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Trends in incidence rates of childhood type 1 diabetes mellitus: A retrospective study in Isfahan province, Iran

Mahin Hashemipour[1], Mohammadreza Maracy[2], Shaghayegh Haghjooy Javanmard[3], Farzane Zamaneh[4], Neda Mostofizadeh[5], Silva Hovsepian[6]*

[1]Metabolic Liver Diseases Research Center, Isfahan Endocrine and Metabolism Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Department of Epidemiology and Biostatistics, School of Health, Isfahan University of Medical Sciences, Isfahan, Iran, [3]Applied Physiology Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [4]Metabolic Liver Diseases Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [5]Department of Pediatric Endocrinology, Isfahan Endocrine and Metabolism Research Center, Imam Hossein Children's Hospital, Isfahan University of Medical Sciences, Isfahan, Iran, and [6]Metabolic Liver Diseases Research Center, Imam Hossein Children's Hospital, Isfahan University of Medical Sciences, Isfahan, Iran

Keywords
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***Correspondence**
Silva Hovsepian
Tel.: 00983137925257
Fax: 00983136688138
E-mail address:
silvahovsepsecret@gmail.com

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ABSTRACT

Aims/Introduction: We aimed to determine the incidence trend of childhood type 1 diabetes mellitus in Isfahan province over a period of 12 years.

Materials and Methods: In this retrospective study, children aged <20 years at the time of type 1 diabetes mellitus diagnosis, from March 2007 to March 2019, were included. The crude and adjusted incidence rate of type 1 diabetes mellitus is calculated as the number of cases per 100,000 person-years by the period. The cumulative, age- and sex-specific incidence rates were also calculated. Age-specific incidence rates were calculated for age and sex groups.

Results: A total of 1,954 (983 boys and 971 girls) cases of type 1 diabetes mellitus were identified. The mean age at diagnosis in all studied populations was 9.89 (standard deviation 4.76). There were no significant differences between the proportion of boys and girls in different years ($P = 0.12$) and different age groups ($P = 0.19$). The average annual percent change of incidence rate for the total population, for girls and boys, was 6.9%, 6.7% and 6.3% respectively. The type 1 diabetes mellitus incidence rate had a significant trend to be increased from 2007 to 2019 ($P < 0.001$, $t = 3.6$).

Conclusion: Our findings showed that currently our region is considered a region with a high incidence rate of type 1 diabetes mellitus. Although we have had fluctuations in the incidence rate over the 12 years, the overall trend is increasing.

INTRODUCTION

Type 1 diabetes mellitus is one of the most common endocrine and chronic metabolic disease, which occurs due to impaired insulin secretion[1]. It consists of two-thirds of all cases of diabetes mellitus among children and adolescents. It is associated with a higher rate of morbidity, and is considered a high-cost disease for both patients and societies[2,3]. The results of different epidemiological studies worldwide showed that the incidence rate of type 1 diabetes mellitus varies significantly in different regions and ethnic populations[4,5]. Although the rate is not similar in different countries and regions, recent studies showed that with the global increase of diabetes mellitus among children and adolescents, there is an overall increasing trend in the incidence of type 1 diabetes mellitus worldwide[6,7].

The reported worldwide incidence rate of type 1 diabetes mellitus in children aged 0–14 years ranged from 1 to 58 per 100,000 person-years[7–11]. Based on International Diabetes Federation reports, >1.2 million children and adolescents worldwide have type 1 diabetes mellitus, and more than half of the patients are aged <15 years[12]. Several studies have investigated the incidence rate and trend of the disease in different populations, and reported various results regarding its incidence in different age and sex groups, but most of them showed that the trend is increasing, and also emphasized that the increasing trend is alarming and needs more comprehensive and effective preventative strategies to decrease the burden of the disease[6,7,10,13]. Results of a study among Chinese children showed

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that with the reported trend rate for type 1 diabetes mellitus, the number of new cases of the disease would double from 2016 to 2020 and sextuple by 2025[14]. According to available data, the average annual increasing incidence rate, which was initiated in the 1950s, is 3–4% over the past decades. However, some studies, mainly from European countries, reported a decreasing or plateau trend for type 1 diabetes mellitus[4,15].

The results of different epidemiological studies varied regarding the incidence of type 1 diabetes mellitus in different age groups and sexes. Some studies reported a higher incidence rate of type 1 diabetes mellitus in children aged 5–9 years, whereas some did not report that[16]. There is evidence that the incidence of type 1 diabetes mellitus is higher among boys in countries with a high overall incidence of the disease, and it is higher among girls in countries with a low overall incidence of type 1 diabetes mellitus. However, some did not report any sex-related incidence rate for type 1 diabetes mellitus[7].

Providing an epidemiological feature of the disease is a priority for each community for proper allocation of healthcare resources and developing prevention studies. Considering that there were few studies in this field in Iran[17–20], we aimed to determine the incidence rate of childhood type 1 diabetes mellitus in Isfahan province and its trend over a period of 12 years. Our findings would help plan nationwide studies in this field.

