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The number of adults with incident type 1 diabetes phenotype in Iceland is half the number in children – A population based study

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ABSTRACT

Aims: Type1 diabetes is generally regarded as an abruptly presenting disease in children without family history.

The incidence and prevalence of insulin requiring diabetes in adults is unclear. The aim of this study was to clarify this issue by examining the epidemiology of type 1 diabetes diagnosed in adulthood in a country´s whole population.

Methods: Complete clinical and prescription data were used to identify cases of insulin requiring diabetes in the Icelandic population 18 years and older during the decade preceding February 2013. Health care databases and the insulin reimbursement system allowed for near 100% ascertainment of cases.

Results: Mean age at diagnosis was 32.1 years. The WHO age-adjusted incidence rate was 4.29/100.000 individuals and the point prevalence 0.10%. One fourth of cases were diagnosed after the age of forty. The male-to-female incidence rate ratio was 1.59. Almost 30% of cases presented with diabetic ketoacidosis and 40% had a positive family history.

Conclusion: Type 1 like diabetes commonly presents in adults and family history is not rare. One can expect one case of type 1 diabetes in adults for every two children diagnosed. These results emphasize the need to acknowledge the possibility of absolute insulin deficiency in any newly presenting adult with diabetes.

1. Introduction

Diabetes Mellitus is a serious global health problem currently reaching epidemic proportions. While the diagnosis rests on a simple measurement of blood glucose, accurate classification is often more involved. Type 1 diabetes diagnosed in childhood often has an abrupt onset with significant acute symptoms and thus easily identified but the progression of autoimmune diabetes is often more insidious in adults. Clinicians are thus commonly faced with considerable uncertainty when deciding whether the adult patient should be considered suffering from type 1 or type 2 diabetes. The results of the few studies that do exist indicate that the incidence of type 1 diabetes in adults might be higher than previously assumed and even similar to what is seen in children [1–4]. Existing studies record broad differences in the

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incidence and prevalence of type 1 diabetes across countries. Some studies hint at a bimodal incidence with a significant second peak in adulthood [1,5] and a recent study suggested that 4% of adult diabetes diagnosed before the age of 60 have type 1 diabetes [6]. Only a few have looked at older age groups. In fact, only one global systematic review on the epidemiology of type 1 diabetes in adults exists [2].

Variable clinical practice, lack of consensus on diagnostic criteria and variable access to immunological tests are factors making it hard for the everyday clinician to reach a correct diagnosis [2,3,7]. The obesity epidemic helps clouding the issue, the phenotype often superficially resembling type 2 diabetes. It is increasingly conceivable that cases of type 1 diabetes in adults are missed, resulting in a delay in appropriate treatment. This could potentially explain the observed increase in deaths in adults due to insulin deficiency related complications, such as diabetic ketoacidosis [8].

In order to ensure appropriate care, guidance and follow-up, physicians encountering adult patients with new diabetes need to be keenly aware of the possibility that their patient might suffer from near absolute insulin deficiency. Our aim was to explore how common this might be by studying the epidemiology of type 1 diabetes in adults in the whole population of Iceland where no such epidemiology study has been done previously. We had at our disposal complete medical records and prescribing information for all individuals receiving insulin in the whole country.

2. Materials and methods

Cases were identified from *The Icelandic Health Insurance* which keeps central records of reimbursement for insulin treatment on a nationwide basis. Insulin was available free of cost to everyone prescribed insulin before May 2013. Case ascertainment is therefore assumed to be near 100% as regards insulin requiring diabetes. Patients diagnosed with diabetes and who died during the first presentation of diabetes could however be missing if the diagnosis of ketoacidosis was also not mentioned in the case summary.

Each person in Iceland has a unique life-long personal identification number which allows perfect tracking in all official systems. Medical records for all individuals identified as having been prescribed insulin during the study period were gathered from hospitals, private endocrine clinics and family practitioners from around the country. The records were then scrutinized in order to confirm the information from the Icelandic Health Insurance.

We only considered cases diagnosed on or after the 18th birthday (the official definition of adulthood in our health system) and specifically sought data from medical records which might point to type 1 diabetes such as abrupt significant glycaemic presenting symptoms (e.g. polyuria, polydipsia, fatigue, weight loss, blurred vision, tingling in feet or hands), evidence of urinary ketones or clinical diabetic ketoacidosis, presence of antibodies associated with type 1 diabetes (glutamic acid decarboxylase; GAD, islet-cell antibodies; ICA). We also noted measurements of C-peptide, insulin, presence of other autoimmune diseases and family history and clinically judged need for permanent insulin treatment within 12 months from diagnosis.

