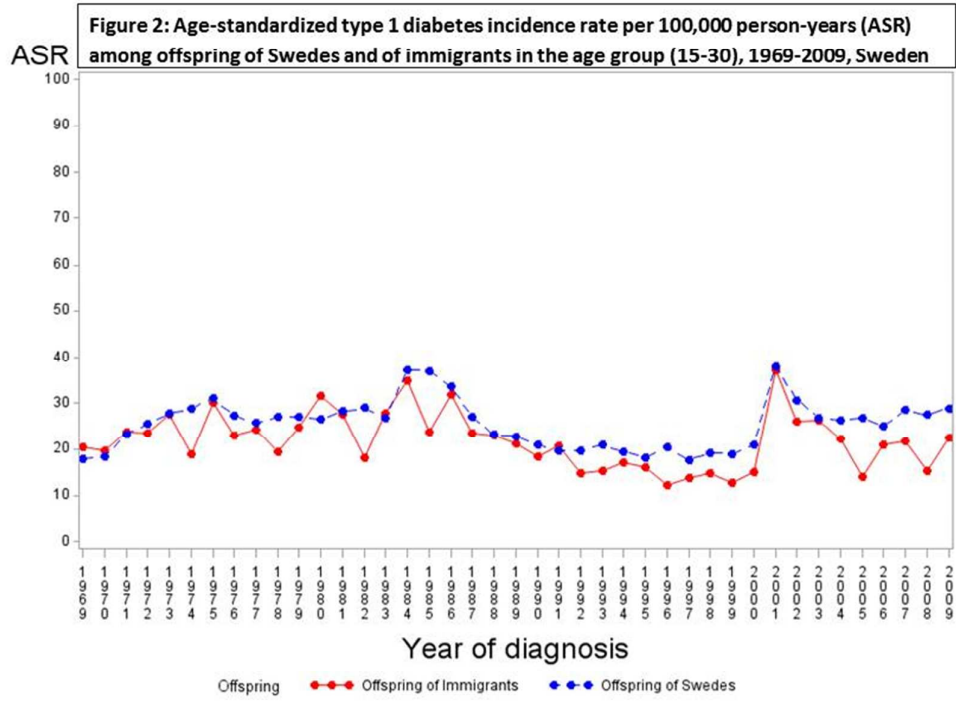
For peer review only

Figures



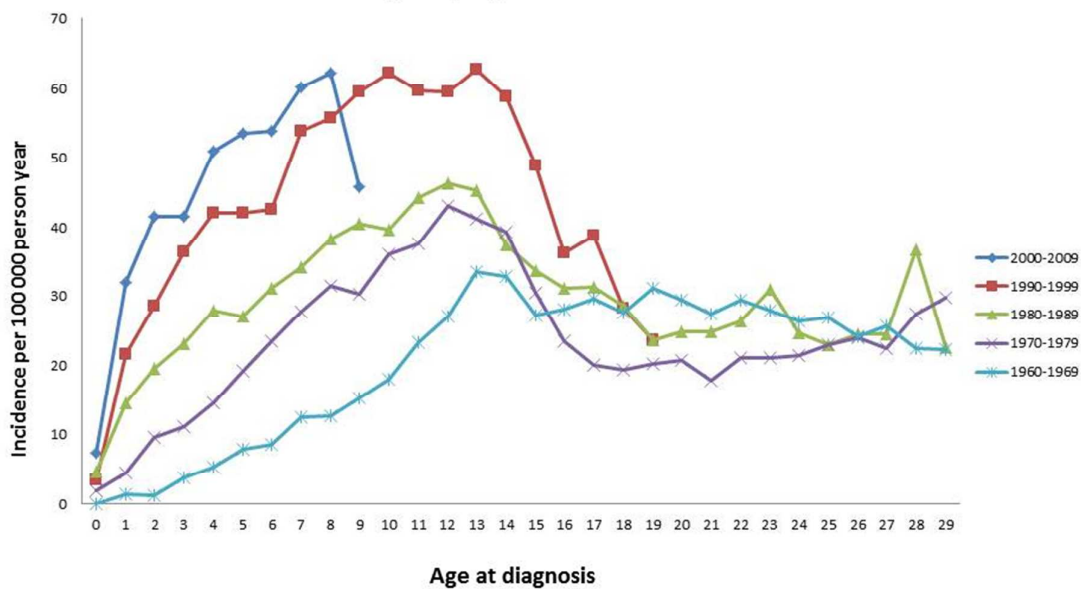
view only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