MATERIALS AND METHODS

The present study was designed as retrospective research. In this study, all children aged 0–19 years at the time of type 1 diabetes mellitus diagnosis, from March 2007 to March 2019, were included. All included children with type 1 diabetes mellitus had been living in Isfahan province for at least 6 months before diagnosis. The protocol of the study was approved by the National Institute for Medical Research Development (NIMAD) with a research project number of 958386.

Isfahan province is situated in the center of Iran with an approximate population of 5,000,000 and a surface area of 107,027 km.

In the present study, we had four sources of information. Considering that almost all (>98%) patients with type 1 diabetes mellitus are hospitalized in pediatric departments at the time of diagnosis and the Hospital Information System in all Iranian hospitals records the cases, the case records of all Isfahan province hospitals served as the primary source of data. The secondary source of data was the records of insurance organizations. The third source of data was the Vice-Chancellery for Health. The fourth source of data was the Isfahan Department of Education and the Isfahan Endocrine and Metabolism Research Center.

Information on all patients with type 1 diabetes mellitus who were admitted to the hospitals of the Isfahan province was provided after coordination with the Vice-Chancellery for Clinical Affairs of Isfahan University of Medical Sciences. In addition, data from all diabetes clinics were collected.

Data from all insurance organizations (Isfahan Health Insurance, Social Security Organization, Armed Forces Insurance and Imam Khomeini Relief Committee) of Isfahan province were provided after coordination with the insurance organizations. Data of all the patients who had registered for insulin therapy (ID number and name, family name, and telephone number) from March 2007 to March 2019 were obtained and recorded.

We used the data of the CIB system, which is used for disease registry by the Vice-Chancellery for Health.

In addition, all schools in Isfahan province reported cases of type 1 diabetes mellitus in their schools.

Using the baseline information of the patients, trained healthcare personnel contacted the patients, and after describing the aim of the study and its methods, they sent the questionnaire and consent form of the study by post to the patients. The questionnaire consists of the following items: sex, date of birth, date at the time of diagnosis, address, symptoms and signs, and history of the disease. They recommended sending back the questionnaire. In cases that did not send the questionnaire back, the questionnaire healthcare personnel went to their home and completed the questionnaire. The questionnaires were reviewed by two general practitioners to exclude cases with type 2 diabetes mellitus, secondary diabetes due to congenital malformations of the pancreas, Down syndrome and steroid use. Cases diagnosed by ketoacidosis or fasting serum C-peptide level ≤0.6 ng/mL and positive anti-islet autoantibodies, and those who were not able to achieve a blood glucose level without insulin injections for 2 years after diagnosis were included.

Statistical analysis

Data were analyzed using SPSS version 21 (SPSS Inc., Chicago, IL, USA) software. Continuous variables are presented as the mean (standard deviation), and frequencies for categorical variables as numbers (%). Comparison of categorical and continuous variables between groups/years was carried out using the χ^2-test and Student's *t*-test, respectively.

The crude and adjusted incidence rate of type 1 diabetes mellitus was calculated as the number of cases per 100,000 person-years by the period. The cumulative, age- and sex-specific incidence rates were also calculated. Age-specific incidence rates were calculated for age and sex groups (girls and boys aged 0–4, 5–9, 10–14 and 15–19 years). Confidence intervals (95% CIs) for incidence rates were calculated using a Poisson distribution.

For comparison of the present data with other populations/countries, the incidence was standardized by the direct method according to the age distribution of the world population using Segi World Standard[21].

To establish the completeness of ascertainment and to estimate the true number of cases, the capture–recapture method was used.

The population in studied years according to sex and region was derived from the censuses carried out in 2006, 2011 and 2016, and the estimates for the other years.

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Average annual percent changes (AAPC) were reported for the study period to characterize trends over time. Data were analyzed using Excel (Microsoft, Redmond, WA, USA) and Joinpoint trend analysis software (version 4.9.1.0; National Cancer Institute, Bethesda, MD, USA).

RESULTS

In the present study, a total of 1,954 (983 boys and 971 girls) cases of type 1 diabetes mellitus were identified. The mean age at diagnosis in all studied populations was 9.89 years (standard deviation 4.76 years). The mean (standard deviation) ages at diagnosis and distribution of the patients by age groups during the studied years are presented in Table 1.

There were no significant differences between the proportion of boys and girls in different years ($P = 0.12$). The mean age at diagnosis was not significantly different between the studied years ($P = 0.12$). There was no significant difference between the proportion of type 1 diabetes mellitus patients in different age groups ($P = 0.19$).

The number of cases, the crude incidence rate in the total population and the standardized incidence rate during the studied years are presented in Table 2. The crude incidence rate had a significant increasing trend during the study period for the total population (*P*-value for trend <0.001), (Figure 1) and girls (*P*-value for trend <0.001) and boys (*P*-value for trend = 0.004). There was no significant difference between boys and girls regarding their increasing trend ($P = 0.63$).

The age-standardized incidence rate according to sex is presented in Figure 2. The age-standardized incidence rate had a significant increasing trend for both girls ($P = 0.002$, $t = 4.2$) and boys ($P = 0.005$, $t = 3.6$). There was no significant difference between boys and girls regarding the trend of age-standardized incidence rate ($P = 0.44$).

