

KRETANJE OBOLEVANJA OD DIJABETES MELITUSA TIP 1 KOD DEČAKA I DEVOJČICA UZRASTA 0-14 GODINA U BEOGRADU U PERIODU OD 1992. DO 2017. GODINE: *JOINPOINT* REGRESIONA ANALIZA

Aleksandra Nikolić¹, Marta Majcan, Sandra Grujičić¹

¹ Institut za epidemiologiju, Medicinski fakultet Univerziteta u Beogradu, Beograd, Srbija

SAŽETAK

Uvod/Cilj: Dijabetes melitus tip 1 (DM1) je jedna od najčešćih hroničnih bolesti kod dece i adolescenata, a stope incidencije na svetskom nivou su u porastu. Cilj ovog rada je bio da ispita kretanje obolevanja od DM1 kod dečaka i devojčica uzrasta 0-14 godina na teritoriji Beograda za period 1992-2017. godine.

Metode: Podaci o broju novoobolelih od DM1, uzrasta 0-14 godina, za period 1992-2017. godine, za područje Beograda, dobijeni su iz bolnica u kojima je postavljena dijagnoza DM1, Instituta za majku i dete „Dr Vukan Čupić“ i Univerzitetske dečje klinike, kao i iz registra za dijabetes. Podaci o broju stanovnika uzrasta 0-14 godina za Beograd su dobijeni iz Republičkog zavoda za statistiku. Na osnovu dobijenih podataka izračunate su sirove, standardizovane i uzrasno specifične stope incidencije DM1.

Rezultati: U Beogradu je, u periodu 1992-2017. godina, prosečna standardizovana stopa incidencije (na 100.000) DM1 bila 13,9 za dečake, a 12,3 za devojčice, uzrasta 0-14 godina. Kod oba pola raste uzrasno specifična stopa incidencije DM1 sa godinama starosti i najviša je u uzrastu 10-14 godina. U posmatranom periodu od 26 godina došlo je do značajnog prosečnog godišnjeg porasta standardizovane stope incidencije DM1 za +3,3% kod dečaka, a kod devojčica za +3,1%. Kod dečaka značajan prosečan godišnji porast uzrasno specifične stope incidencije DM1 je bio u uzrastu od 5 do 9 godina (+5,1%), a kod devojčica u uzrasnoj grupi 0-4 godine (+12,9%).

Zaključak: Potrebno je dalje praćenje kretanja obolevanja od DM1 dece uzrasta 0-14 godina u cilju identifikovanja faktora rizika koji doprinose nastanku ovog oboljenja i preduzimanja adekvatnih preventivnih mera i dobre organizacije zdravstvene zaštite.

Ključne reči: dijabetes melitus tip 1, incidencija, trend, joinpoint regresiona analiza

Uvod

Dijabetes melitus je česta metabolička i endokrina bolest koja pogađa decu. Iako pojava dijabetesa melitusa tipa 2 (DM2) kod dece i adolescenata privlači mnogo pažnje, dijabetes melitus tip 1 (DM1) ostaje preovlađujući oblik ove bolesti tokom detinjstva. Rizik od komplikacija dijabetesa i dalje je visok. Dijabetes je vodeći uzrok nefropatije, retinopatije, neuropatije i koronarnih i perifernih vaskularnih bolesti i predstavlja ogroman teret za javno zdravlje. Lečenje je doživotno, bolno, ometa svakodnevni život, zahteva samodisciplinu i uravnoteženu ishranu.

U svetu je, 2019. godine, bilo oko 98.200 novih slučajeva DM1 kod dece uzrasta 0-14 godina, dok je ukupan broj dece koja žive sa ovim

oboljenjem iznosio 600.000 (1). Incidencija DM1 značajno varira u različitim zemljama, ali se globalno povećava (2). Stope incidencije se kreću od 0,1 na 100.000 u regionu Zuni u Kini do više od 40 na 100.000 u Finskoj, što govori da je razlika u stopama incidencije između zemalja i do 400 puta (3). Podaci iz Finske, koja ima jednu od najvećih incidencija DM1 ukazuju na „ubrzavajuću“ epidemiju, sa stopom rasta većom od ranijih procena (4). Sličan trend porasta beleži se i u drugim evropskim zemljama, gde postoje razlike u trendovima, a porast je najveći u zemljama Centralne i Istočne Evrope koje su ranije imale najniže stope incidencije (4,5). Procenjuje se da je u Evropi ukupan godišnji porast incidencije 3% (5). Takođe, postoje dobri dokazi koji ukazuju na to da je najveće povećanje

TREND OF TYPE 1 DIABETES MELLITUS IN BOYS AND GIRLS UNDER 14 YEARS OF AGE IN BELGRADE IN THE PERIOD FROM 1992 TO 2017: JOINPOINT REGRESSION ANALYSIS

Aleksandra Nikolic¹, Marta Majcan, Sandra Grujicic¹

¹ Institute of Epidemiology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

SUMMARY

Introduction/Aim: Type 1 diabetes (DM1) is one of the most common chronic diseases of childhood and adolescence. The incidence of DM1 in children and adolescents has increased worldwide. The aim of this study was to analyze the trend of DM1 in boys and girls aged 0-14 years in Belgrade during period 1992-2017.

Methods: Data on the number of children with diabetes for the period 1992-2017 were obtained from two hospitals, the Institute for Mother and Child Dr Vukan Cupic and the University Children's Hospitals, as well as from the registers. Belgrade population figures are official data from the Statistical Office of The Republic of Serbia. Based on the data obtained, crude, standardized and age-specific incidence rates of DM1 were calculated.