Cases were excluded (not considered true type 1 diabetes) if features clearly suggesting type 2 diabetes were present (metabolic syndrome or obesity, absence of weight loss around time of diagnosis along with absence of ketonuria, improvement on a diet or oral medications and no need of insulin treatment during the first 12 months from diagnosis), gestational diabetes, secondary diabetes (e.g. secondary to chronic pancreatitis, hemochromatosis, steroid treatment) or if cases were diagnosed in childhood up to the age of 18. People of other nationality than Icelandic were excluded.

The study period was the decade spanning from February 2003 to February 2013 and during that time insulin was prescribed for 1454 individuals. At the end of December 2012 the whole population of Iceland counted 321.890 people. The cases were scrutinized according to the inclusion and exclusion criteria described above and three groups defined; type 1 diabetes (T1D), insulin-requiring-diabetes 1 (IR1) and insulin-requiring-diabetes 2 (IR2) based on the initiation of insulin treatment from the time of diagnosis; immediately, within six months (IR1) and from six to twelve months (IR2).

Population statistics in Iceland for the study period were supplied by *Statistics Iceland*, the Centre for official statistics in Iceland. Incidence rates per 100.000 persons years at risk and 95% CI were calculated using the Icelandic population, standardized for sex and age. Incidence rates per year during the study period were calculated for males and females and for age groups 18–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69 and 70–79 years olds. The age adjusted incidence rates were then calculated using the WHO standard world population [9].

Contingency tables and Fisher's exact tests were performed to assess whether an association could be found between the time of start of insulin treatment (from diagnosis, within six months or within 12 months) and the age at diagnosis, presence of weight loss, ketonuria, antibody positivity, family history and other autoimmune diseases. A logistic regression model was built incorporated with the same dependent variable (insulin at the time of diagnosis) and various predictors of interest (age at time of diagnosis, sex, presence of weight loss, ketonuria, family history and other autoimmune diseases). The likelihood ratio test was used to assess the significance of variables. We compared a full model with a reduced model without the age group term and the likelihood ratio test used showed that the age group term as a whole is significant. We then carried out the goodness of fit test that indicated that the model was appropriate. All tests were 2-sided. P values less than 0.05 were considered to be statistically significant. All confidence intervals used were 95% and were estimated using an approximated Poisson or binomial distribution. Statistical and graphic analyses and calculations were done using the MS-Office Excel 2007 and Stata/IC version 13.1. This study was approved by *The National Bioethics Committee of Iceland* (ref. nr. VSNb2012110013/03.07), *The Data Protection Authority of Iceland* (ref. nr. 2012111318ThS/-), *The Icelandic Health Insurance* and *The Medical Director at Landspitali, The National University Hospital of Iceland* (ref. nr. 16).

3. Results

Applying the criteria outlined in the section above a total of 349 cases were classified as T1D, IR1 or IR2, having been prescribed insulin during the time period from February 2003 to February 2013. This amounted to 24.0% of insulin-treated patients during that time period. Age at the time of diagnosis ranged from 18 to 72 years with a mean age of 30.7 years (95% CI 29.61–31.69) and median age 29.0 (IQR 22.5–36.5). The majority of cases were diagnosed before the age of forty or 84.2% (n. 294) but 15.8% (n. 55) of the cases were older when diagnosed. Of these cases 206 men and 143 women were identified giving a male-to-female rate ratio of 1.44 (95% CI 1.16–1.79). The mentioned sex specific difference was mostly accounted for by the younger age groups – up to the age of 40 (Fig. 1). The point prevalence of type 1 diabetes in adults remained relatively stable, only increasing slightly from 0.09 to 0.11% over the ten years, giving an average yearly prevalence of 0.10%.

