

Correlating the global increase in type 1 diabetes incidence across age groups with national economic prosperity: A systematic review

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Abstract

BACKGROUND

The global epidemiology of type 1 diabetes (T1D) is not yet well known, as no precise data are available from many countries. T1D is, however, characterized by an important variation in incidences among countries and a dramatic increase of these incidences during the last decades, predominantly in younger children. In the United States and Europe, the increase has been associated with the gross domestic product (GDP) per capita. In our previous systematic review, geographical variation of incidence was correlated with socio-economic factors.

AIM

To investigate variation in the incidence of T1D in age categories and search to what extent these variations correlated with the GDP per capita.

METHODS

A systematic review was performed to retrieve information about the global incidence of T1D among those younger than 14 years of age. The study was carried out according to the PRISMA recommendations. For the analysis, the incidence was organized in the periods: 1975-1999 and 2000-2017. We searched the incidence of T1D in the age-groups 0-4, 5-9 and 10-14. We compared the incidences in countries for which information was available for the two periods. We obtained the GDP from the World Bank. We analysed the relationship between the incidence of T1D with the GDP in countries reporting data at the national level.

RESULTS

We retrieved information for 84 out of 194 countries around the world. We found a wide geographic variation in the incidence of T1D and a worldwide increase

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during the two periods. The largest contribution to this increase was observed in the youngest group of children with T1D, with a relative increase of almost double when comparing the two periods (P value = 2.5×10^{-5}). Twenty-six countries had information on the incidence of T1D at the national level for the two periods. There was a positive correlation between GDP and the incidence of T1D in both periods (Spearman correlation = 0.52 from 1975-1999 and Spearman correlation = 0.53 from 2000-2017).

CONCLUSION

The incidence increase was higher in the youngest group (0-4 years of age), and the highest incidences of T1D were found in wealthier countries.

Key words: Type 1 diabetes; Incidence; Children; Age categories; Gross domestic product per capita

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Core tip: Currently, there is information on the incidence of T1D of 43.3% of the 194 countries of the world, of which only 44 countries have national coverage information. We found a wide geographic variation in the incidence of T1D and a worldwide increase in the two periods (1975-1999 and 2000-2017). Comparing the two periods, the relative increase in the incidence occurred in the 0-4 group (1.9 times), followed by the 5-9 group (1.8 times) and 10-14 group (1.4 times). There was a positive correlation between GDP per capita, and the incidence of T1D, where wealthier countries have higher values of incidence.

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INTRODUCTION

Type 1 diabetes (T1D) is one of the most common endocrine diseases in childhood and adolescence. Additionally, the diagnosis of T1D has increased considerably in adults^[1]. According to the International Diabetes Federation (IDF), it was estimated that more than 86000 children were living with T1D in 2015 around the world^[2]. There is a wide geographic variation in the incidence of T1D, both among countries and within the different regions in these countries. In North America and Europe, the incidence varies between 4 and 41 per 100000. The countries that report the highest rates are Switzerland, Finland, Norway, the United Kingdom and Sardinia, with values > 20 per 100000 per year. In contrast, T1D is rare in Asian countries, such as China, where the incidence is approximately 0.1 case per 100000 people each year^[3-5]. In Latin America, according to IDF, it is estimated that 45100 children younger than 15 years have T1D^[6]. (Table 1)

There are differences in the incidence rates among age categories (0-4, 5-9, 10-14) in almost all countries. According to DIAMOND^[6], for the period between 1991-1996, it was noted that the incidence increased with age; children between 5 and 9 years had 1.62 times the risk of children 0-4 years, *i.e.*, a 62% excess risk, and the 10-14 age group had 1.93 times the risk of the 0-4 age group. Recently, there have been signs suggesting that this trend is changing. Records of the Patterson *et al*^[7] between 1999 and 2008, showed that the incidence was highest in the youngest age group (0 to 4 years), with an increase of 5.4% compared to 4.3% in the 5-9 age group and 2.9% in the 10-14 age group.

In addition, the IDF has suggested the existence of a relationship between income level and the incidence of T1D^[2]. In the United States, where the incidence of T1D in different socio-economic groups was studied, it was found that there was a higher incidence of T1D in the highest income groups^[8]. The same pattern occurs in Europe, where it was shown that the incidence of T1D correlates strongly with the gross domestic product (GDP). GDP is most commonly used to measure the size of a

Table 1 Incidence of type 1 diabetes in individuals aged 0-14 years

Country	Area	Study period	Inc	Asce %	InfoSource	Datacollection	Ref.
Algeria	Oran	1990-1999	8.60	NA	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
Argentina	Cordoba	1991-1992	7.00	90.0	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
	Avellaneda	1990-1996	6.30	94.0	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
	Tierra del Fuego	1993-1996	10.30	100.0	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
	Corrientes	1992-1999	6.60	95.0	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
	Australia	NW ^a	2000-2011	23.6	97	PBDR	H
Austria	NW	2004-2008	17.50	97.2	PBDR	P	Patterson <i>et al</i> ^[19]
Bahamas	NW	2001-2002	10.10	NA	MBR	P	Peter <i>et al</i> ^[20]
Barbados	NW	1990-1993	2.00	NA	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
Belarus	Gomel, Minsk	1997-2002	5.60	100.0	PBDR	NA	Zalutskaya <i>et al</i> ^[21]
Belgium	Antwerp	2004-2008	15.90	94.9	PBDR	P	Patterson <i>et al</i> ^[19]
Bosnia and Herzegovina	Tuzla Canton	1995-2004	6.93	100.0	PBDR	P	Tahirović <i>et al</i> ^[22]
	Republic of Srpska	1998-2010	8.13	100.0	PBDR	P	Radosevic <i>et al</i> ^[23]
Brazil	São Paulo ^a (Bauru)	1986-2015	12.8	97.7	PBDR	P	Negrato <i>et al</i> ^[24]
	Rio Grande do Sul (Passo Fundo)	1996-1999	7.00	82.5	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
Bulgaria	Eastern	1989-1994	6.80	99.9	PBDR	P	Patterson <i>et al</i> ^[7]
	Varna	1990-1999	8.10	100.0	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
	Western	1990-1999	10.70	99.5	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
Canada	Toronto	1976-1978	9.00	97.2	PBDR	P, H	Ehrlich <i>et al</i> ^[25]
	Manitoba	1985-1993	20.65	95.0	PBDR	P	Blanchard <i>et al</i> ^[26]
	Prince Edward Island	1990-1993	24.50	100.0	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
	Alberta (Edmonton)	1990-1996	23.30	85.5	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
	Calgary	1990-1999	20.60	100.0	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
	Québec	1989-2000	15.34	NA	PBDR	P	Legault <i>et al</i> ^[27]
	Newfoundland and Labrador	1987-2010	38.68	NA	PBDR	P, H	Newhook <i>et al</i> ^[28]
Chile	IX Region	1980-1993	1.37	97.0	PBDR	P	Larenas <i>et al</i> ^[29]
	Santiago of Chile (Communes of Metropolitan region)	2000-2005	6.30	100.0	PBDR	P	Torres-Avilés <i>et al</i> ^[30]
China	NW	1988-1994	0.47	93.0	PBDR	P, H	Yang <i>et al</i> ^[31]
	Zhejiang ^a	2007-2013	2.02	94.6	PBDR	H	Wu <i>et al</i> ^[32]
	Beijing ^a	1995-2010	1.7	NA	PBDR	H	Gong <i>et al</i> ^[33]
	Shanghai ^a	1997-2011	3.1	90	PBDR	H	Zhao <i>et al</i> ^[34]
Colombia							