Results: In Belgrade in the period 1992-2017 the average standardized incidence rate (per 100,000) is 13.9 for boys and 12.3 for girls aged 0-14 years. In both sexes, the age-specific incidence rate of DM1 increases with age and is highest at the age of 10-14 years. In the observed period of 26 years, there was a significant average annual increase in the standardized incidence rate of DM1 of + 3.3% in boys and + 3.1% in girls. In boys, a significant average annual increase in the age-specific incidence rate of DM1 was at the age of 5 to 9 years (+ 5.1%), and in girls in the age group 0-4 years (+ 12.9%).

Conclusion: A further follow-up of DM1 in children aged 0-14 years is needed in order to identify risk factors that contribute to the development of this disease and to take adequate preventive measures, as well as to organize the health care.

Key words: type 1 diabetes mellitus, incidence, trend, joinpoint regression analysis

Introduction

Diabetes mellitus is a common metabolic and endocrine disease, which affects children. Although the appearance of diabetes mellitus type 2 (DM2) in children and adolescents attracts a lot of attention, diabetes mellitus type 1 (DM1) remains the predominant type of this disease during childhood. The risk of diabetes complications is still high. Diabetes is a leading cause of nephropathy, retinopathy, neuropathy, coronary and peripheral vascular diseases, and it presents the great public health burden. The treatment is lifelong, painful, and it can disrupt daily life. It requires self-discipline and a balanced diet.

There were around 98,200 new cases of diabetes mellitus in children aged 0-14 in the

world in 2019, whereas the total number of children with this disease amounted to 600,000 (1). The incidence of DM1 significantly varies in different countries, and it has been increasing globally (2). The incidence rates vary from 0.1 per 100.000 in the region Zuni in China to more than 40 per 100.000 in Finland, which means that the rates vary 400-fold between countries (3). Data from Finland, which has one of the highest incidence rates of DM1, point to the "accelerating" epidemic with the rate of increase which is higher than the previous estimates (4). A similar trend of increase has been noted in other European countries, where difference in trends exists, while the highest increase is in the countries of Central and Eastern Europe, which had lower incidence rates before (4,5). The

stope incidencije kod dece uzrasta 0-4 godine (6).

Cilj ovog rada bio je da se ispita kretanje obolevanja od DM1 kod dečaka i devojčica uzrasta 0-14 godina u Beogradu za period 1992. do 2017. godine.

Metode

Podaci o broju obolelih od DM1 za period od 1992. do 2017. godine dobijeni su iz dve beogradske bolnice (Instituta za majku i dete „Dr Vukan Čupić“ i Univerzitetske dečje klinike

Tiršova) u kojima je postavljena dijagnoza DM1, prema kriterijumima Svetske zdravstvene organizacije (6). Dve pedijatrijske bolnice su jedine bolnice u Beogradu u kojima je postavljena konačna dijagnoza DM1 i odluka o terapiji. Takođe, podaci su preuzeti iz registra za dijabetes za period od 2006. do 2017. godine. U ovoj deskriptivnoj studiji prikazani su podaci samo za decu, uzrasta 0-14 godina, čije je prebivalište u Beogradu. Podaci o broju stanovnika Beograda po polu za uzrasne grupe 0-4, 5-9, 10-14 godina dobijeni su od Republičkog zavoda za statistiku

Tabela 1. Broj novoobolelih, sirove i standardizovane stope incidencije (na 100.000) od dijabetesa melitusa tip 1 za dečake i devojčice uzrasta 0-14 godina, Beograd, 1992-2017. godine

Godine/ Years	Dečaci/Boys			Devojčice/Girls		
	Broj obolelih/ No of new cases	Stope incidencije/ Incidence rates	Standardizovane stope/ Standardized rates	Broj obolelih/ No of new cases	Stope incidencije/ Incidence rates	Standardizovane stope/ Standardized rates
1992	15	10.2	9.8	11	7.9	6.9
1993	14	9.5	8.6	14	10.1	9.6
1994	18	12.2	11.7	13	9.4	8.8
1995	19	12.9	12.3	14	10.1	9.2
1996	26	17.7	16.3	19	13.7	12.4
1997	17	11.5	11.2	19	13.7	11.9
1998	16	10.9	9.9	11	7.9	7.3
1999	14	9.5	8.3	19	13.7	12.0
2000	18	12.2	11.8	13	9.4	8.3
2001	18	12.2	11.0	15	10.8	9.4
2002	17	11.6	10.5	14	10.1	8.9
2003	21	14.3	13.5	19	13.7	13.8
2004	24	4.0	3.9	12	8.6	7.6
2005	24	16.4	16.1	12	8.6	7.6
2006	15	10.2	9.0	12	15.8	14.1
2007	16	10.9	9.2	13	9.4	8.4
2008	25	17.1	16.4	24	17.3	17.1
2009	22	15.0	13.2	21	15.1	14.7
2010	18	12.3	13.3	17	12.2	11.7
2011	23	19.2	19.3	16	14.1	14.2
2012	19	15.9	15.4	26	22.9	22.5
2013	22	18.4	18.0	11	9.7	9.3
2014	30	25.0	24.6	24	21.2	20.8
2015	29	24.2	23.8	13	11.5	11.0
2016	32	26.7	26.1	22	19.4	18.5
2017	24	20.0	19.2	29	25.6	24.8
Prosek/ Average	536	14.6	13.9	433	13.1	12.3

overall annual increase in Europe is estimated at 3% (5). Also, there is firm evidence that the highest increase of the incidence rate is among children aged 0-4 years (6).

The aim of this work was to examine the trend of DM1 in boys and girls under 14 years of age in Belgrade in the period from 1992 to 2017.