review only

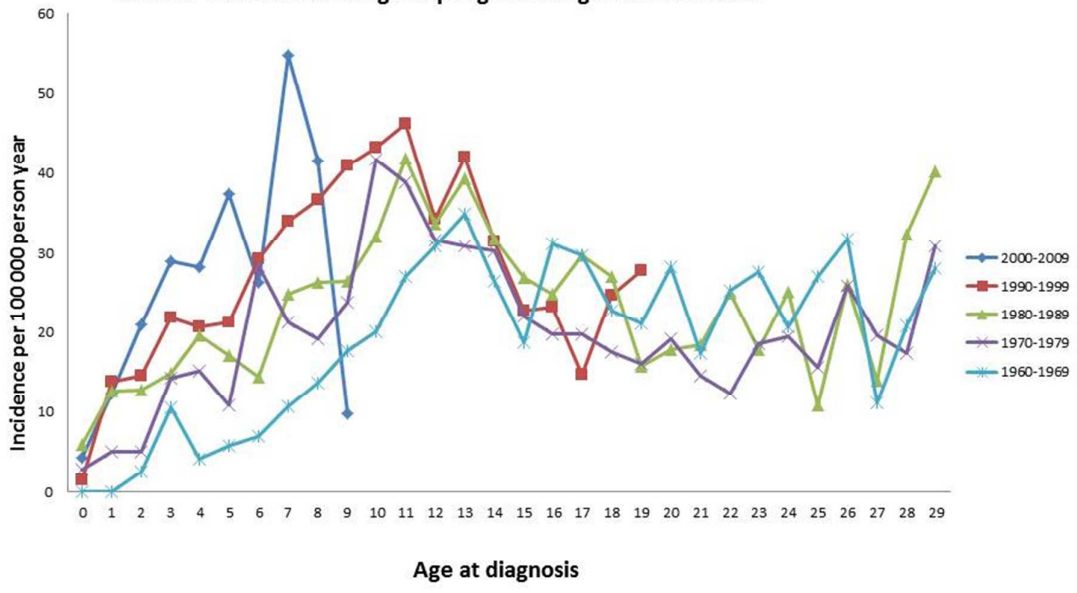
Figure 3.A. : Incidence of type 1 diabetes by age at diagnosis (0-30 years) and birth cohorts 1960-2009 among offspring of Swedes in Sweden



Review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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



review only

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.

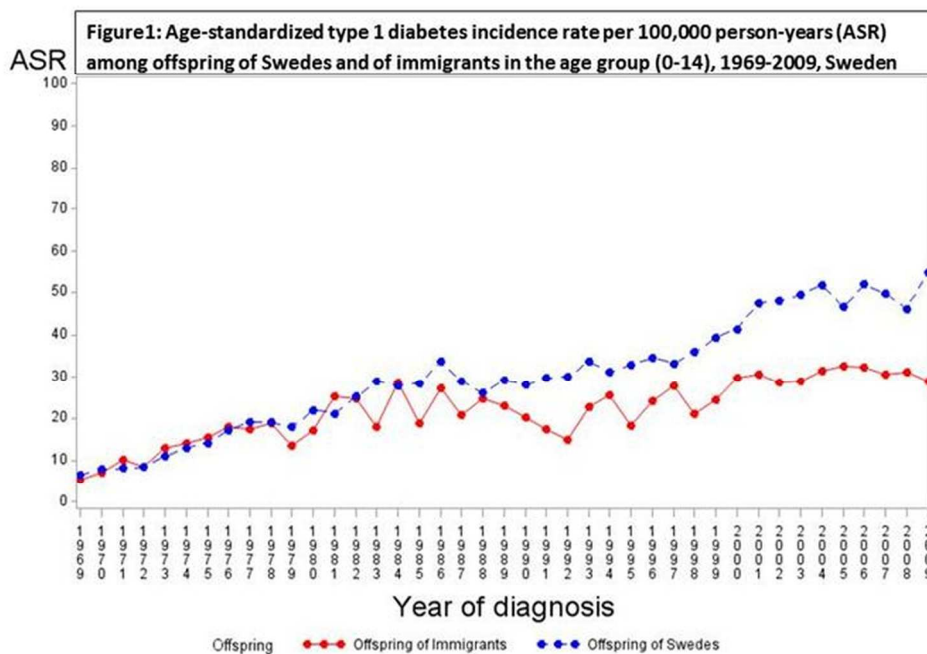
Parental country of birth	IRR* (95 % CI)											
	Male						Female					
	cases	Offspring of Mother	cases	Offspring of Father	Cases	Offspring of both Parents	cases	Offspring of Mother	cases	Offspring of Father	Cases	Offspring of both Parents
Sweden	16358	1	16358	1	16358	1	14044	1	14044	1	14044	1
Africa	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.