	Bogotá	1990-1990	3.80	97.0	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
	Cali	1995-1999	0.50	NA	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
Croatia	NW ^a	2004-2012	17.2	96.69	PBDR	H	Rojnic Putarek <i>et al</i> ^[35]
Cuba	NW	1990-1999	2.30	62.5	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
Cyprus	NW	1990-2009	12.34	50.0	PBDR	NA	Skordis <i>et al</i> ^[36]
Czech Republic	NW	2004-2008	19.30	97.4	PBDR	P	Patterson <i>et al</i> ^[19]
Dem. People's Republic of Korea	NW ^a	2012-2014	3.1	NA	PBDR	P or H	Kim <i>et al</i> ^[37]
Denmark	NW	2004-2008	25.10	99.2	PBDR	P	Patterson <i>et al</i> ^[19]
Dominican Republic	NW	1995-1999	0.50	53.0	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
Egypt	Alexandria, Damanhour	1992-1992	8.00	NA	OPD	NA	Arab <i>et al</i> ^[38]
	Northern ^a	1996-2011	1.93	NA	MBR	H	El-Ziny <i>et al</i> ^[39]
Estonia	NW	1983-2006	13.09	98.0	PBDR	P, H	Teeäär <i>et al</i> ^[40]
Ethiopia	Gondar	1995-2008	0.33	NA	MBR	P	Alemu S <i>et al</i> ^[41]
	Jimma	2002-2008	0.33	NA	MBR	P	Alemu S <i>et al</i> ^[41]
Fiji	NW ^a	2001-2012	0.93	NA	PBDR	H	Ogle <i>et al</i> ^[42]
Finland	NW	2006-2011	62.42	NS	OPD	NA	Harjutsalo <i>et al</i> ^[43]
France	Franche-Comté	1980-1998	7.01	80.6	PBDR	H	Mauny <i>et al</i> ^[44]
	Aquitanie, Lorraine, Normandia Basse, Normandia Haut	1990-1994	8.50	97.0	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
	Aquitaine	1998-2004	12.20	NA	OPD	NA	Barat <i>et al</i> ^[45]
	Languedoc- Roussillon ^a	2000-2010	16.2	NA	PBDR	NA	Trellu <i>et al</i> ^[46]
Georgia	NW	1998-1999	4.60	NA	OPD	NA	Arab <i>et al</i> ^[38]
Germany	NW ^a	2004-2008	22.9	97	PBDR	H	Bendas <i>et al</i> ^[47]
Greece	NW	1992-1992	6.03	NA	PBDR	P	Dacou-Voutetakis <i>et al</i> ^[48]
Hungary	18 of 19 countries (All, less Budapest)	2004-2008	18.30	98.7	PBDR	P	Patterson <i>et al</i> ^[19]
Iceland	NW	1989-1994	13.50	100.0	PBDR	P	Patterson <i>et al</i> ^[7]
India	Madras	1991-1994	11.00	90.0	PBDR	H	Ramachandran <i>et al</i> ^[49]
Iran (Islamic Republic of)	Fars	1991-1996	3.68	100.0	PBDR	P	Pishdad ^[50]
Ireland	NW ^a	2008-2013	28.3	96,8	PBDR	P	Roche <i>et al</i> ^[51]

Israel	NW ^a ; Population: Arabs	2004-2010	9.14	NA	PBDR	P	Blumenfeld <i>et al</i> ^[52]
	NW ^a ; Population: Jews	2004-2010	13	NA	PBDR	P	Blumenfeld <i>et al</i> ^[52]
Italy	Apulia ^a	2001-2013	17.99	NA	PBDR	P	Di Ciaula ^[53]
	Friuli-Venezia Giulia ^a	2010-2013	17.55	NA	MBR	H	Valent <i>et al</i> ^[54]
	Abruzzo ^a	1999-2008	14.30	95	PBDR	H	Altobelli <i>et al</i> ^[55]
	Veneto ^a	2006-2013	17.00	NA	PBDR	H	Marigliano <i>et al</i> ^[56]
	NW-39.7% population	1990-2003	12.55	NA	PBDR	P	Bruno <i>et al</i> ^[57]
Japan	NW ^a	2005-2012	2.14	NA	PBDR	H	Onda <i>et al</i> ^[58]
Jordan	NW	1992-1996	3.33	95.0	NS	P, H	Ajlouni <i>et al</i> ^[59]
Kuwait	NW ^a	2011-2013	41.7	96.7	PBDR	H	Shaltout <i>et al</i> ^[60]
Latvia	NW	1990-1999	7.40	NA	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
Libyan Arab Jamahiriya	Benghazi	1991-1999	9.00	NA	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
Lithuania	NW	2004-2008	14.20	NA	PBDR	P	Patterson <i>et al</i> ^[19]
Luxembourg	NW	2004-2008	19.00	100.0	PBDR	P	Patterson <i>et al</i> ^[19]
Malta	NW	2006-2010	23.87	100.0	PBDR	P	Formosa <i>et al</i> ^[61]
Mauritius	NW	1990-1994	1.30	67.5	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
Mexico	NW	2000-2010	5.93	NA	PBDR	H	Gómez-Díaz <i>et al</i> ^[62]
Montenegro	NW ^a	1997-2011	18.6	100	PBDR	H	Samardžić <i>et al</i> ^[63]
Netherlands	NW ^a	1999-2011	25.2	NA	PBDR	H	Fazeli <i>et al</i> ^[64]
New Zealand	NW	1999-2000	18.00	95.0	PBDR	NA	Campbell-Stokes <i>et al</i> ^[65]
Norway	NW ^a	2004-2012	32.7	NA	PBDR	H	Skrivarhaug <i>et al</i> ^[66]
Oman	NW	1993-1995	2.59	96.0	PBDR	P	Soliman <i>et al</i> ^[67]
Pakistan	Karachi	1990-1999	0.50	51.0	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
Papua New Guinea	NW	1996-2000	0.08	NA	MBR	P	Ogle <i>et al</i> ^[68]
Paraguay	NW	1990-1999	0.90	NA	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
Peru	Lima	1990-1994	0.50	67.5	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
Poland	NW	1989-2004	11.23	NA	PBDR	P	Jarosz-Chobot <i>et al</i> ^[69]