Methods

Data on the number of patients with DM1 for the period 1992-2017 were obtained

from two hospitals in Belgrade (The Institute for Mother and Child Dr Vukan Cupic and the University Children's Hospital), where DM1 was diagnosed, according to the criteria of the World Health Organization (6). The two pediatric hospitals were the only hospitals in Belgrade, where the final diagnosis of DM1 was confirmed and the decision about therapy was made, as well. Also, data were taken from the register for diabetes for the period 1992-2017. In this descriptive study, data were shown only for children aged 0-14, whose place of residence

Table 1. Number of new cases, crude and standardized incidence rates (per 100,000) of type 1 diabetes mellitus for boys and girls aged 0-14, Belgrade, 1992-2017

Godine/ Years	Dečaci/Boys			Devojčice/Girls		
	Broj obolelih/ No of new cases	Stope incidencije/ Incidence rates	Standardizovane stope/ Standardized rates	Broj obolelih/ No of new cases	Stope incidencije/ Incidence rates	Standardizovane stope/ Standardized rates
1992	15	10.2	9.8	11	7.9	6.9
1993	14	9.5	8.6	14	10.1	9.6
1994	18	12.2	11.7	13	9.4	8.8
1995	19	12.9	12.3	14	10.1	9.2
1996	26	17.7	16.3	19	13.7	12.4
1997	17	11.5	11.2	19	13.7	11.9
1998	16	10.9	9.9	11	7.9	7.3
1999	14	9.5	8.3	19	13.7	12.0
2000	18	12.2	11.8	13	9.4	8.3
2001	18	12.2	11.0	15	10.8	9.4
2002	17	11.6	10.5	14	10.1	8.9
2003	21	14.3	13.5	19	13.7	13.8
2004	24	4.0	3.9	12	8.6	7.6
2005	24	16.4	16.1	12	8.6	7.6
2006	15	10.2	9.0	12	15.8	14.1
2007	16	10.9	9.2	13	9.4	8.4
2008	25	17.1	16.4	24	17.3	17.1
2009	22	15.0	13.2	21	15.1	14.7
2010	18	12.3	13.3	17	12.2	11.7
2011	23	19.2	19.3	16	14.1	14.2
2012	19	15.9	15.4	26	22.9	22.5
2013	22	18.4	18.0	11	9.7	9.3
2014	30	25.0	24.6	24	21.2	20.8
2015	29	24.2	23.8	13	11.5	11.0
2016	32	26.7	26.1	22	19.4	18.5
2017	24	20.0	19.2	29	25.6	24.8
Prosek/ Average	536	14.6	13.9	433	13.1	12.3

Tabela 2. Ukupan i prosečan broj novoobolelih od dijabetesa melitusa tip 1, prosečne uzrasno specifične stope incidencije (na 100.000) i joinpoint regresiona analiza kretanja incidencije, dečaci, Beograd, 1992-2017. godine

Uzrasne grupe/ <i>Age groups</i> (godine/years)	Ukupan broj obolelih od 1992. do 2017. godine/ <i>Total number of cases from 1992 till 2017</i>	Prosečan broj obolelih/ <i>Average number of new cases</i>	Prosečne stope incidencije/ <i>Average incidence rates</i>	AAPC (95% IP) AAPC (95% CI)
0 - 4	102	4	8.9	1.9 (-5.9 do 10.3)
5 - 9	197	8	16.2	5.1^ (2.5 do 7.7)
10 - 14	237	9	18.1	2.1 (-0.2 do 4.4)
0-14	536	21	13.9*	3.3^ (1.4 do 5.2)

AAPC –proseča godišnja promena procenta za period 1992-2017.godina; ^-AAPC je značajno različito od 0 za alfa 0,05; 95% IP – 95% interval poverenja; * standardizovana stopa na 100.000

prema popisima 1991, 2002. i 2011. godine. Na osnovu dobijenih podataka izračunate su opšte, uzrasno specifične i standardizovane stope incidencije DM1.

Trendovi stopa incidencije su izračunati korišćenjem joinpoint regresione analize (*Joinpoint Regression Program, Version 4.7.0.0. February, 2019; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute*), prema metodu Kim et al. (7). Joinpoint regresionom analizom određena je prosečna procentualna godišnja promena (engl. *AAPC – Average annual percent change*). Kao nezavisna varijabla postavljene su godine, dok je zavisna varijabla bila odgovarajuća uzrasno specifična stopa. Korišćen je *Grid Search* metod (8). Pored toga, 95% intervali poverenja računati su za svaku procenu AAPC kako bi se utvrdilo da li je AAPC

različit od 0. Koristili smo test uporedivosti da uporedimo linije regresije. Glavni cilj testa uporedivosti bio je upoređivanje dva niza podataka o trendovima čije su srednje funkcije predstavljene joinpoint regresijom. Poseban interes bio je ispitivanje da li su dve srednje vrednosti regresije paralelne (test paralelizma).

Rezultati

U periodu od 1992. do 2017. godine, u Beogradu je obolelo 536 dečaka i 433 devojčice od DM1 (tabela 1), odnosno prosečno godišnje oboleo je 21 dečak i 17 devojčica. Prosečna standardizovana stopa incidencije bila je neznatno viša za dečake uzasta 0-14 godina (13,9 na 100.000), nego za devojčice (12,3 na 100.000) istog uzrasta. Kod oba pola došlo je porasta standardizovane stope incidencije (na 100.000) i to kod dečaka sa 9,8 u 1992. godini

Tabela 3. Ukupan i prosečan broj novoobolelih od dijabetesa melitusa tip 1, prosečne uzrasno specifične stope incidencije (na 100.000) i joinpoint regresiona analiza kretanja incidencije, devojčice, Beograd, 1992-2017. godine

Uzrasne grupe/ <i>Age groups</i> (godine/years)	Ukupan broj obolelih od 1992. do 2017. godine/ <i>Total number of cases from 1992 till 2017</i>	Prosečan broj obolelih/ <i>Average number of new cases</i>	Prosečne stope incidencije/ <i>Average incidence rates</i>	AAPC (95% IP) AAPC (95% CI)
0 - 4	67	3	6.4	12.9^ (1.3 do 25.8)
5 - 9	160	6	14.0	3.5^ (0.8 do 6.3)
10 - 14	216	8	18.4	2.3 (-0.1 do 4.7)
0-14	433	17	12.3	3.1^ (1.5 do 4.7)

AAPC –proseča godišnja promena procenta za period 1992-2017.godina; ^-AAPC je značajno različito od 0 za alfa 0,05; 95% IP – 95% interval poverenja; * standardizovana stopa na 100.000.