For incidence calculations purposes only the 99 new diagnoses made during the 10 study years were considered. The majority of those or 84.8% (95% CI 76.78–91.22%) were categorized as T1D, 7.1% (95% CI 2.04–12.16%) as IR1 and 8.1% (95% CI 2.73–13.47%) as IR2. The calculated incidence rate in the whole cohort was **4.35 per 100.000** persons per year (**95% CI 3.54–5.30**). In group T1D the calculated incidence rate was 3.69 per 100.000 per year (95% CI 2.95–4.57), in IR1 0.31 per 100.000 per year (95% CI 0.12–0.63) and in IR2 0.35 per 100.000 per year (95% CI 0.15–0.69). When adjusted by the WHO age standardization the incidence rate was **4.29 per 100.000.** The incidence rate overall was highest in the youngest age group 18 to 19 years or 13.39 per 100.000 per year and then decreased with higher age (Table 1 in supplement and Fig. 2). The incidence rate in women was highest in the age group 18–19 years but in age group 20–24 years in men. Overall a total of 61 men and 38 women were diagnosed during the study period giving a male-to-female incidence rate ratio of **1.59 (95% CI 1.05–2.46)**. A statistically significant difference was found in the incidence rate between the sexes overall, **5.35 vs. 3.35 per 100.000 per year ($p < 0.05$ (midp = 0.0115))**, as well as in the age groups 20–24 years ($p < 0.05$) and 35–39 years ($p < 0.05$). In the subclass T1D males had an almost twofold higher incidence compared to female subjects, incidence rate ratio **1.88 (95% CI 1.18–3.06)**. Significant differences were not found in the other two subgroups IR1 (incidence rate ratio 0.74, 95% CI 0.11–4.40) and IR2 (incidence rate ratio 0.60, 95% CI 0.09–3.06) (Table 1 in supplement).

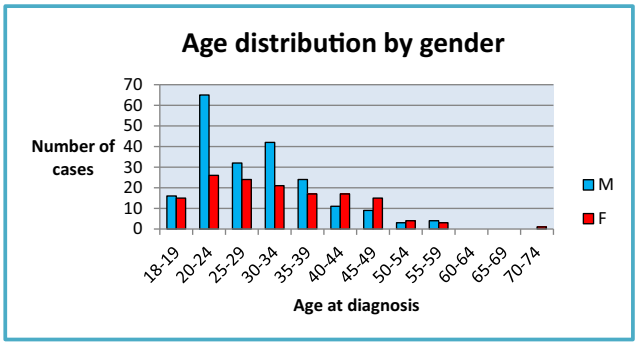

Fig. 1 – Number of patients with type 1 diabetes from February 2003-February 2013 diagnosed in adulthood by age at diagnosis and sex.

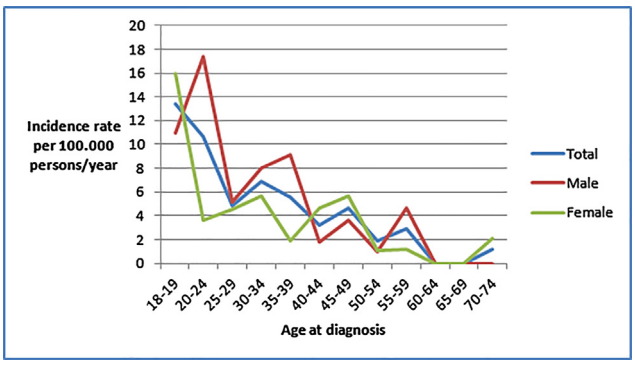

Fig. 2 – Incidence rates per 100.000 persons years of type 1 diabetes in the Icelandic population from February 2003-February 2013.

The mean age at diagnosis for the 99 patients was 32.1 years (95% CI 29.7–34.5) and the median age 31.0 years (IQR 21.5–39.5). In the three different groups; T1D, IR1 and IR2, the mean age was 30.2 years (95% CI 27.85–32.56), 48.9 years (95% CI 37.44–60.28) and 36.9 years (95% CI 28.50–45.26) respectively.

Of these 99 patients 72.7% were noted to have weight loss, 70.7% presented with ketonuria and 26.3% with diabetic ketoacidosis at diagnosis (Table 2). Beta-cell autoimmunity assessment with measurement of antibodies was done in only 40,4% of the patients (n. 40). Some subjects were tested for either anti-GAD or anti-ICA antibodies only, and more often only anti-GAD was measured. C-peptide or s-insulin was measured in only 11 subjects of 99 and when measured was low in 72.7%. The proportion of tested subjects with any positive antibody was 67.5%. Family history was present in 39.4% of subjects and other autoimmune diseases in 16.2%, ¾ of them being Hashimoto's hypothyroidism. Five patients were diagnosed with three autoimmune diseases.