	Krakov and the Lesser Poland ^a	2004-2011	15.87	NA	PBDR	H	Wojcik <i>et al</i> ^[70]
	Podlasie, Silesia, Łódzkie, Pomorskie, Bydgoszcz ^a	2005-2012	20.22	NA	PBDR	H	Chobot <i>et al</i> ^[71]
Portugal	Algarve	1990-1994	14.60	87.0	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
	Portoalegre	1990-1994	21.30	93.0	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
	Coimbra	1990-1999	9.60	100.0	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
	Madeira Island	1990-1999	6.90	100.0	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
Qatar	NW	1992-1996	11.40	NA	OPD	NA	Al-Zyouud <i>et al</i> ^[72]
Republic of China (Taiwan)	NW ^a	2003-2010	5.45	NA	PBDR	H	Lin <i>et al</i> ^[73]
Romania	NW ^a	2002-2011	9.6	96.2	PBDR	H	Serban <i>et al</i> ^[74]
Russian Federation	Novosibirsk	1990-1999	6.90	93.5	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
	Moscow	1996-2005	12.07	94.0	PBDR	P	Pronina <i>et al</i> ^[75]
Rwanda	capital and 6 regions ^a	2004-2011	2.7	NA	MBR	H	Marshal <i>et al</i> ^[76]
Saudi Arabia	Eastern Province	1986-1997	12.30	100.0	PBDR	NA	Kulaylat <i>et al</i> ^[77]
	Al-Madinah (North West)	2004-2009	30.88	NA	PBDR	P	Habeb <i>et al</i> ^[78]
Serbia	Belgrade	2000-2004	12.90	NA	OPD	NA	Vlajinac <i>et al</i> ^[79]
Singapore	NW	1992-1994	2.42	92.2	PBDR	P	Lee <i>et al</i> ^[80]
Slovakia	NW	1999-2003	13.60	100.0	PBDR	P	Patterson <i>et al</i> ^[19]
Slovenia	NW	1998-2010	13.83	100.0	PBDR	P	Radosevic <i>et al</i> ^[23]
Spain	Madrid	1985-1988	10.60	90.0	PBDR	H	Serrano Ríos <i>et al</i> ^[81]
	Cáceres	1988-1999	16.67	99.2	PBDR	H	Lora-Gómez <i>et al</i> ^[82]
	Badajoz	1992-1996	17.23	95.0	PBDR	P	Morales-Pérez <i>et al</i> ^[83]
	Navarre ^a	1975-2011	13.2	NA	PBDR	H	Forga <i>et al</i> ^[84]
	Catalonia	2004-2008	12.10	97.6	PBDR	P	Patterson <i>et al</i> ^[19]
	Castilla y León ^a	2000-2013	10.8	NA	PBDR	H	Vega <i>et al</i> ^[85]
	Biscay ^a	1990-2013	10.7	99.1	PBDR	H or P	Fernández-Ramos <i>et al</i> ^[86]
Sudan	Gezira	1990-1990	5.00	100.0	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
	Khartoum	1991-1995	10.10	97.0	PBDR	NA	Elamin <i>et al</i> ^[87]
Sweden	NW ^a	2007-2011	42	99	PBDR	N	Rawshani <i>et al</i> ^[88]
Switzerland	NW	2004-2008	13.10	91.3	PBDR	P	Patterson <i>et al</i> ^[19]
TFYR Macedonia	NW	2004-2008	5.80	100.0	PBDR	P	Patterson <i>et al</i> ^[19]
Thailand	North-eastern	1996-2005	0.58	NA	MBR	H	Panamonta <i>et al</i> ^[89]

Tunisia							
	Beja, Monastir, Gafsa	1990-1994	6.69	96.0	PBDR	P	Ben Khalifa <i>et al</i> ^[90]
	Kairoan	1991-1993	7.60	NA	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
	Beja	1990-1999	7.70	NA	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
	Gafsa	1990-1999	8.50	NA	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
	Monastir	1990-1999	5.80	NA	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
Turkey							
	NW ^a	2011-2013	10.8	99	PBDR	H	Yeşilkaya <i>et al</i> ^[91]
Ukraine							
	NW	1985-1992	8.10	NA	OPD	NA	Timchenko <i>et al</i> ^[92]
United Kingdom							
	NW	1991-2008	19.32	NA	PBDR	P	Imkampe <i>et al</i> ^[93]
United Republic of Tanzania							
	Dar es Salaam	1982-1991	0.92	NA	MBR	P	Swai <i>et al</i> ^[94]
United States of America							
	Olmsted, Minnesota ^a	1994-2010	19.9	NA	MBR	H	Cartee <i>et al</i> ^[95]
	Five areas ^a	2002-2013	19.5	98,9	PBDR	H	Mayer-Davis <i>et al</i> ^[96]
Uruguay							
	Montevideo	1992-1992	8.30	97.0	PBDR	P or H	DIAMOND <i>et al</i> ^[6]
Uzbekistan							
	NW ^a	1998-2014	2.48	100	PBDR	H	Rakhimova <i>et al</i> ^[97]
Venezuela (Bolivarian Republic of)							
	Caracas	1990-1994	0.10	NA	PBDR	P or H	DIAMOND <i>et al</i> ^[6]

Update of the publications that report the incidence of type 1 diabetes from population-based studies.

^aUpdated studies. Area and NW: Study at the national level. ASCE%: Percentage of completeness between primary and secondary sources of registers. PBDR: Registration of population-based data; MBR: Medical-based record; OPD: Other population denominators; NS: Non-specified; P: Prospective - incident cases collected prospectively-; H: Historical -incident cases collected retrospectively-; NA: Information not available.

country's economy. However, there have been conflicting results. For example, an ecological study carried out in North Rhine-Westphalia, Germany showed that the risk of T1D was higher in children living in socially disadvantaged areas^[9].

In a previous systematic review, we identified T1D incidence in 80 out of 194 countries and found significant associations between the geographical variation of incidence and a series of economic, climatic and environmental, and health conditions factors^[10]. Among these factors, GDP per capita was highly correlated with the 0-14-year incidence of T1D (Spearman Correlation = 0.72, P value = 9.05×10^{-14}).