Table 2. Total and average number of new cases of type 1 diabetes mellitus, average age-specific incidence rates (per 100,000) and joinpoint regression analysis of incidence trend, boys, Belgrade, 1992-2017

Uzrasne grupe/ Age groups (godine/years)	Ukupan broj obolelih od 1992. do 2017. godine/ Total number of cases from 1992 till 2017	Prosečan broj obolelih/ Average number of new cases	Prosečne stope incidencije/ Average incidence rates	AAPC (95% IP) AAPC (95% CI)
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10 - 14	237	9	18.1	2.1 (-0.2 do 4.4)
0-14	536	21	13.9*	3.3^ (1.4 do 5.2)

AAPC –Average Annual Percent Change for the period 1992-2017; ^ -AAPC is significantly different from 0 for alpha 0.05; 95% CI– 95% confidence interval; *standardized rate per 100,000.

was in Belgrade. Data on the number of residents of Belgrade for the gender-specific groups aged 0-4, 5-9, 10-14 years were obtained from the Statistical Office of The Republic of Serbia according to the Census from 1991, 2002 and 2011. General, age-specific and standardized incidence rates of DM1 were calculated on the basis of the obtained data.

Trends of the incidence rates were calculated with the help of joinpoint regression analysis (Joinpoint Regression Program, Version 4.7.0.0 February, 2019; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute), based on the method of Kim et al. (7). The average annual percentage change (AAPC) was determined with the help of joinpoint regression analysis. Age was set as an independent variable, while the corresponding age-specific rate was a dependent variable. Grid Search Method was

used (8). Besides, the 95% confidence interval was calculated for each estimate of AAPC in order to determine whether the AAPC was different from 0. The test of compatibility was used in order to compare regression lines. The main aim of the compatibility test was to compare two sets of trend data, whose mean functions were presented by joinpoint regression. A specific interest was testing whether the two regression mean functions were parallel (test of parallelism).

Results

In Belgrade, during the period 1992-2017, 536 boys and 433 girls were diagnosed with DM1 (Table 1), that is, on average, 21 boys and 17 girls annually. An average standardized incidence rate was slightly higher in boys aged 0-14 years (13.9 per 100,000), than in girls (12.3 per 100,000) of the same age. The standardized

Table 3. Total and average number of new cases of type 1 diabetes mellitus, average age-specific incidence rates (per 100,000) and joinpoint regression analysis of incidence trend, girls, Belgrade, 1992-2017

Uzrasne grupe/ Age groups (godine/years)	Ukupan broj obolelih od 1992. do 2017. godine/ Total number of cases from 1992 till 2017	Prosečan broj obolelih/ Average number of new cases	Prosečne stope incidencije/ Average incidence rates	AAPC (95% IP) AAPC (95% CI)
0 - 4	67	3	6.4	12.9^ (1.3 do 25.8)
5 - 9	160	6	14.0	3.5^ (0.8 do 6.3)
10 - 14	216	8	18.4	2.3 (-0.1 do 4.7)
0-14	433	17	12.3	3.1^ (1.5 do 4.7)

AAAPC –Average Annual Percent Change for the period 1992-2017; ^ -AAPC is significantly different from 0 for alpha 0.05; 95% CI– 95% confidence interval; *standardized rate per 100,000.

na 19,2 u 2017. godini, a kod devojčica sa 6,9 u 1992. godini na 24,8 u 2017. godini.

Kod oba pola sa godinama starosti raste uzrasno specifična stopa incidencije DM1 (grafikon 2 i 3). Značajan prosečan godišnji porast uzrasno specifičnih stopa incidencije DM1, u posmatranom periodu, je zabeležen kod dečaka u uzrastu 5-9 godina (+ 5,3%), a kod devojčica u uzrastima 0-4 godine (+12,9%) i 5-9 godina (+3,5%).

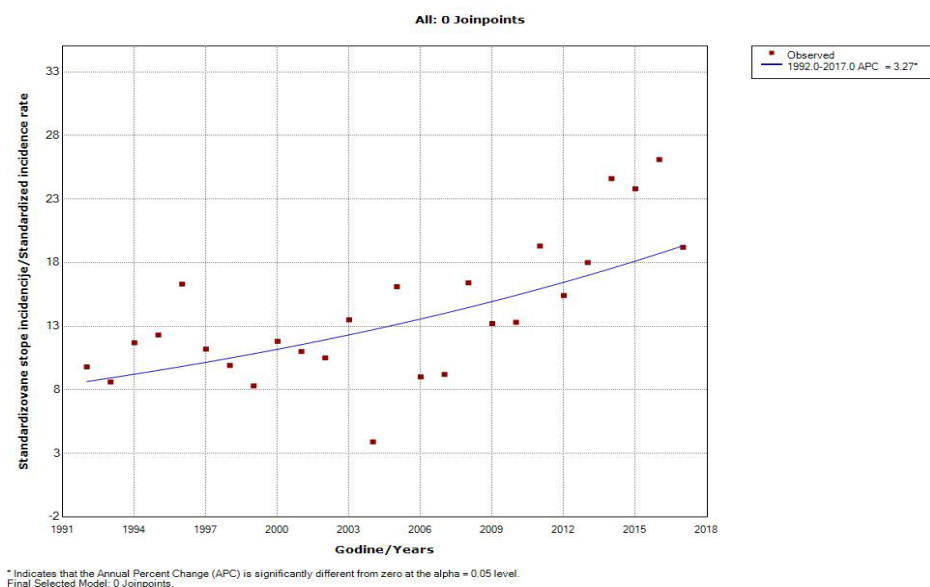
Takođe, kod oba pola uzrasta 0-14 godina dolazi do značajnog prosečnog godišnjeg porasta standardizovanih stopa incidencije DM1 tokom posmatranog dvadesetšestogodišnjeg perioda i to za +3,3% kod dečaka i za +3,1% kod devojčica (grafikon 1).