The incidence rate in different age groups and their trend are presented in Table 3.

The incidence rate was significantly higher in 10–14 years age groups than in 15–19 years age groups ($P < 0.001$).

The incidence rate was not significantly different between the 0–4 years age groups and 5–9 years ($P = 0.75$), 10–14 years ($P = 0.61$) and 15–19 years ($P = 0.28$) age groups. The incidence rate was not significantly different between 5–9 years age groups and 10–14 years ($P = 0.92$) and 15–19 years ($P = 0.54$) age groups. The incidence rate was not significantly different between 10–14 years age groups and 15–19 years ($P = 0.67$) age groups.

Age-specific incidence rates of type 1 diabetes mellitus in Isfahan province during 2007–2019 according to age groups are presented in Figure 3. The age-specific incidence rate had a significant increasing trend for 5–9 years ($P = 0.009$, $t = 3.2$), 10–14 years ($P = 0.001$, $t = 5.0$) and 15–19 years ($P < 0.001$, $t = 6.3$) age groups.

Average annual percent changes for 0–4 years, 5–9 years, 10–14 years and 15–19 years age groups were 3.9%, 6.3%, 7.9% and 8.58%, respectively.

Table 1 | The mean (standard deviation) ages at diagnosis and distribution of the patients by sex and age groups during the study period in Isfahan province

	1,386 (March 2007–2008)	1,387 (March 2008–2009)	1,388 (March 2009–2010)	1,389 (March 2010–2011)	1,390 (March 2011–2012)	1,391 (March 2012–2013)	1,392 (March 2013–2014)	1,393 (March 2014–2015)	1,394 (March 2015–2016)	1,395 (March 2016–2017)	1,396 (March 2017–2018)	1,397 (March 2018–2019)	*P*-value
Total No. cases	89	116	106	132	146	145	193	171	208	178	205	180	0.12
Boys	41	65	47	69	88	67	98	76	97	93	114	87	
Girls	48	51	59	63	58	78	95	95	111	88	91	93	
Mean (SD) age at diagnosis (years)	9.82 (5.06)	9.93 (4.57)	10.09 (5.02)	9.77 (4.64)	9.41 (4.38)	9.18 (4.67)	9.50 (4.56)	9.21 (4.09)	9.33 (4.46)	9.76 (4.25)	9.37 (4.56)	10.22 (4.45)	0.12
Proportion by age groups (%)													
0–4 years	20.2	15.5	14.2	15.9	17.1	17.9	15.5	13.5	17.3	12.4	17.1	10.6	0.19
5–9 years	25.8	32.8	31.1	32.6	32.2	37.9	36.8	43.8	33.2	30.8	33.2	35.0	
10–14 years	32.6	31.9	33.0	32.3	36.3	28.3	31.1	29.8	34.6	44.4	33.6	33.3	
15–19 years	21.4	19.8	21.7	18.2	14.4	15.9	16.6	12.9	14.9	12.4	16.1	21.1	

SD, standard deviation.

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Table 2 | Incidence (95% confidence interval) per 100,000 for type 1 diabetes mellitus in the Isfahan population aged 0–19 years, between 2007 and 2019

Year	Boys			Girls			Total		
	No. cases	Crude incidence (95% CI)	Age-standardized incidence (95% CI)	No. cases	Crude incidence (95% CI)	Age-standardized incidence (95% CI)	No. cases	Crude incidence (95% CI)	Age-standardized incidence (95% CI)
1,386 (March 2007–2008)	41	6.35 (4.72, 7.99)	6.51 (2.31, 10.71)	48	7.82 (5.96, 9.67)	8.03 (3.37, 12.69)	89	7.07 (5.83, 8.30)	7.08 (2.70, 11.46)
1,387 (March 2008–2009)	65	10.34 (8.23, 12.45)	10.27 (5.00, 15.54)	51	8.52 (6.56, 10.48)	8.57 (3.76, 13.38)	116	9.45 (8.01, 10.90)	10.26 (4.99, 15.53)
1,388 (March 2009–2010)	47	7.61 (5.78, 9.43)	7.46 (2.97, 11.95)	59	10.03 (7.88, 12.17)	9.96 (4.77, 15.15)	106	8.79 (7.38, 10.19)	8.61 (3.78, 13.44)
1,389 (March 2010–2011)	69	11.33 (9.09, 13.75)	12.18 (6.44, 17.92)	63	10.85 (8.60, 13.10)	10.97 (5.52, 16.42)	132	11.09 (9.51, 12.68)	10.89 (5.46, 16.32)
1,390 (March 2011–2012)	88	14.52 (11.97, 17.06)	14.33 (8.10, 20.56)	58	10.02 (7.85, 12.18)	9.59 (4.50, 14.68)	146	12.32 (10.64, 14.00)	12.03 (6.33, 17.73)
1,391 (March 2012–2013)	67	11.08 (8.85, 13.31)	11.03 (5.57, 16.49)	78	13.50 (10.99, 16.02)	13.07 (7.12, 19.02)	145	12.26 (10.59, 13.94)	12.04 (6.33, 17.75)
1,392 (March 2013–2014)	98	16.15 (13.47, 18.83)	15.76 (9.23, 22.29)	95	16.40 (13.63, 19.17)	16.39 (9.73, 23.05)	193	16.27 (14.35, 18.20)	15.88 (9.33, 22.43)
1,393 (March 2014–2015)	76	12.40 (10.06, 14.74)	12.02 (6.32, 17.72)	95	16.27 (13.52, 19.01)	15.86 (9.31, 22.41)	171	14.29 (12.49, 16.09)	13.79 (7.68, 19.90)
1,394 (March 2015–2016)	97	15.62 (13.02, 18.23)	15.17 (8.76, 21.58)	111	18.79 (15.86, 21.73)	18.57 (11.48, 25.66)	208	17.17 (15.21, 19.13)	18.60 (11.51, 25.69)
1,395 (March 2016–2017)	93	14.87 (12.34, 17.41)	14.41 (8.17, 20.65)	85	14.29 (11.74, 16.84)	13.88 (7.75, 20.01)	178	14.59 (12.79, 16.39)	14.09 (7.92, 20.26)
1,396 (March 2017–2018)	114	18.10 (15.31, 20.89)	18.18 (11.17, 25.19)	91	15.22 (12.60, 17.84)	14.65 (8.36, 20.94)	205	16.70 (14.78, 18.62)	16.31 (9.67, 22.95)
1,397 (March 2018–2019)	87	13.80 (11.37, 16.23)	13.92 (7.78, 20.06)	93	15.55 (12.90, 18.21)	15.18 (8.77, 21.59)	180	14.65 (12.86, 16.45)	14.45 (8.20, 20.70)
P-value for crude incidence trend (t)		0.004 (3.7)			<0.001 (4.5)			<0.001 (3.6)	
AAPC		6.3			6.7			6.9	