Here, we focus on three age categories (0-4, 5-9, 10-14) and two periods (1975-1999 and 2000-2017). We searched, through a systematic review of the literature, the global variation in the incidence of T1D in these age categories and periods. We then searched to what extent these variations correlated with the GDP per capita in these countries.

MATERIALS AND METHODS

In this study, we updated the review on the global T1D incidence published by Diaz-Valencia *et al*^[10] with new papers. Once the incidence data were obtained through the systematic review, we conducted an exploratory ecological analysis. Following the procedures mentioned by Morgenstern^[11] for ecological studies, we analysed the relations of population rates of T1D incidence and the average GDP of these countries, retrieved from the World Bank database. This analysis was divided into two periods (1975-1999 and 2000-2017).

We extracted information on the incidence of T1D in children under 14 years from population-based studies conducted in clearly defined geographical areas at the local, regional or national level, published in original articles in English, Spanish or French, following the PRISMA recommendations. The databases used for the literature search

were Medline and Thomson Reuters (Web of Knowledge). Additionally, we explored Google Scholar. This study followed the protocol search deposited in the International Prospective of Systematic Reviews with the Registration Number: CRD42012002369. **Figure 1** presents the flow diagram of the bibliographic search.

During this systematic review, several procedures were standardized to minimize the possibility of incurring biases in the identification of literature, selection and the interpretation of evidence. To reduce potential biases during the design and execution of the systematic review, a team was created; initially, this team was formed by a senior expert researcher (AJV) and a researcher (PAD). During the update of this systematic review, the team consisted of two researchers (NGL and PAD). The initial search was undertaken between November 2011 and January 2014 and the update between January and June 2017. For this systematic review a query equation was used, which implemented the same strategy as that validated by Diaz-Valencia *et al*^[10] (Supplementary material). To build the original query equation, we performed an exploratory search, from which 92 references were selected that reported on the incidence of T1D. From these 92 references, we analysed the MeSH terms and incorporated them into a preliminary search equation. Using this equation, we excluded the MeSH terms of references that did not report the incidence of T1D in the search equation. We repeated this process until the search equation included the 92 references used initially.

For all query equations, studies were excluded if (1) The main objective was not to study the incidence of T1D (*e.g.*, genetic factors, complications, treatments); (2) The study was not population-based and instead it was performed in selected groups, such as studies based on volunteer subjects or people belonging to a specific health insurance organization; (3) The study did not report using the World Health Organization (1985 or 1999) or American Diabetes Association (1997 or 2011) diagnosis criteria; (4) The study described the incidence of T1D as a general topic, with no description by year and age at diagnosis; (5) We could not translate the article; or (6) The full text of the article was unavailable.

Quality assessment

The quality of the included studies was evaluated independently by 2 reviewers (NGL-PAD) using the evaluation criteria proposed by Loney *et al*^[12] as an external validation. We also implemented an internal quality assessment. The external validation consisted of eight criteria, (1) Was the target population clearly described? (2) Were cases ascertained either by survey of the entire population or by probability sampling? (3) Was the response rate > 70%? (4) Were the non-responders clearly described? (5) Was the sample representative of the population? (6) Were data collection methods standardized? (7) Were validated diagnostic criteria or approaches used to assess the presence/absence of disease? and (8) Were the estimates of incidence given with confidence intervals? An article's score was obtained by adding up the number of criteria it satisfied. Every satisfied criterion was given 1 point. There was no cut-off score for rating low-quality studies; we arbitrarily considered 0-4, 5-6 and 7-8 points as high, medium and low risk of bias, respectively.

The internal validation was based on 5 criteria. (1) The percentage of completeness between primary and secondary sources of registers. A percentage greater than 90 scored a 1, less than 90 scored a 0.5 and unavailable information scored a 0; (2) Information source: If the data came from the registration of population-based data, it was assigned a 1; if the data came from medical-based records or population denominators it was assigned a 0.5; and if the source was non-specified, it scored a 0; (3) Data collection: If the cases were collected prospectively (P) or retrospectively (H) was assigned a 1; and if the information was not available, it scored a 0; (4) Clear criterion for diagnosis scored a 1; And (5) if the study was population-based, it scored a 1. We arbitrarily considered 0-3, 3.5 and 4-5 as high, medium and low risk of bias, respectively.

Data collection

Two reviewers (Diaz-Valencia PA and Gomez-Lopera N) extracted and reached agreement on the data from included articles using a standard data collection form. We included in this systematic review the most updated and comprehensive data. In each of the articles analysed, we extracted the following information: (1) Identification of the study: Authors, title, journal, year of publication; (2) Period and country of study: Countries were categorized by region according to the United Nations^[13]; (3) Geographical coverage of the study: Nationwide (when the study was conducted across the whole nation) or local (when it was restricted to a region, city or geographically defined population); (4) Incidence rates expressed as new cases per 100000 people (both sexes) per year in the age categories 0-4, 5-9, 10-14, and 0-14. The rates were retrieved from either tables or graphs. If we found incidence values in the