Prema rezultatima testa uporedivosti (grafikon 2) trendovi standardizovanih stopa incidencije DM1 kod dečaka i devojčica bili su paralelni (*final selected model failed to reject parallelism $p = 0,867$*).

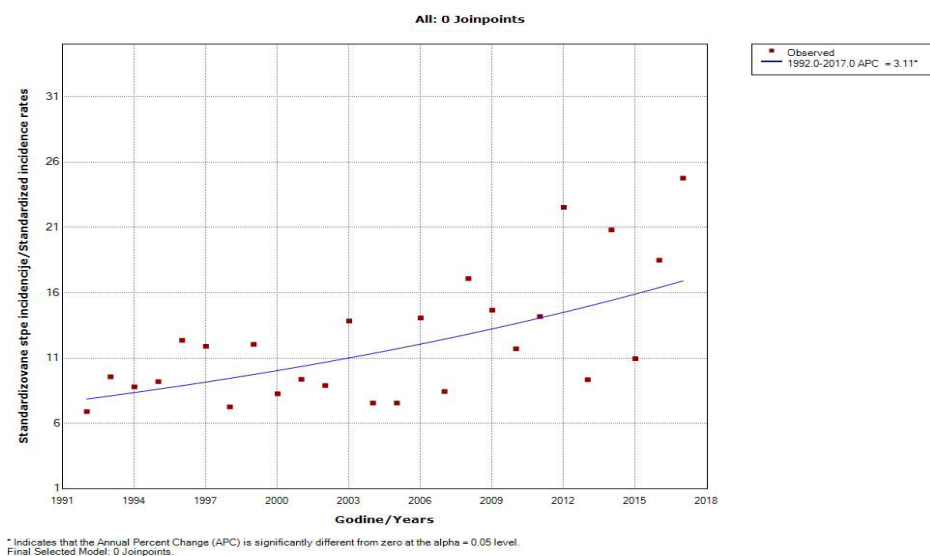
Diskusija

Na globalnom nivou, zemlje se prema vrednostima stopa incidencije DM1 grupišu u zemalje sa vrlo niskim (<1/100.000), niskim (1-4/100.000), srednjim (5-9,9/100.000), visokim (10-19,9/100.000) i vrlo visokim ($\geq 20/100.000$) stopama incidencije (12). Prema ovoj klasifikaciji, Beograd sa prosečnom standardizovanom stopom incidencije za DM1 od 13,9 na 100.000 za dečake i 12,3 na 100.000

a)



b)



Grafikon 1. Jointpoint regresiona analiza: kretanje standardizovanih stopa incidencije dijabetesa melitusa tip 1 kod dečaka (a) i devojčica (b) uzrasta 0-14 godina, Beograd, 1992-2017. godina

incidence rate increased in both sexes (per 100,000), that is, in boys it increased from 9.8 in 1992 to 19.2 in 2017, while in girls it increased from 6.9 in 1992 to 24.8 in 2017.

In both sexes, as they got older, the age-specific incidence rate of DM1 increased (Figures 2 and 3). A significant annual increase of the age-specific incidence rates of DM1 in the observed period was recorded in boys aged 5-9 (+5.3%), and in girls aged 0-4 (+12.9%) and 5-9 (+3.5%).

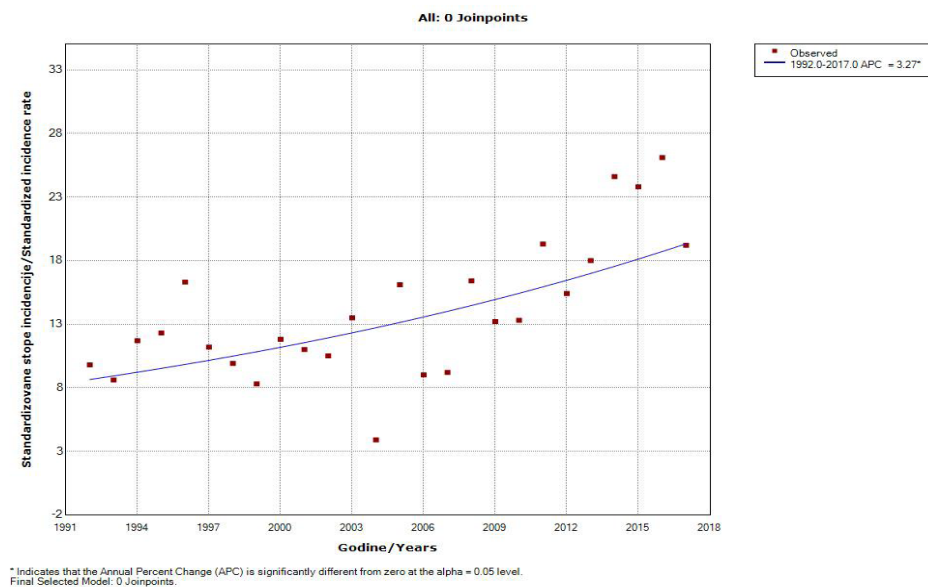
Also, in both sexes aged 0-14 there came to the significant increase in the standardized incidence rates of DM1 during the observed 26 years long period, that is, for 3.3% in boys and for 3.1% in girls (Figure 1).

According to the results of the compatibility test (Figure 2), the trends of standardized incidence rates of DM1 in boys and girls were parallel (final selected model failed to reject parallelism $p = 0.867$).