AAPC, average annual percent changes; CI, confidence interval.

DISCUSSION

In the present study, we reported the incidence of type 1 diabetes mellitus in the <20 years-of-age population of Isfahan province in Iran for 12 years. Based on our findings, the mean age of type 1 diabetes mellitus patients was in the range of 9–10.5 years. Approximately 60–70% of type 1 diabetes mellitus patients were aged 5–14 years. During most of the studied years, the rate was similar in boys and girls. AAPC showed that, although we have some fluctuations in the incidence of type 1 diabetes mellitus, the overall incidence rate showed a trend to increase by 6.9% during the period. The AAPC was not significant between boys and girls, and it was higher in older age groups than younger (>15 years vs <15 years). The age-specific incidence rate was significantly higher in 5–14 years age groups than in other age groups.

In the present study age, the standardized incidence rate of type 1 diabetes mellitus was 7.08 in 100,000 in 1,386 patients (March 2007–March 2008) and reached 14.45 in 100,000 in 1,397 patients (March 2018–March 2019). The incidence rate of the total population in 2018 is considered a high incidence rate based on the World Health Organization Diabetes Mondiale (DiaMond) projection group classification[22]. The rate altered from intermediate to high in this region. Comparing the age-specific incidence rate during the study period, the rate showed an increasing trend.

Reports from different countries also showed transient periods of steep increase and stabilizations, although the overall trend remained upward.

In a recent study in Turkey, the incidence rate of type 1 diabetes mellitus was calculated for 10 years (2009–2019) among children aged <15 years. They reported a significant increasing trend from 10.2 to 24.1/100,000 persons per year. The reported incidence rate in Turkey was higher than in the present study. This might be due to the studied age group[23]. We included children aged <20 years, and the rate in children aged 15–19 years is lower than children aged 5–15 years. This might be also due to ethnic or regional differences[7].

In the present study, the mean age of diagnosis was 9.89 years, which was higher than that reported in the study of Esen *et al.* in Turkey[23].

The cyclical variation in the incidence of type 1 diabetes mellitus has been reported in many countries[7,24,25]. Reports from Poland and Australia show 5 years fluctuations[26,27]. There is no exact rationale for the cyclic patterns worldwide[24]. Previous studies reported that the temporal variation and peaks in the incidence of type 1 diabetes mellitus are well-known patterns and occur each 5–6 years worldwide.

These periodic variations might be due to different environmental factors; viral, bacterial and fungal infections; or climatic changes in various regions. Given that the clinical diagnosis of type 1 diabetes mellitus occurs a long time after the autoimmune destruction of β-cells, explanations of such fluctuations would be carried out with consideration of this fact[15,26,28].