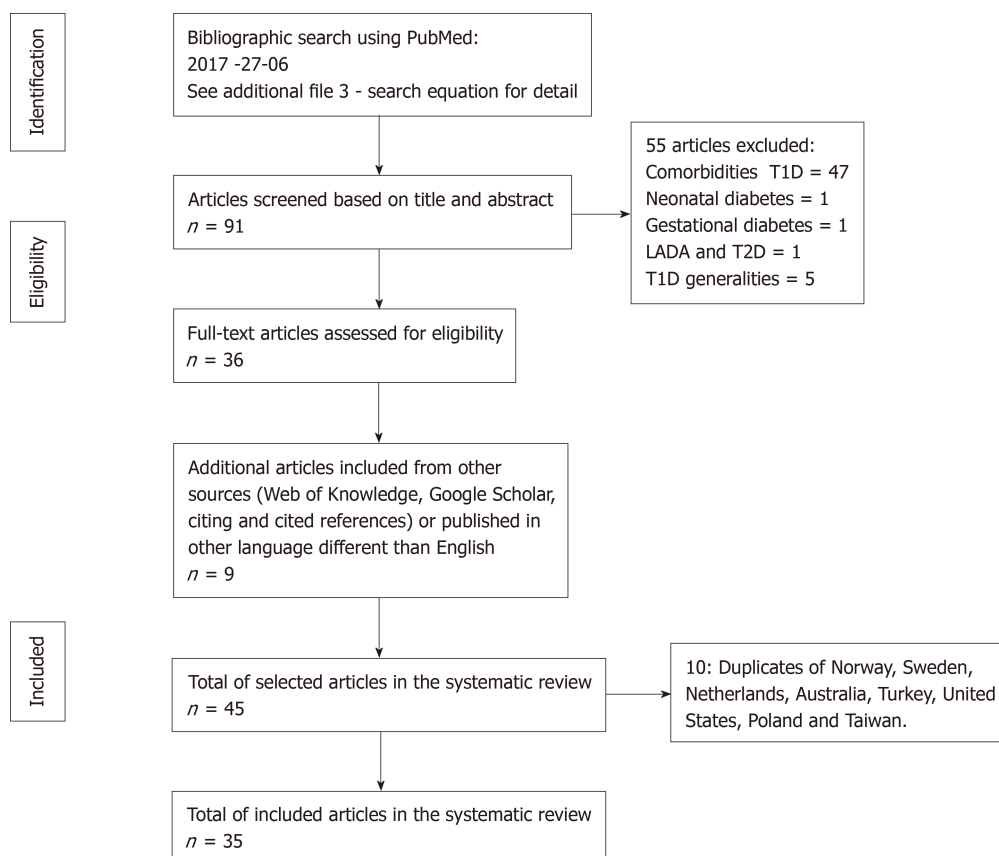


Figure 1 Flow diagram of the bibliographic search strategy. T1D: Type 1 diabetes; T2D: Type 2 diabetes; LADA: Latent autoimmune diabetes in adults.

graphics, we extracted them using GraphClick^[14]. This program allows the user to automatically retrieve the original data from the x and y coordinates of images. Efforts were made to obtain the value of incidence of T1D for each country at the national level. When no information was retrieved at the national level, local studies were considered. In the database, we identified the level of coverage as national or local; (5) The incidence information from two periods was searched: The first was between 1975-1999, and the second was between 2000-2017. We based this separation on a bimodal trend observed in the years of the publications identified in the previous systematic review^[10]; And (6) We collected the percentage of completeness/ascertainment when available.

GPD per capita

The GDP per capita was used to carry out an exploratory ecologic analysis of the relationship between the change in the incidence of T1D and the differences in socio-economic levels during two periods (1975-1999 and 2000-2017). The World Bank database^[15] was used to extract the information for GDP per capita that indicated the relationship between the total value of all the goods and services generated during a year by the economy of a nation or state and the number of its inhabitants in that year. For each study period, we calculated the average of the values of the T1D incidence. In addition, for homogeneity in our analysis, we only chose countries with data at the national level.

Statistical analysis

We presented all the collected data graphically on maps that contain the information obtained from countries at the national level, in two timeframes (1975-1999 and 2000-2017) using the software Tableau^[16]. We compared the incidence of T1D for countries that have information from 1975-1999 and 2000-2017 at the national level in the categories of ages 0-4, 5-9 and 10-14, comparing the means of paired samples.

We performed a correlation to analyse the relationship between the change in incidence of T1D and the change in GDP per capita using the Spearman test and linear regression models to predict the change in the incidence of T1D according to change in the GDP per capita by countries at the national level. Model assumptions for linear models were checked by visual inspection of the residuals. We used the

program R version 3.3.3^[17] to perform the statistical analysis and create graphics related to the study. In all cases, we considered that a *P* value less than 0.05 was statistically significant.

RESULTS

This systematic review of the literature presented information available at the global level on the incidence of T1D and retrieved data for 84 countries, representing 43.3% of the 194 countries of the world. We included 35 additional studies from the previous systematic review^[10]. Among these 35 new papers, we retrieved information for 25 countries; some of them reported data at the national and others at the local level (Figure 1). Updated studies were identified by superscript letters (a) in Table 1. It was possible to update the information published by Diaz-Valencia *et al.*^[10] for 21 countries and obtain data for 4 additional countries: Fiji, Turkey, Rwanda and Republic of China (Taiwan). Of the 84 countries, data were collected at the national level for 44 and the local level for 40.

The median study quality score for studies reporting on the incidence of T1D was high in both cases, with a mean quality score of 7.18 of 8 possible [standard deviation (SD): 0.80] using the external validation, and with a mean quality score of 4.37 of 5 possible [standard deviation (SD): 0.71] using the internal validation. All studies described the target population in detail and used validated diagnostic criteria to assess the presence of disease. Most studies used standardized data collection methods and reported estimates with their accompanying confidence intervals. We found 93.94% concordance between the internal and external validation.

We observed a wide geographical variation in the incidence of T1D at the global level (Table 1). In general, the incidence of T1D was highest in Europe (> 15 per 100000 per year), followed by North America, Australia, Asia, Central and South America. In children from 0-14 years-old, the lowest incidence at the national level (< 1 per 100000 per year) occurred in Thailand; Papua, New Guinea; Fiji; the Dominican Republic; and Paraguay. In contrast, the highest incidence at the national level occurred in Finland, Sweden, Norway and Kuwait, with 62.42, 42, 32.7 and 41.7 per 100000 inhabitants per year, respectively.

We retrieved and compared 26 countries that had information at the national level regarding the incidence of T1D for the periods 1975-1999 and 2000-2017 in individuals from 0-14 years (Figures 2 and 3). In general, an increase in the incidence of T1D is noted at the global level. In the 26 countries, these values were almost double. For example, in Kuwait, the incidence value was 22.3 for the period of 1992-1997^[98] and 41.7 for the period of 2011-2013^[60] (equivalent to a ratio of 1.86).

Additionally, we analysed three distinct categories for age in 15 countries that had information at the national level in the two periods considered in this study (Table 2). We observed an increased in the incidence. In absolute numbers, the period 1975-1999 showed that the incidence increased with age, where the lowest incidence was found in children under the age of 5 years and the highest in children older than 10 years. In the period 2000-2017, there was a higher incidence in the category of 5-9 years, followed by 10-14, and the lowest was found in 0-4. However, comparing the two periods, the relative increase in the incidence of T1D occurred in the 0-4 group (1.9 times), followed by the 5-9 group (1.8 times) and 10-14 group (1.4 times). We performed an extra analysis of all countries reporting incidence values for each age category without taking into account whether they reported the incidence at the local or national level, finding equivalent results (data not shown).

GDP per capita

In general, there was a positive correlation between GDP per capita and the incidence of T1D. A positive correlation was found for the relation between the relative change in T1D incidence and the relative change in GDP for the countries reporting data at national level (Spearman correlation 0.35) (Figure 4).