Discussion

At the global level, countries are, according to the values of incidence rates of DM1, classified into countries with the very low ($<1/100,000$), low ($1-4/100,000$), moderate ($5-9.9/100,000$), high ($10-19.9/100,000$) and very high ($>20/100,000$) incidence rates (12). According to this classification, Belgrade with the average standardized incidence rate of DM1, which was 13.9 per 100,000 in boys and 12.3

a)



b)

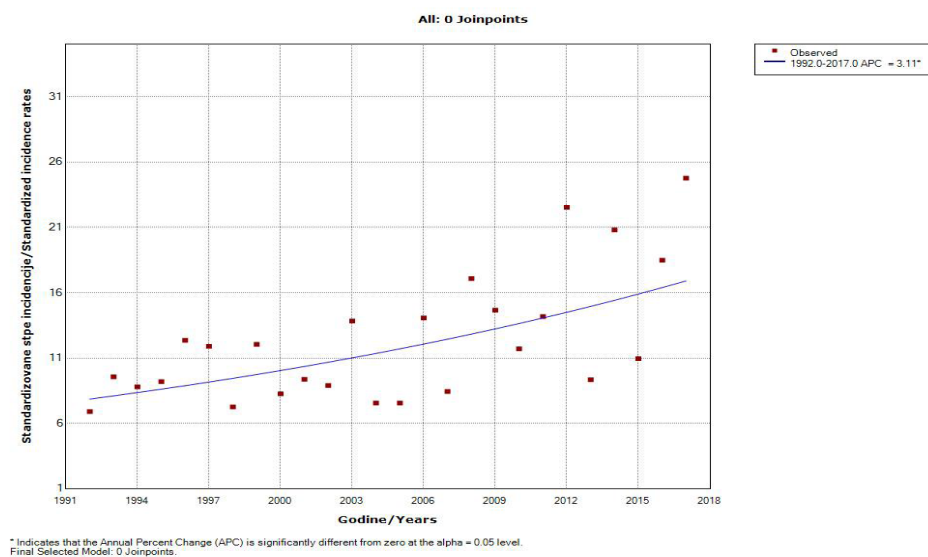


Figure 1. Joinpoint regression analysis: trend of standardized incidence rates of type 1 diabetes mellitus in boys (a) and girls (b) aged 0-14 years, Belgrade, 1992-2007

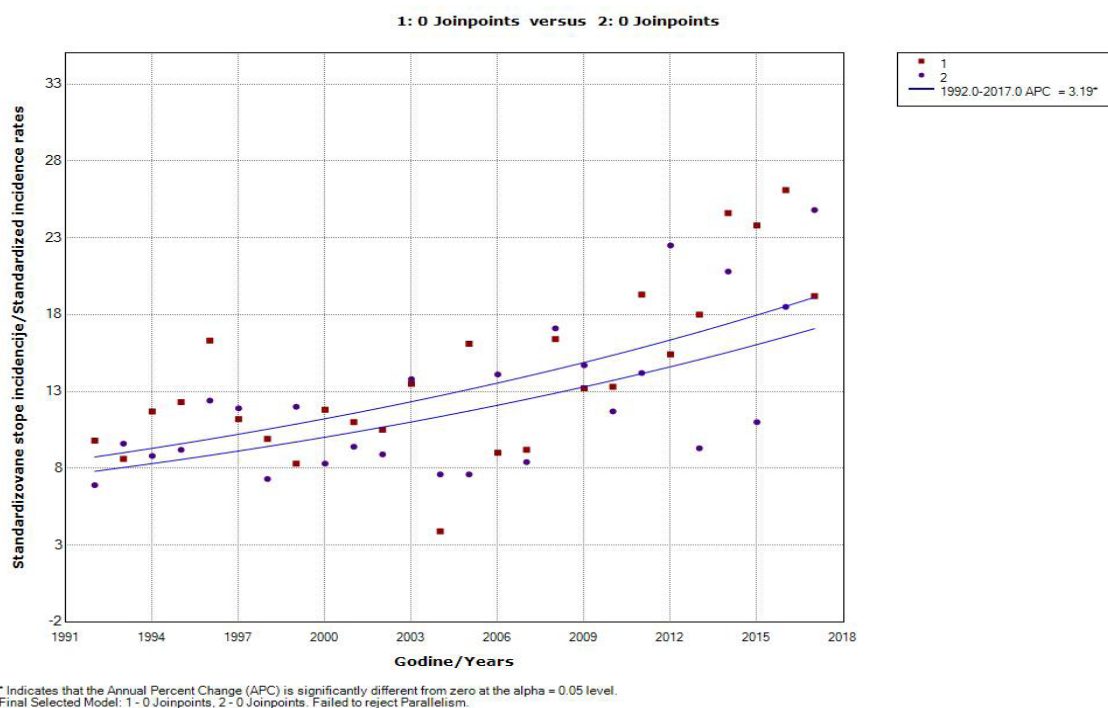
za devojčice pripada području sa visokom stopom incidencije. Takođe, podaci studije o incidenciji DM1 u Beogradu za period 1992-2005. godine, pokazuju da je Beograd sa ukupnom standardizovanom stopom incidencije od 10,4 na 100.000 stanovnika i tada pripadao područjima sa visokom stopom incidencije za DM1 (13).

EURODIAB registrom obuhvaćeno je 29.311 dece sa DM1 mlađe od 15 godina na osnovu podataka 20 populacionih registara iz 17 zemalja za period 1989-2003. godine (4). Prema ovim podacima, stope incidencije su se kretale od 4,7 na 100.000 u Rumuniji do 39,9 na 100.000 u Finskoj. Porast incidencije, tokom petnaestogodišnjeg perioda, je bio najbrži među zemljama koje su u početku imale najniže stope incidencije. Najveći porast incidencije primećen u najmlađoj starosnoj grupi. Ukupni godišnji porast incidencije DM1 za sve centre zajedno je bio za +3,9% (95%IP 3,6-4,2), a za uzrast 0-4 godine +5,4%, 5-9 godina +4,3%, a za uzrast 10-14 godina +2,9%. Ovaj brz porast incidencije DM1 među najmlađima je primećen za regione centralne i istočne Evrope. U Hrvatskoj je, u periodu 2004-2012. godine, došlo do godišnjeg porasta incidencije DM1 za +5,9% kod dece mlađe od 15 godina, a za +7,8% kod dečaka i

+4,8% kod devojčica (14). Kod oba pola porast incidencije je bio najviši u uzrasnoj grupi 10-14 godina.