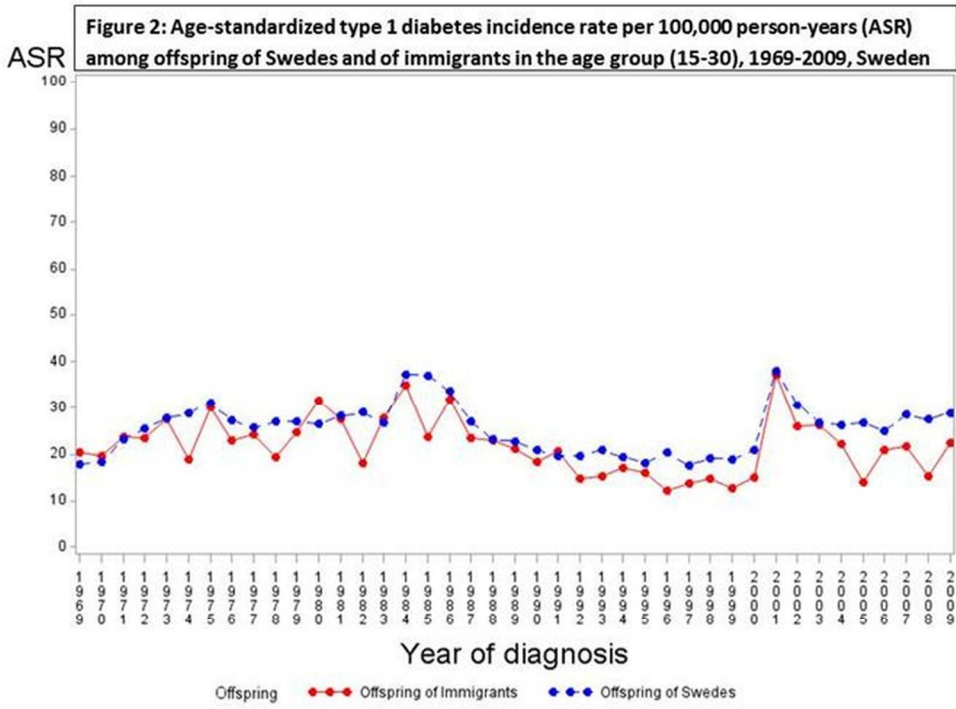
IRR significantly different from 1 are bolded.



126x90mm (300 x 300 DPI)

view only

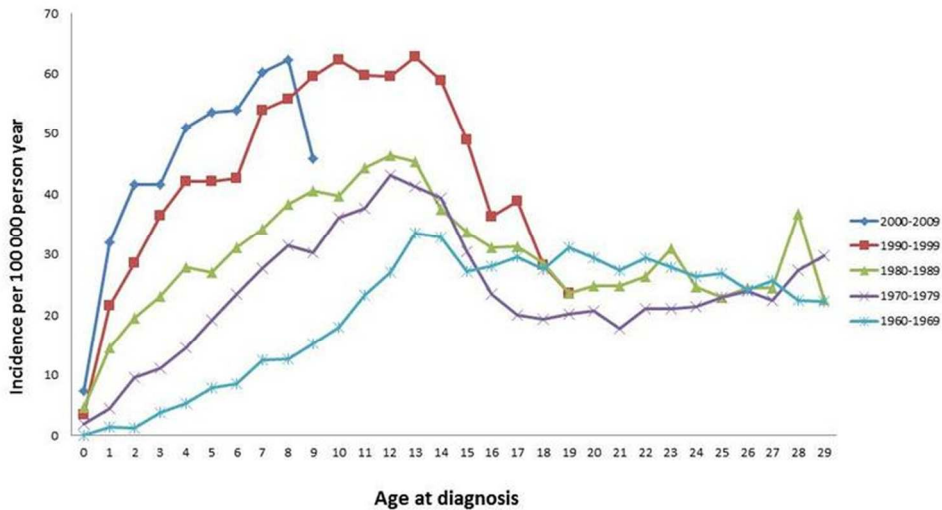
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



119x90mm (300 x 300 DPI)

View only

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

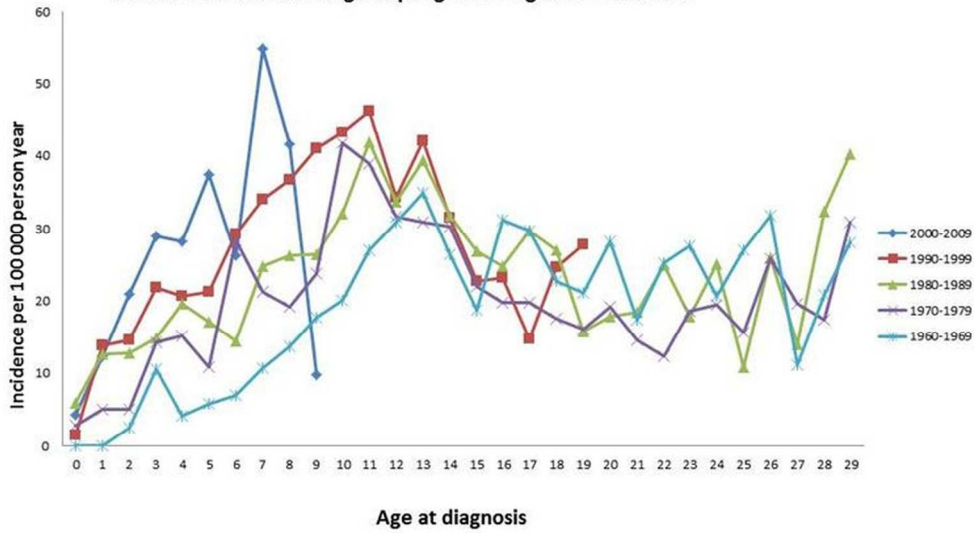


142x90mm (300 x 300 DPI)

review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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



149x90mm (300 x 300 DPI)

Review only