Analysing the two periods, we found a positive correlation between incidence of T1D and GDP per capita among 26 countries (Spearman correlation = 0.52 between 1975-1999 and Spearman correlation = 0.53 between 2000-2017). Excluding Finland and Switzerland because of their extreme values in T1D incidence and GDP per capita, respectively, we retrieved a Spearman correlation = 0.69 between 1975-1999 and Spearman correlation = 0.62 between 2000-2017 (Figure 5). From the linear regression model, including the 26 countries, it was suggested that for 1991 the country-to-country variation in GDP explained 9% of the country-to-country variation in incidence (adjusted R^2 of the model 0.09), while, for the year 2006, it was 17% (adjusted R^2 of 0.17) (Table 3). We performed the same analysis excluding Finland and

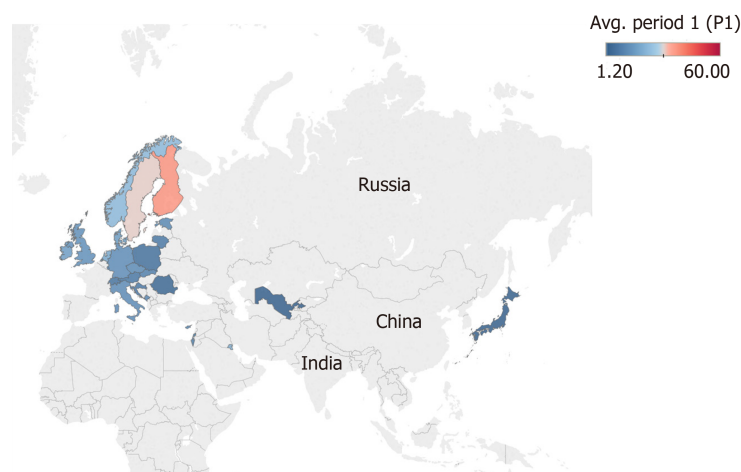


Figure 2 Map showing the mean incidence of type 1 diabetes in 26 countries from 1975-1999. The colour scale represents the level of incidence ranging from 1.20 in blue to 60 per 100000 individuals in red aged 0-14 years.

Switzerland. We found for 1991 that the change in the GDP explained 44% the change in incidence of T1D (adjusted R^2 of the model 0.44), while, for 2006, it was 22% (adjusted R^2 of 0.22) (Table 4).

DISCUSSION

In this study, we updated our previous results on the global incidence of T1D in individuals aged 0-14 years and its variation over time. We analysed the trend in two periods for age categories and GDP per capita. In general, there was a wide geographic variation in the 84 countries for which the incidence of T1D was reported. This variability could be explained to some extent by ethnic differences in allele and haplotype frequencies of risk alleles between populations, for example, in the HLA region, which explains almost 50% of the genetic component of the disease^[99]. There has been a strong association between a high frequency of pre-disposition for HLA haplotypes and a high incidence of T1D. For example, research in the United States, based on the presence of two high-risk haplotypes of HLA-DR3/DR4, revealed that Caucasians have a higher risk of developing T1D than other ethnic groups^[100]. It has been demonstrated that unlike Europeans, DR susceptibility alleles in Asian populations (whose incidence is lower) are in strong linkage disequilibrium with DQ neutral alleles or even protectors, and it is believed that these effects contribute to the low incidence of T1D in these populations^[101,102].

Although there is a consensus on the effect of the genetic susceptibility to T1D between different ethnic groups, these differences cannot fully explain the global variability and the increase in incidence. In this study, we observed an increase in the incidence of T1D worldwide when comparing the periods 1975-1999 and 2000-2017 (Figures 2 and 3). The mechanisms behind the enigma in the increase in the incidence are unknown. However, the mechanism have been attributed to external factors, such as those related to the environment and lifestyle, which may be involved in the epidemiology of the disease^[103].

We also observed an increase in the incidence of T1D in all age categories (0-4, 5-9 and 10-14). In the period 1975-1999, the incidence increased with age, with a peak in children aged 10-14 years. This pattern could be attributed to the onset of puberty with resistance to insulin; therefore, the demand for insulin secretion increases^[104]. In contrast, for the period 2000-2017, there appeared to be an increasing number of patients in the 5-9 age group and a greater relative rise in the 0-4 age group. The mechanisms underlying the increased incidence of T1D in the youngest children are unknown but have largely been attributed to environmental influences^[55].

The environment may act in diverse ways, either by enhancing autoimmunity or modulating normal mechanisms of protection against the development of the disease^[105]. It can be speculated that the plausible causes of temporal changes in the incidence of T1D are attributed to environmental factors, such as social, economic, dietary and health-related factors, which have changed rapidly over the last century.

An example of these changes is socio-economic factors. This study analysed the relationship between one socio-economic indicator (GDP per capita) and the incidence of T1D and found that the highest incidences of the disease were reported in wealthier

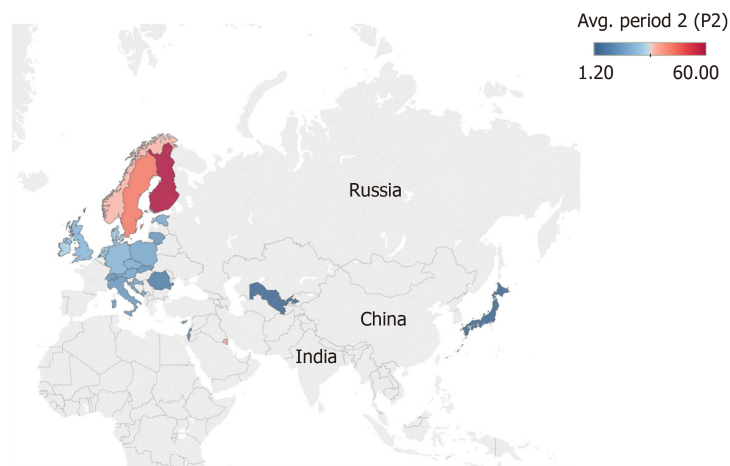


Figure 3 Map showing the mean incidence of type 1 diabetes in 26 countries from 2000-2017. The colour scale represents the level of incidence ranging from 1.20 in blue to 60 per 100000 individuals in red aged 0-14 years.

countries. This same pattern was found by Patterson *et al*^[106] in a study conducted throughout Europe. Similarly, studies conducted at the country level in Sweden^[107], United Kingdom^[108], and Italy^[109] described similar associations between T1D and the socio-economic variables. The influence of changes in GDP per capita on the incidence of the disease was higher for the average year 1991 than that after 2006. We wonder if this behaviour could be explained because 2006 was before the financial crisis of 2008 that provoked a fall in the economies of all regions^[15].