U Beogradu je, u periodu 1992-2017. godine, došlo do značajnog godišnjeg porasta standardizovane stope incidencije DM1 za +3,3% kod dečaka i +3,1% kod devojčica uzrasta 0-14 godina. Kod dečaka je godišnji porast incidencije bio najveći za uzrast od 5 do 9 godina (+5,1%), a kod devojčica u najmlađoj uzrasnoj grupi 0-4 godine (+12,9%). Međutim, najveće stope incidencije kod oba pola bile su u uzrastu 10-14 godina.

Uprkos porastu incidencije DM1 u velikom broju zemalja, malo je verovatno da se ovaj porast može pripisati izmenama u genetskoj strukturi stanovništva. Najverovatnije su glavni razlozi porasta incidencije izmene u izloženosti faktorima spoljne sredine. U tom kontekstu postavljeno je nekoliko teorija koje objašnjavaju porast incidencije DM1 u detinjstvu u razvijenim zemljama (2). One uključuju povećanu stopu carskih rezova, nutritivne faktore (na primer, nedostatak vitamina D ili ranu izloženost proteinima kravljeg mleka ili cerealijama), smanjenu izloženost dečijim infekcijama i povećanu dečiju gojaznost. Na primer, prema „hipotezi o higijeni“, smatra se da smanjena



Grafikon 2. Jointpoint regresiona analiza: kretanje standardizovanih stopa incidencije dijabetesa melitusa tip 1 kod dečaka i devojčica uzrasta 0-14 godina, Beograd, 1992-2007. godina: test uporedivosti

per 100,000 in girls, belongs to the regions with the high incidence rates. Also, study data on the incidence of DM1 in Belgrade during the period 1992-2005 show that Belgrade with the overall standardized incidence rate of 10.4 per 100,000 residents belonged even then to the regions with the high incidence rates of DM1 (13).

EURODIAB register included 29,311 children with DM1, who were younger than 15 years, on the basis of data from 20 population registers from 17 countries for the period 1989-2003 (4). According to these data, the incidence rates ranged from 4.7 per 100,000 in Romania to 39.9 per 100,000 in Finland. The increase of incidence, during the fifteen year long period, was fastest in countries which had had the lowest incidence rates in the beginning. The highest increase in incidence was noted in the youngest age group. The overall annual increase in DM1 incidence for all groups together was +3.9% (95% IP 3.6-4.2), while for the age group 0-4 it was +5.4%, for the group 5-9 years +4.3%, and for the group 10-14 years +2.9%. This fast increase of DM1 incidence among children was noted in the regions of Central and Eastern Europe. In Croatia, during the period 2004-2012, there came to the annual increase in DM1 incidence for +5.9% in children younger than 15

years, and for +7.8% in boys and +4.8% in girls (14). In both sexes, the increase in incidence was highest in the age group 10-14 years.

In Belgrade, during the period 1992-2017, there came to the significant annual increase in the standardized incidence rate of DM1 of +3.3% in boys and +3.1% in girls aged 0-14 years. In boys, the annual increase in incidence was highest in the age group 5 to 9 years (+5.1%), and in girls in the youngest age group 0-4 years (+12.9%). However, the highest incidence rates for both sexes were in the age group 10-14 years.

Despite the increase in incidence of DM1 in a large number of countries, it is not very likely that this increase may be attributed to the changes in the genetic structure of population. It is quite likely that the main reasons for the incidence increase are changes in exposure to environmental factors. In this context, there are a few theories that explain the increase in DM1 incidence in childhood in developed countries (2). They include the increased rate of Caesarean sections, dietary factors (for example, vitamin D deficiency or early exposure to cow's milk proteins or cereals), less contact with childhood infections and the rise in childhood obesity. For example, according