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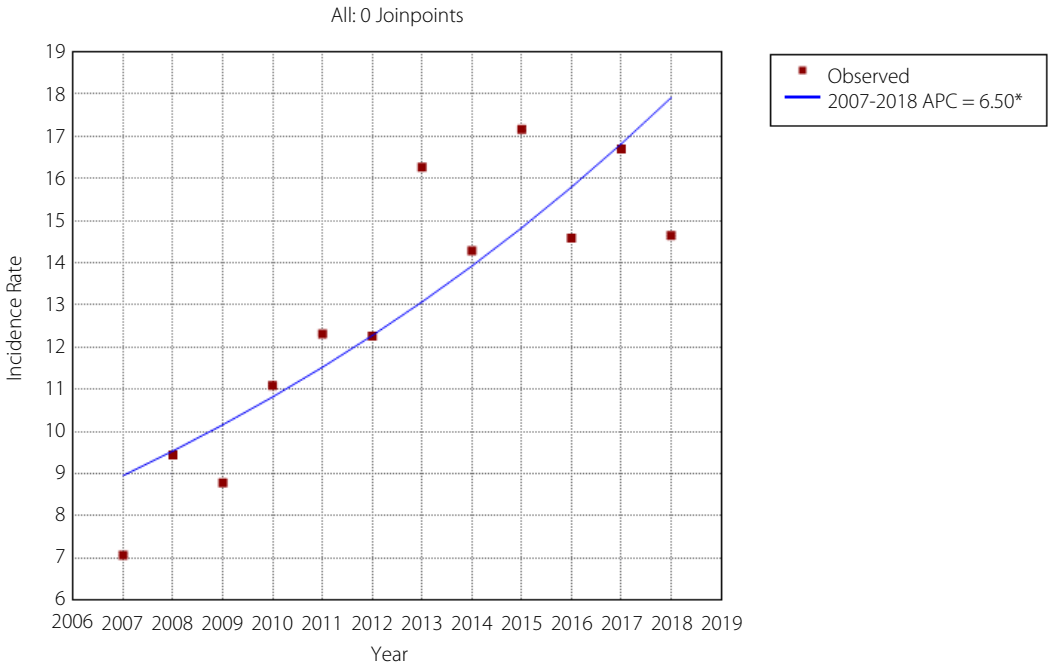

Figure 1 | Trend of type 1 diabetes mellitus incidence rate in Isfahan province during 2007–2019 (1,386–1,397 Hijri Shamsi). *Annual percent change (APC) = 6.50, the *P*-value for incidence rate trend <0.001.

It is suggested that some important environmental factors in our community that could explain the increasing trend of type 1 diabetes mellitus are influenza outbreaks, vitamin D deficiency, and improving perinatal care in mothers and postnatal care in children[29]. Given that there is evidence regarding the role of vitamin D deficiency and type 1 diabetes mellitus, and the reported higher rate of vitamin D deficiency among Iranian children and adolescents, as well as the Iranian adult population[30–32], it is suggested that vitamin D deficiency is considered as one of the most important factors for the reported high increasing rate of type 1 diabetes mellitus in our population.

Other suggested environmental factors are air pollution and lifestyle modification. Air pollution and its components are considered endocrine disruptor chemicals, which could have an important role in the pathogenesis of type 1 diabetes mellitus[33–35]. In addition, the association between air pollution and vitamin D deficiency could also explain the suggested association[36,37].

Based on available data, the incidence of type 1 diabetes mellitus has an increasing trend in many countries worldwide, with an overall annual increase rate of 3–5%[38]. The increasing trend is steeper in some countries with currently low incidence rates, but in others with currently high incidence rates, the trend is leveling off[22]. Suggested factors for the reported decreasing incidence rate of some countries are fortification of milk products, increased use of vitamin D supplements, increased consumption of probiotics among infants and children, reduced coverage of Calmette–Guérin vaccine and increased coverage of the rotavirus vaccine[15].

In contrast, some studies showed that the decreasing incidence rate is mainly related to children aged <4 years, and in other age groups, the incidence has an almost increasing trend[39].

The rate was in the mentioned range for most European countries and Korea[16,19,28]. It was lower in some other countries, including the USA (1.8%)[40], Canada (1.3%)[41] and Australia (0.4%)[27]. In some other countries, including Iran (7.6%), Croatia (9%)[42], China (12%)[43], Chile (13.4%)[44] and Mali (18%)[38], the rate was higher. Recent studies reported that although the annual increase rate is stabilized in some countries, it is higher in middle-income countries[45].

The higher rate of annual increase rate in our community emphasizes the importance of identifying the factors responsible for the high reported rate.

The overall incidence rate for 18-year-old children in our community was approximately 13 in 100,000. The rate is lower than that reported by European countries[46] and the USA[47]. In comparison with neighboring countries, it was higher than Turkey[48] and Iraq[49], but lower than Qatar[50], Kuwait[51] and Saudi Arabia[52].

As mentioned, there were few studies in this field in Iran. In a prospective study that was carried out in Fars province from 21 March 1991 to 20 March 1996, the incidence of type 1