An association was found between the time at the start of insulin treatment and age with younger people more often needing insulin at the time of diagnosis ($p < 0.001$) vs. later (Fisher's exact test). Subjects in group T1D had significantly more often ketonuria at presentation in comparison to groups IR1 and IR2 ($p < 0.001$), but no relationship was found between weight loss and earlier need of insulin ($p = 0.4$). No difference was found between males and females concerning start of insulin treatment ($p = 0.91$). When measured, no relationship was found between antibody positivity and earlier need of insulin ($p = 0.7$), although antibodies were only measured in 40 of 99 subjects. There was also no significant difference concerning presence of family history or other autoimmune diseases between the three groups ($p = 0.4$ and $p = 0.09$ respectively).

We further assessed the roles of sex, age, weight loss, ketonuria, family history and other autoimmune diseases on the time of start of insulin treatment (immediately at the time of diagnosis vs. later but less than 12 months from diagnosis) by analyzing the variables together (Table 3). The results

Table 2 – Proportion of patients presenting with weight loss, ketonuria, diabetic ketoacidosis, positive antibodies at diagnosis as well as proportion of patients with postitive family history or other autoimmune diseases.

	Total	T1D	IR1	IR2
Mean age in years	32.1	30.2	48.9	36.9
Total subjects (n)	99	84	7	8
Male subjects (n)	61	55	3	3
Female subjects (n)	38	29	4	5
Weight loss at diagnosis in % of subgroup (n. of cases)	72.7 (72)	75.0 (63)	57.1 (4)	62.5 (5)
Ketonuria in % of subgroup (n. of cases)	70.7 (70)	78.6 (66)	42.9 (3)	12.5 (1)
DKA in % of subgroup (n. of cases)	26.3 (26)	31.0 (26)	0	0
Ab measured in % (n. of cases)	40.4 (40)	35.7 (30)	57.1 (4)	75.0 (6)
Ab positive[a] in % of subgroup (n. of cases)	67.5 (27)	73.3 (22)	50.0 (2)	50.0 (3)
GAD only positive[b] in % (n. of cases)	30.0 (12)	33.3 (10)	25.0 (1)	16.7 (1)
ICA only positive[b] in % (n. of cases)	15.0 (6)	13.3 (4)	25.0 (1)	16.7 (1)
GAD and ICA positive[b] in %(n. of cases)	22.5 (9)	26.7 (8)	0	16.7 (1)
GAD or ICA positive[b] in % (n. of cases)	45.0 (18)	46.7 (14)	50.0 (2)	33.3 (2)
Family history in % (n. of cases)	39.4 (39)	36.9 (31)	42.9 (3)	62.5 (5)
Other autoimmune diseases in %(n. of cases)	16.2(16)	15.5 (13)	42.9 (3)	0

[a] Proportion in tested subjects.
[b] Proportion of positive Ab in tested subjects.

Table 3 – Adjusted odds ratios (OR) for the effect of demographic and metabolic variables on the start of insulin treatment (immediately at the time of diagnosis vs. later but less than 12 months from diagnosis) in subjects diagnosed with type 1 diabetes in adulthood from February 2002- February 2013 in Iceland. Estimates and values were obtained from a logistic regression analysis. * OR is adjusted for all the other variables in the table. ** Statistically significant.

	Insulin treatment at the time of diagnosis		
	OR*	95% CI for OR	p value
Sex (Female/male)	0.55	0.14–2.18	0.40
18–29 years old	1.00		
30–44 years old	0.41	0.064–2.58	0.34
≥45 years old	0.078	**0.012–0.52****	**0.009****
Weight loss	1.12	0.27–4.69	0.88
Ketonuria	7.45	**1.62–34.38****	**0.010****
Family history	0.40	0.10–1.58	0.19
Other autoimmune diseases	0.82	0.12–5.49	0.83

The bold values are statistically significant values ($p < 0.05$).

indicate a significant relationship between ketonuria status and start of insulin treatment. The odds of needing insulin immediately at the time of diagnosis were 7.45 fold greater in patients with ketonuria than in those without ketonuria. The odds of insulin treatment at the time of diagnosis were reduced 92% in patients 45 years of age or older when compared to patients aged 18–29 years of age. There was no association between insulin use at the time of diagnosis and sex, weight loss, family history of type 1 diabetes, or history of other autoimmune diseases.