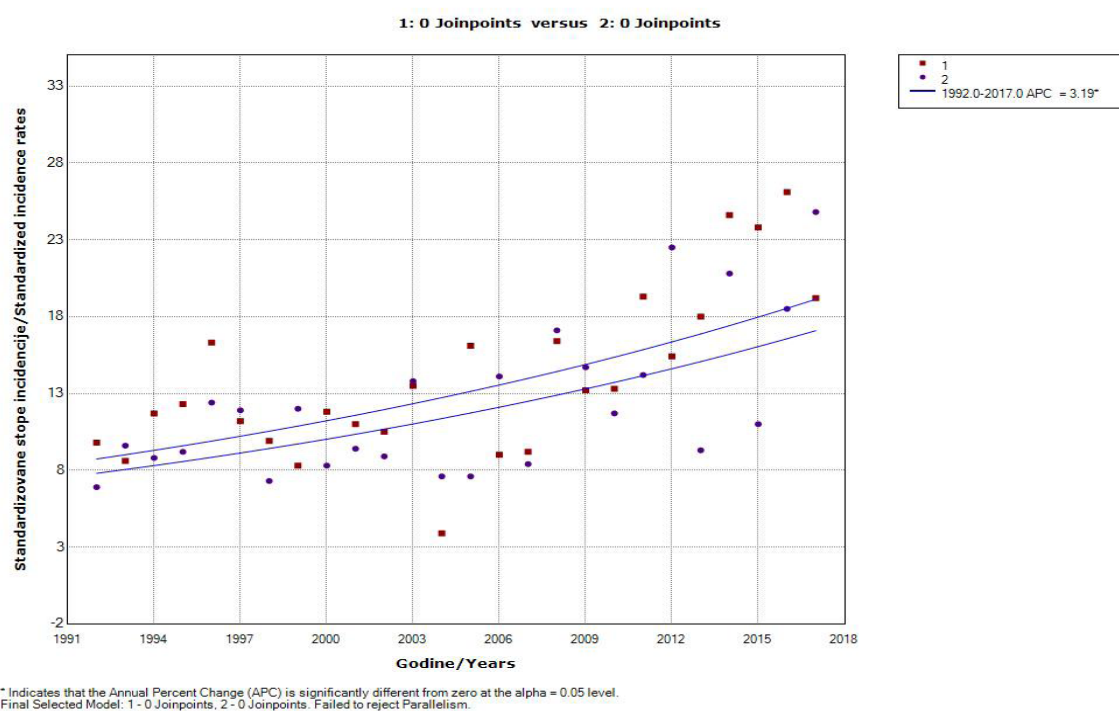


Figure 2. Joinpoint regression analysis: trend of standardized incidence rates of type 1 diabetes mellitus in boys and girls aged 0-14 years, Belgrade, 1992-2007: test of parallelism

izloženost patogenima u detinjstvu može dovesti do povećane atopije, astme i autoimunih bolesti poput DM1 (5). Od posebnog značaja je povezanost DM1 sa visokom telesnom težinom i ranim povećanjem telesne težine (15). Dečija gojaznost, s njom povezana insulinska rezistencija i zapaljenja, mogu dovesti do ubrzane apoptoze β ćelija, a time i ranije manifestacija DM1 kod osoba koje imaju povećanu genetsku sklonost (16). U prilog ovoj teoriji ide i činjenica da ubrzani porast incidencije DM1 prati rastuću prevalenciju dečije gojaznosti u Evropi (17).

Učestalost DM1 kod mlađih odraslih osoba starosti preko 15 godina pokazuje malo dokaza o porastu (18,19), ali zapažene su više stope incidencije kod muškaraca nego kod žena za ovu uzrasnu grupu (20). Ukoliko se javljanje DM1 zaista pomera prema mlađim uzrastima, onda niža stopa incidencije kod žena od 15 i više godina mogla bi objasniti niske stope porasta incidencije kod devojčica u uzrastu od 10 do 14 godina (4).

Predviđeni porast DM1 u detinjstvu i porast proporcije slučajeva dijagnostikovanih u mlađim uzrastima nego što su bili pre, može dovesti do većeg broja slučajeva komplikacija, zbog čega su pravovremena dijagnoza i terapija od presudnog značaja (21). U nedostatku bilo kakvih efikasnih sredstava za prevenciju DM1, mora se obezbediti odgovarajuće planiranje usluga i resursi za obezbeđivanje visokokvalitetne nege za povećan broj dece kojoj će biti dijagnostikovana dijabetes u narednim godinama.

Zaključak

Na osnovu standardizovanih stopa incidencije za DM1 za decu uzrasta 0-14 godina, može se zaključiti da Beograd pripada područjima sa visokom stopom incidencije i da se beleži značajan porast stope incidencije kod oba pola u periodu 1992-2017. godine. Ovaj porast je neznatno veći kod dečaka nego devojčica. Potrebno je dalje praćenje kretanja obolevanja od DM1 dece uzrasta 0-14 godina, kako bi se identifikovali faktori rizika koji doprinose ovom porastu i preduzele adekvatne preventivne mere, kao i da bi se adekvatno organizovala zdravstvena služba.

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to the “hygiene hypothesis”, it is claimed that the reduced exposure to pathogens during childhood can lead to the increased atopy, asthma, and autoimmune diseases such as DM1 (5). An association between DM1 and obesity, as well as early increase in body weight, is of great importance (15). Childhood obesity, as well as insulin resistance and inflammations, which are associated with it, lead to the faster apoptosis of β cells, and therefore, to earlier manifestations of DM1 in people who have increased genetic susceptibility (16). The fact that the faster increase in DM1 follows the growing prevalence of childhood obesity in Europe speaks in favor of this theory (17).

There is little evidence about the increase in incidence of DM1 in younger adolescents older than 15 years (18,19), however, higher incidence rates have been noted in men rather than in women for this age group (20). If the appearance of DM1 actually shifts towards younger age groups, then the lower incidence rate in women aged 15 and older could explain the low increase in incidence rates in girls aged 10 to 14 (4).

The estimated increase in DM1 during childhood and the increase in cases diagnosed in younger age groups than before, could lead to a larger number of complications, due to which the timely diagnosis and therapy are of utmost importance (21). In regard to the fact that there are no efficient means to prevent DM1, the adequate planning of services and the high quality care should be provided for the larger number of children, who will be diagnosed with diabetes in the years to come.

Conclusion

On the basis of standardized incidence rates of DM1 in children aged 0-14 years, conclusion can be made that Belgrade belongs to the regions with the high incidence rates and that the significant increase in incidence rates was registered in both sexes for the period 1992-2017. This increase is slightly higher in boys than in girls. A further follow-up of DM1 in children aged 0-14 years is necessary in order to identify risk factors which contribute to this increase and to take adequate preventive measures, as well as to organize the healthcare service in an adequate way.

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Autor za korespondenciju: Sandra Šipetić Grujičić, Institut za pidemiologiju, Medicinski fakultet, Univerzitet u Beogradu, Višegradska 26a, 11000 Beograd, Srbija; e-mail: sandra.grujicic2014@gmail.com

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Corresponding author: Sandra Sipetic Grujicic, Institute of Epidemiology, Faculty of Medicine, University of Belgrade, Visegradska 26, 11000 Belgrade, Serbia; e-mail: sandra.grujicic2014@gmail.com