The geographical associations between the socio-economic situation and the incidence of T1D could be attributed to spatial patterns in the composition of the population, which leads to differences in lifestyle and diet. A positive relationship has been demonstrated between the prosperity of the nation, as measured by GDP, with body mass index (BMI)^[110]. Recently, the overload and accelerator hypothesis has been proposed for the increase in body size, BMI and insulin resistance, as well as risk factors for developing T1D^[111]. This hypothesis suggests that the increase in BMI and a more sedentary lifestyle cause resistance to insulin, which leads to β -cells being overworked. This process results in apoptosis and increased production of antigens, which triggers an autoimmune response. Therefore, individuals with a genetic predisposition to T1D will develop an autoimmune response, further accelerating the loss of β -cells. Although an increase in weight contributes to insulin resistance, another consequence of overweight is the storage of ectopic fat with glucotoxicity associated with inflammation resulting in an inhibition of gene expression of insulin, which is also involved in the process of apoptosis of β -cells^[112].

Additionally, the relationship of the socio-economic level with the incidence of T1D could be explained by the improvement of the standards of hygiene, low rates of infection in childhood and low social contact in early childhood, which are possibly experienced in wealthy countries. This theory is known as the hygiene hypothesis, proposed by Gale^[113] in 2002. This hypothesis suggests that changes in hygiene and infection patterns in early childhood alter the development of the immune system and the normal mechanisms of protection against autoimmunity. A study in non-obese diabetic mice, showed that there was a 40%-50% increase in the incidence of T1D when the animals were raised in environments free of pathogens^[114]. In general, there has been an inverse trend between the incidence of infectious diseases and the incidence of autoimmune and allergic diseases^[115].

Other environmental factors potentially related to national economic prosperity must be mentioned. One of these is the nutritional component that has undergone major changes in many developed countries. Early nutrition seems to modulate the development of T1D, for example, the absence or short duration of breastfeeding and early introduction of cow's milk formulae are thought to be risk factors for this disease^[116]. Also, rapid weight gain in infancy, associated with improper feeding, increases the risk of developing T1D^[117]. Other possible factors that experiment in wealthier countries are a higher degree of urbanization, which are associated with an increased incidence of T1D, supporting the hygiene hypothesis^[10]. In addition, there are differences in caesarean deliveries between low- and high-income countries, where wealthier countries have high levels of caesarean use without medical indication^[118]. Delivered by caesarean section are at slightly increased risk of T1D, and it has been postulated that differences in the gut microbiota of these children

Table 2 Summary values for the comparison of the incidence of type 1 diabetes for countries with nationwide data by age category in the periods analysed in the study

	0-4 yr		5-9 yr		10-14 yr	
	1975-1999	2000-2017	1975-1999	2000-2017	1975-1999	2000-2017
Mean	6.68	12.59	11.92	21.99	14.04	19.54
95%CI	(4.49, 8.87)	(9.23, 15.96)	(7.95, 15.96)	(14.80, 29.18)	(9.72, 18.38)	(15.09, 23.99)
T student	-6.31		-4.58		-3.22	
P value	0.00002		0.00043		0.006	
Ratio periods	1.9		1.8		1.4	

CI: Confidence Interval.

compared with those born by normal vaginally delivery^[103]. Also, the wealth of countries is associated with environmental pollution. An association between air pollution and T1D incidence has been described. Researchers proposed that chemical and air pollutant exposures have multiple effects that may directly affect the risk of T1D^[119].

However, a single environmental factor or interaction between factors, has not been identified that could explain these changes in the incidence of T1D. Moreover, there are complex interactions between genetic and environmental factors that remain to be discovered. More epidemiological studies of T1D are needed to develop new hypotheses about the genetic and environmental factors that trigger the disease, which should be further tested.

Currently, there is information on the incidence of 43.3% of the 194 countries of the world, of which only 44 countries have national coverage information; most of them are European. Despite the efforts of the DIAMOND project^[6] to describe the incidence of T1D at a global level, there is little information for countries in Africa, Central and South America. Moreover, the data are not entirely representative for some countries. To extrapolate this information for the whole country, there would be a substantial bias, as there may be variability within large nations in both the genetic component and environmental exposures that trigger the disease.

Another aspect to consider is the lack of continuity of the epidemiological studies. Only 21 countries have updated incidence rates in the systematic review conducted between 2014 and 2017. Moreover, this lack of continuity implies a limitation for our study since we retrieved available information to conduct comparisons in two periods, 1975-1999 and 2000-2017; only 26 countries had data at the national level, and age category data are even less available. These 26 countries are mainly from Europe ($n = 23$), and Asia ($n = 3$). Regrettably, we do not have information to conduct comparison in the two periods for countries in Africa, Oceania, and America. It is very important to generate more studies on the epidemiology of T1D. This approach will contribute to understanding the dynamic changes in the disease, which, together with studies in basic sciences such as genetics, could identify the factors that modify the risk to the disease and could probably slow down the current increase in the incidence of T1D.

Limitations of this study are worth noting. Although several procedures were standardized during this systematic review to minimize the possibilities of incurring biases in the identification of literature, selection and interpretation of evidence, we cannot rule out having missed relevant studies also due to publication bias. For example, studies that were published in languages other than English, Spanish or French were not included. An important limitation that is shared by all ecological studies is the possibility of making an ecological fallacy. The implication is that the associations we found are only at the group level, and we cannot assume that they are inferred to each individual in these groups. For example, our results do not necessarily imply that all wealthy countries have a higher incidence of T1D, and our findings only reveal potential associations between GPD and population rates of T1D incidence at the group level. Another limitation of our study is the heterogeneity of the different countries included in the statistical analysis. In addition, available secondary sources of GPD data may not have the same accuracy for all countries, leading to imprecise correlation with the incidence of T1D.

We found a wide geographic variation in the incidence of T1D and a worldwide increase in the two periods considered in this study. The greatest increase was observed in the youngest group of children with T1D (0-4 years), with a relative increase of almost double (P value = $2.47 \times e^{-0.5}$). Finally, there was a positive

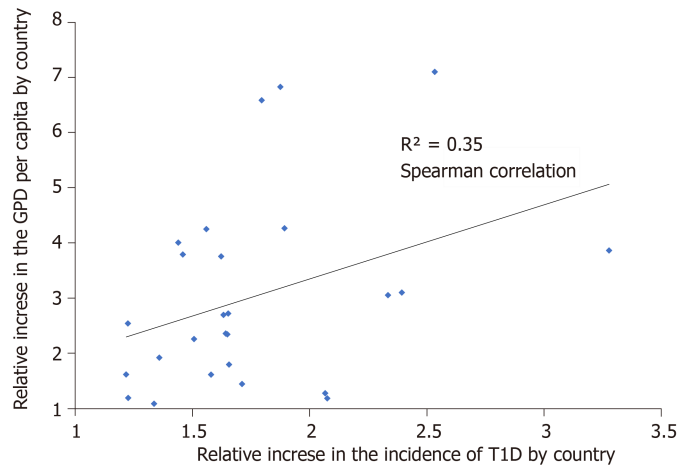


Figure 4 Observed relation between the ratios of the increase in incidence and gross domestic product in 26 countries.

correlation between the socio-economic level, as measured by GDP per capita, and the incidence of T1D, where wealthier countries have higher values of incidence.