During the study period on average 10 patients were diagnosed each year with the disease (Fig. 3). In comparison on average 17 children 15 years and younger were diagnosed each year with type 1 diabetes in Iceland during the same time period [10,11]

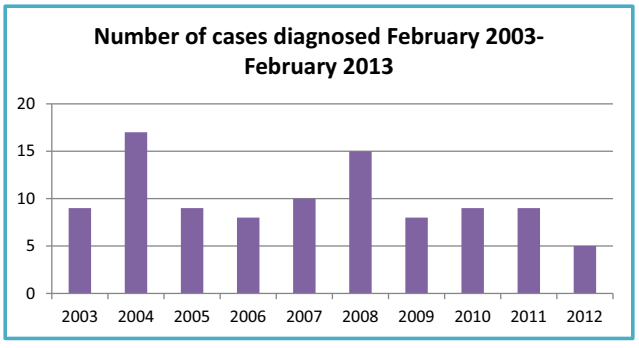

Fig. 3 – Number of patients diagnosed with type 1 diabetes in adulthood in Iceland each year during the study period.

4. Discussion

This is the first epidemiological study on the incidence and prevalence of type 1 diabetes diagnosed in adulthood in Iceland, providing data on a subject with scarce information globally. Our study is nationally based and not limited to a certain geographical area within the country. Every single patient in Iceland in need of insulin gets reimbursement from the Icelandic Health Insurance therefore making it possible to identify all incident cases in the population. We enriched the data source by collecting clinical and laboratory information

from the time of diagnosis and by that enhancing the accuracy of the information and making the completeness of ascertainment near 100%.

Our main finding is that, in Iceland, one needs to consider the possibility that a newly presenting adult with diabetes might have absolute insulin deficiency and type 1 diabetes. The incidence rate varies by age but there exists a possibility of the diagnosis at any age. The WHO age-adjusted incidence rate of type 1 diabetes in adulthood in Iceland from February 2003- February 2013 was 4.29 per 100.000 per year in the total cohort. Incidence rates were highest in the youngest age groups and declined thereafter. However, ¼ of the cohort (25/99) were diagnosed at the age of forty or higher. Subjects aged ≥ 45 years had a 92% lower risk of needing insulin at the time of diagnosis compared to subjects aged 18–29 ($p = 0.009$). Overall, one can expect one case of adult type 1 diabetes for every two children diagnosed in Iceland.

Similar epidemiological studies from other countries show great geographical variation in incidence rates. In China the incidence of type 1 diabetes in 15–29 year olds is 1.28 per 100.000 per year and 0.69 per 100.000 per year in people over 30 years of age, particularly low compared to other countries [12]. In Spain the incidence of type 1 diabetes in people aged 15 and over was found to be 6.67 per 100.000 per year [13], whereas in the US the incidence has been found to be 18.6 per 100.000 per year in the age group 20–64 years [14] and in Sweden in the age group 20 and over it was found to be 27.1 per 100.000 per year [15].

Few studies have specifically looked at the highest age-groups, mostly focusing on the 15–29 years age group, making it difficult to compare our results to other incidence rates in nearby countries. In Iceland we found the incidence rate for 18–29 years old to be 8.66 per 100.000 per year (95% CI 6.37–11.52). In comparison the incidence rate for 15–29 year olds in Norway, our closest and most related neighbor is 17 per 100.000/year [16], it is 10.8 per 100.000 in 15–29 year olds in Sweden [17] and 15.9 per 100.000/year in 15–29 year olds in Finland [18]. An important factor affecting the differences could be the lack of data concerning age-group 16–17 years in our study.

In comparison the incidence in Mediterranean countries has been estimated to be 15.58 per 100.000 per year in Spain [13] and 12.5 per 100.000 per year in Sardinia [17], but 5.83 per 100.000 per year in other parts of Italy [19]. These results show no specific trend with regards to geographical closeness when comparing Mediterranean countries to Scandinavian countries. Differences have even been found between different areas within the same country making specific but unknown environmental factors a more plausible culprit of type 1 diabetes than genetic factors [16]. The relatively high frequency of positive family history in our cohort however is interesting and contradicts the dogma that usually individuals with type 1 diabetes do not recall relatives suffering from the disease.

We found a statistically higher incidence in men compared to women up to the age of forty and the overall male-to-female ratio was 1.59 (95% CI 1.05–2.46). Similar results showing male predominance have been found in several other studies, especially in European countries in people younger than forty [20–22]. A recent systematic review concerning the global epidemiology of type 1 diabetes in adults found a male-to-female ratio 1.47 (95% CI 1.33–1.60) [2]. In Finland, a ratio of 1.70 was found in the age group 15–39 years [18], and in Sweden 1.80 in the age groups 15–34 years [23]. This is an interesting observation as autoimmune diseases tend to have a higher incidence in women overall [24]. The reason for this paradox is still unknown but speculations have been made on the effect of different life style choices, hormonal factors, different environmental exposures between the sexes and different susceptibility to environmental factors [21,22,25].