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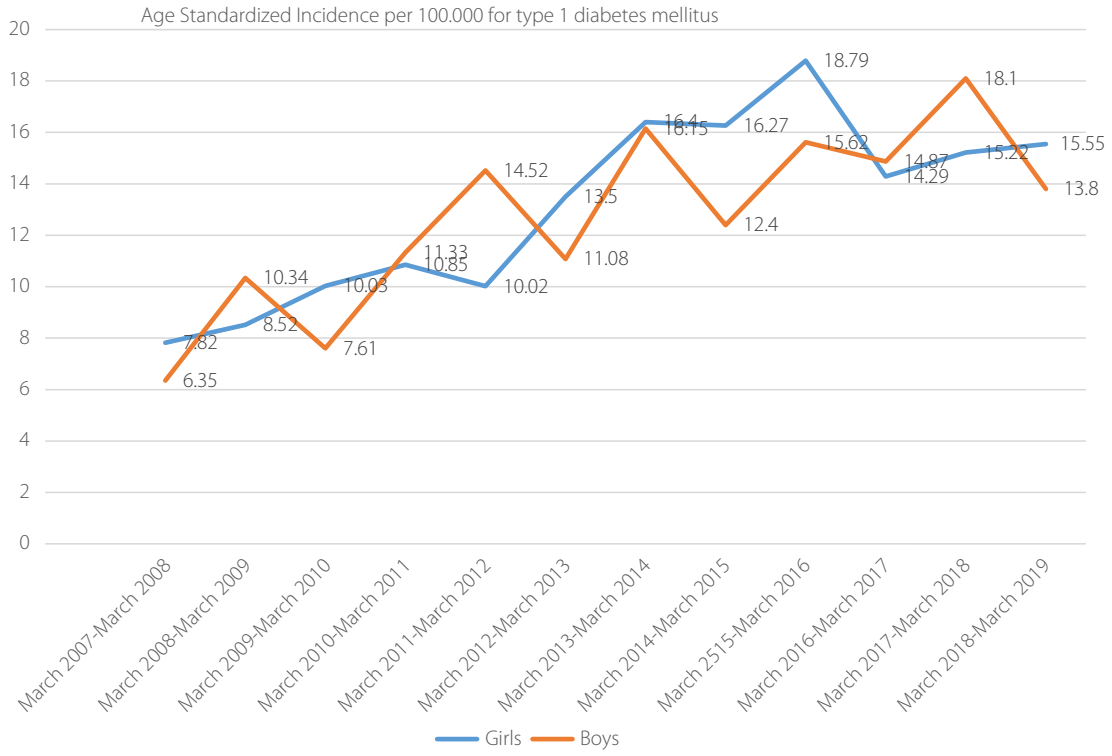

Figure 2 | The age standardized incidence per 100,000 for type 1 diabetes mellitus in the Isfahan population according to sex groups during 2007–2019 (1,386–1,397 Hijri Shamsi). **P*-value for trend for girls 0.002, *P*-value for trend for boys 0.005; ***P*-value for between groups trend comparison 0.44.

diabetes mellitus among the population aged <30 years was reported to be 3.7 in 100,000, with a significantly higher incidence rate in girls than boys[20]. In another study in Mazandaran, the prevalence of type 1 diabetes mellitus was reported to be 48 in 100,000 among the population aged 18 years[18]. In one recent study from Fars Province, Amiri *et al.*[19] reported the incidence of type 1 diabetes mellitus using the insurance archived prescription for 2 years. Based on their findings, the incidence rate was 27.4 in 100,000. These recent findings from different parts of Iran confirm the increasing trend of type 1 diabetes mellitus in Iran. In two different regions of Iran, Isfahan and Fars provinces, the incidence rate was different; one was classified as high and the other as very high. This might be due to different environmental factors, as well as different data collection methods. There were similar reports from Turkey from two different regions with different incidence rates[48,53].

Recent epidemiological data showed a fast-growing incidence rate in the Middle East and Asia[54,55]. It is suggested that in addition to genetic and environmental risk factors, consanguinity is one of the potential risk factors for type 1 diabetes mellitus in this region.

It seems that the global increasing trend of type 1 diabetes mellitus per variability in its incidence rate between countries and geographical regions worldwide could not be explained only by genetic factors, and the interaction of gene–environmental factors is more acceptable for the current situation. Suggested factors are the increasing prevalence of overweight and obesity, feeding of cow's milk, cesarean section, fetal and childhood infections, improved hygienic conditions, rapid intrauterine growth probably due to intrauterine overfeeding, and rapid growth during the first few years of life[56–58]. In addition, other socioeconomic factors, such as changing lifestyles, such as high-calorie diets, air pollution and environmental exposures, and improvement in economic conditions in combination with mentioned factors enhance the damaging process of β-cells. The combination of these factors is complex and is not yet determined[59–61].

Considering that most of the above-mentioned factors, especially the increasing rate of overweight/obesity, cesarean section, lifestyle modification and air pollution, are present in our community[62–64], it is suggested that the interaction of the factors might result in a higher incidence rate of type 1 diabetes mellitus. However, the role of each factor separately should be evaluated in future studies.

In the present study, there were no significant differences between boys and girls regarding the incidence rate in the studied period. Evidence showed that in high-incidence countries, the incidence of type 1 diabetes mellitus is more prominent in

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Table 3 | Incidence (95% confidence interval) per 100,000 for type 1 diabetes mellitus in the Isfahan population aged 0–19 years according to age groups during 2007–2019