More than 20% of our study cases in group T1D did not present with urinary ketones at the time of diagnosis. Similar results have been found in other cohort studies showing that around 20% of patients with adult onset type 1 diabetes do not have ketonuria at presentation [26]. Diabetic ketoacidosis was present in nearly 30% of the cases at the time of diagnosis in our study. Interestingly this is very similar to what is seen in children where the prevalence of ketoacidosis at diagnosis is thought to be 25–30% [27,28].

A higher proportion of our cases had positive anti-GAD antibodies than anti-ICA (12/40 vs. 6/40) which is in accordance with previous suggestions that GAD might be more useful than ICA in predicting insulin dependency [29]. Antibodies were measured more often in groups IR1 and IR2 which could suggest that they are used more frequently by doctors faced with more challenging cases when insulin dependence is not clinically obvious. No relationship was found between antibody positivity and earlier need of insulin. True assessment of antibody positivity frequency in our study however is difficult as several subjects were not considered for antibody assessment. Around 20–30% of adults with absolute insulin dependency are thought to be antibody negative which is in stark contrast to the situation in children where this is very seldomly seen [30]. No relationship was found between presence of weight loss and earlier need of insulin, nor a difference concerning presence of family history or other autoimmune diseases and the earlier need of insulin.

Limitations of the study. Careful scrutiny of detailed clinical and laboratory data on insulin-dependent cases was done in order to minimize the possibility of wrongly labelling type 2 diabetes as type 1 diabetes. It is though never possible to be completely certain since a gold standard on which to base the diagnosis does not exist. It is clear that obligate insulin dependency is not always associated with currently available antibodies nor is their role in the development of absolute insulin deficiency completely understood. Some studies have used positive antibodies and/ or low serum C- peptide as markers of insulin requirement and classified all other cases as type 2 diabetes [15]. Being a retrospective study this has not been possible as these measurements are not always used in day to day clinical practice and as for now not routinely recommended [31]. Other studies have used similar approach as ours by using clinical insulin requirement within a specified timeframe, as sufficient criteria, but antibody positivity or low C- peptide being used to support the correct diagnosis [4,26].

Our figures may underestimate the true burden of insulin requiring diabetes in adults as we only considered individuals

starting insulin treatment within 12 months from presentation. This would exclude slower progressing cases of autoimmune diabetes not being included in our study, e.g. the so- called LADA (Latent Autoimmune Diabetes of Adulthood) patients. Patients with LADA are defined by, among other, lack of requirement for insulin during the first six months from diagnosis but progression to insulin dependence within six years [32–34]. This specific form of diabetes however is controversial and not recognized by the World Health Organization (WHO) which recommends rather that it represents a continuum to type 1 diabetes with a slower process. The organization advocates the use of the term "type 1 diabetes" for every case with pancreatic islet beta-cell destruction and proneness to ketoacidosis [35]. Whichever name one might want to call it, it has been shown that older adults can have a different presentation of type 1 diabetes than children, with slower onset, less abrupt symptoms, more insidious presentation of weight loss and ketonuria and a drawn out progression to dependency on insulin, a course which may even last several years [29]. This is in accordance with our results as younger subjects up to the age of 29 years had a significantly higher risk of needing insulin immediately from the time of diagnosis vs. later.

As the study period was the decade spanning February 2003 -February 2013 and the last diagnoses were made at the end of the year 2012 we could also be underestimating the true number of patients diagnosed during the end of the study period but who didn't need insulin immediately at diagnosis and would have fallen into the IR1 or IR2 categories with a longer follow-up.

We have found that type 1 diabetes commonly presents in adults and we should expect one adult for every two children diagnosed each year in Iceland. The incidence is highest in the youngest adults, although a quarter of the diagnoses in adults were made in individuals older than 40 years. This gives a WHO age-adjusted incidence rate of 4.29 per 100.000 per year for the time period from February 2003- February 2013. The point prevalence has remained relatively stable over the years. Diabetic ketoacidosis was present in 26% of the cohort at the time of diagnosis. These results emphasize the need to acknowledge the presence of autoimmune diabetes in all age groups and the importance of correct identification and follow-up.

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Conflicts of interest

We declare that we have no conflicts of interest.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.04.023.

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