	1,386 (March 2007–2008)	1,387 (March 2008–2009)	1,388 (March 2009–2010)	1,389 (March 2010–2011)	1,390 (March 2011–2012)	1,391 (March 2012–2013)	1,392 (March 2013–2014)	1,393 (March 2014–2015)	1,394 (March 2015–2016)	1,395 (March 2016–2017)	1,396 (March 2017–2018)	1,397 (March 2018–2019)	Total	*P*-value for trend (t)
0–4 years old														
No. cases	18	18	15	21	25	26	30	23	36	22	35	19	288	0.10
Incidence	6.26	6.10	4.88	6.63	7.75	7.90	8.94	6.73	10.29	6.16	8.89	5.53	7.31	1.8
(95% CI)	(3.79, 9.9)	(3.62, 9.64)	(2.73, 8.04)	(4.11, 10.14)	(5.02, 11.44)	(5.16, 11.58)	(6.03, 12.77)	(4.27, 10.11)	(7.47, 13.11)	(4.0, 8.32)	(7.14, 12.64)	(3.44, 7.61)	(5.41, 14.13)	
5–9 years old														
No. of cases	23	38	33	43	47	55	71	75	69	55	68	65	640	0.009
Incidence	7.89	10.83	11.34	14.70	15.88	18.08	22.77	23.21	21.06	16.66	20.20	18.96	16.85	3.2
(95% CI)	(5.0, 11.83)	(7.66, 14.86)	(7.81, 15.93)	(10.64, 19.8)	(11.67, 21.11)	(5.32, 12.13)	(17.79, 28.72)	(18.25, 29.09)	(16.89, 25.23)	(12.97, 20.36)	(16.17, 24.23)	(15.10, 22.83)	(12.18, 20.94)	
10–14 years old														
No. cases	29	37	35	44	53	41	60	51	72	79	69	60	630	0.001
Incidence	9.10	12.06	11.64	14.67	17.46	13.62	20.05	17.26	24.30	26.43	22.63	19.27	17.32	5.0
(95% CI)	(6.09, 13.07)	(8.49, 16.63)	(8.11, 16.18)	(10.66, 19.69)	(13.08, 22.83)	(9.77, 18.47)	(15.3, 25.81)	(12.85, 22.69)	(19.59, 29.01)	(21.54, 31.32)	(18.15, 27.11)	(15.18, 23.37)	(13.15, 22.56)	
15–19 years old														
No. cases	19	23	23	24	21	23	32	22	31	22	33	38	311	<0.001
Incidence	5.25	6.91	7.49	8.55	7.99	9.27	13.36	9.30	13.04	9.42	14.22	16.49	9.71	6.4
(95% CI)	(3.16, 8.21)	(4.38, 10.37)	(4.75, 11.24)	(6.92, 14.84)	(5.55, 13.12)	(5.24, 12.94)	(9.14, 18.85)	(5.83, 14.08)	(19.9, 16.90)	(6.11, 12.72)	(10.15, 18.29)	(12.09, 20.88)	(5.43, 12.32)	

CI, confidence interval.

boys, but in low-incidence countries, type 1 diabetes mellitus is more frequently reported in girls[7,18,19]. However, recent studies from Sweden, Alabama, Iran, Kuwait, Turkey and Egypt did not report any significant difference regarding the sex difference in type 1 diabetes mellitus incidence[19,22,46,51,59,60].

Based on the results of some studies the rate is mostly similar in children aged <14 years. Some studies showed that the rate is different between girls and boys in different age groups. Analysis of the results related to sex differences could be useful for understanding the role of hormonal and physiological factors in sex groups, and their interaction with other genetic and environmental factors in the occurrence of type 1 diabetes mellitus.

In the present study, the age-specific incidence rate was significantly higher in the 4–9 years and 10–14 years age groups than in other age groups. The incidence rate was significantly higher in the 10–14 years age group than in the 15–19 years age group. The present results were similar to the reports of several studies in this field, including many European countries, Kuwait and Turkey[18,19,25,51–53]. There was some differences regarding the difference between the 5–9 years age group and 10–14 years age group. Some reported a higher rate in the 5–9 years age groups and others in the 10–14 years age group.

Findings of the Diabetes Mondiale study, a multinational study from 57 countries and 112 centers, showed a higher incidence rate in the 5–9 years age group during 1990–1999[12].

The results of SEARCH for Diabetes in Youth showed that type 1 diabetes mellitus was more frequent in girls aged 5–9 years and boys aged 10–14 years[61]. Considering that such patterns are also reported in other studies, it is also suggested that sex differences might have a role in the reported features.

Based on the suggestion of Amiri *et al.*[19] in Shiraz, two different factors during school entry and puberty, including exposure to different infections and growth hormones peak, respectively, are considered trigger factors for type 1 diabetes mellitus in children aged 5–9 years and 10–14 years.

In the present study, the AAPC for the 0–4, 5–9, 10–14 and 15–19 years age groups were 3.9%, 6.3%, 7.9% and 8.58%, respectively. Although the rate was increasing for all age groups, it was higher in the 15–19 years age group. Children aged 5–14 years were in the second position for an increasing trend of type 1 diabetes mellitus. Saito *et al.*[65] in Japan showed an increased incidence rate for the 5–9 years age group, with an AAPC of 5.35% for this age group. They did not include children aged 15–19 years. The differences might be due to the design of the studies or the overall incidence rate of type 1 diabetes mellitus in the countries. Japan is considered a country with a low incidence rate of type 1 diabetes mellitus, whereas Iran is categorized as a country with an intermediate-to-high incidence rate for type 1 diabetes mellitus[65].

It seems that in recent decades, the incidence rate feature was changed. Based on reviewed literature an increase in incidence rate has been reported in both age groups (5–14 years old and 15–19 years old). The suggested explanations for the

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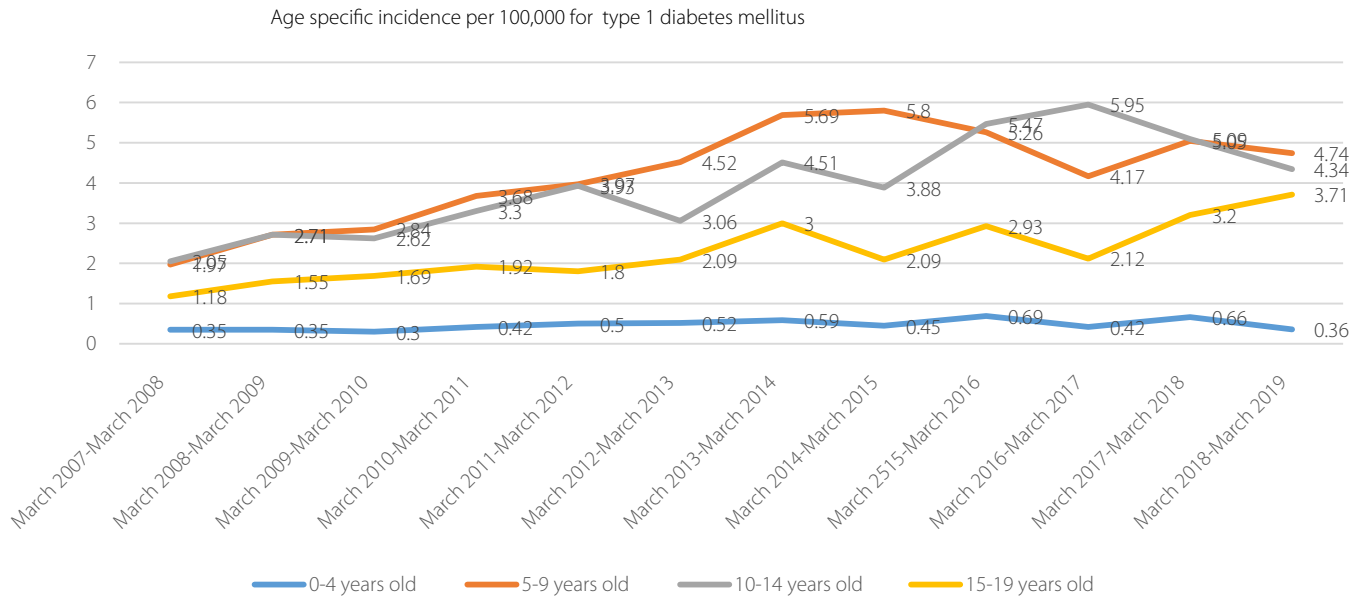

Figure 3 | Age-specific incidence per 100,000 for type 1 diabetes mellitus in Isfahan province according to age groups during 2007–2019 (1,386–1,397 Hijri Shamsi). **P*-value for trend for 0–4 years age group (0.09), for 5–9 years age group (0.009), for 10–14 years age group (0.001) and for 14–19 years age group (<0.001).

increasing rate in this age rage are earlier outcomes of different environmental triggers and puberty. However, evidence showed that sex hormones release could induce insulin resistance and trigger the onset of type 1 diabetes mellitus[66–68]. In addition, the age of puberty in the past decade decreased, which could also explain the findings[69].

The decreasing trend of type 1 diabetes mellitus in preschool children in Europe might be due to better perinatal care.

Analysis of the results related to the incidence of type 1 diabetes mellitus in different age groups would be helpful for the identification of important environmental trigger factors.

The strength of this study was that it was the first study to evaluate the incidence trend of type 1 diabetes mellitus in Iran over a period of 12 years.

The main limitation of the current study was the retrospective design of the study. Thus, we had some missing data, especially because we have no diabetes registry in Iran. It was not possible to investigate the related risk factors.

The present findings showed that currently our region is considered to have a high incidence rate of type 1 diabetes mellitus. Although we had fluctuations in the incidence rate over the 12 years, the overall trend is increasing. The cyclic pattern of incidence rates supports the dynamic process of type 1 diabetes mellitus, and more likely suggests the role of different environmental, socioeconomic and perinatal factors for the increasing trend of the disease, which should be investigated in future studies. The average annual change rate was high in this region in comparison with other countries. Furthermore, it is important to develop more effective prevention strategies by long-term monitoring of the disease, and provide facilities for the registry of type 1 diabetes mellitus in our region to plan appropriate management strategies for the disease for the increased cases of type 1 diabetes mellitus, and prevent type 1 diabetes mellitus-related morbidity and mortality.

DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: National Institute for Medical Research Development (NIMAD) with a research project number of 958,386.

Informed consent: Written informed consent was obtained from the participants.

Registry and the registration no. of the study/trial: National Institute for Medical Research Development (NIMAD), 958,386; 2020.

Animal studies: N/A.

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