Table 3 Models of change in the incidence of type 1 diabetes for 26 countries with nationwide data according to the change in gross domestic product

Model GDP per capita	Coefficient	Est	CI 2.5%	CI 97.5%	SE	t value	P value
Year 1991: Residual standard error: 6.63 Adjusted R ² : 0.09509; F-statistic: 3.312 on 1 and 21 DF; P value: 0.08307	Intercept	8.99	4.63	13.36	2.1	4.28	0.0003
	GDP per capita	0.0002	0.0000	0.0005	0.0001	1.8000	0.0830
Year 2006: Residual standard error: 8.6; Adjusted R ² : 0.176; F-statistic: 5.698 on 1 and 21 DF. P value: 0.02647	Intercept	13.5	7.34	19.66	2.96	4.56	0.0002
	GDP per capita	0.0000	0.0000	0.0000	0.0000	2.39	0.0260

Est: Estimator; CI: Confidence Interval; SE: Standard Error; DF: Degree freedom; GDP: Gross domestic product.

Table 4 Models of change in the incidence of type 1 diabetes for countries with nationwide data according to the change in gross domestic product, excluding Finland and Switzerland

Model GDP per capita	Coefficient	Est.	CI 2.5%	CI 97.5%	SE	t value	P value
Year 1991: standard residual error: 5.08; adjusted R ² : 0.44. F statistic: 19.37. 22 DF. P value: 0.0002	Intercept	5.82	2.27	9.36	1.71	3.40	0.002
	GDP Per capita	0.0005	0.0003	0.0008	0.0001	4.1220	0.0002
Year 2006: Standard residual error: 8.08; adjusted R ² : 0.22; F statistic: 7.62. 22 DF. P value: 0.01	Intercept	13.57	8.16	18.98	2.61	5.21	0.00003
	GDP Per capita	0.0002	0.00004	0.0003	0.0001	2.76	0.01

Est: Estimator; CI: Confidence Interval; SE: Standard Error; DF: Degree freedom; GDP: Gross domestic product.

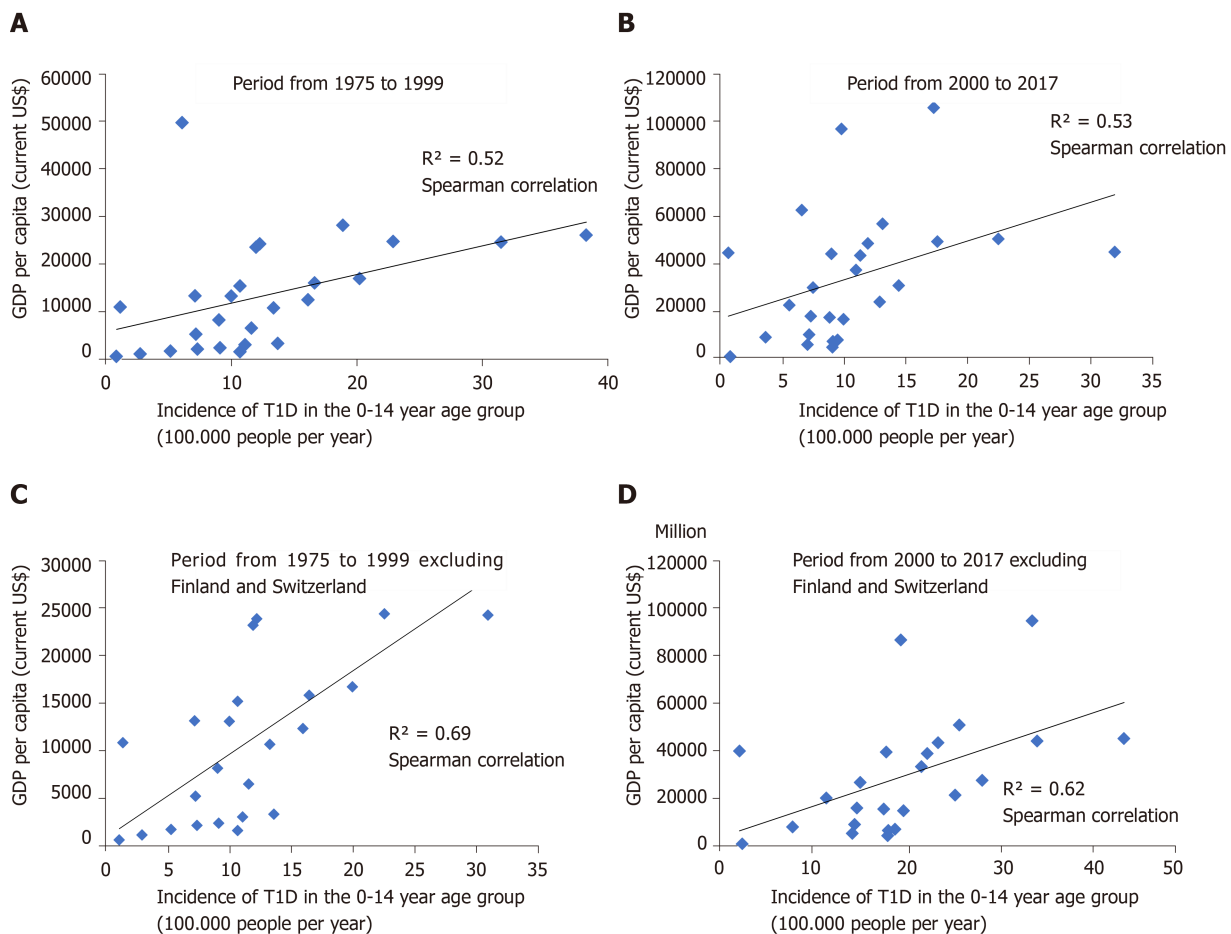


Figure 5 Correlation between incidence of type 1 diabetes and gross domestic product per capita for countries with information at the national level in two periods. A: Analysis for 26 countries period from 1975 to 1999; B: Analysis for 26 countries, period from 2000 to 2017; C: Analysis excluding Finland and Switzerland, period from 1975 to 1999; D: Analysis excluding Finland and Switzerland, period from 2000 to 2017.

ARTICLE HIGHLIGHTS

Research background

Type 1 Diabetes (T1D) is a complex disease resulting from the interplay of genetic, epigenetic, and environmental factors. There is a dramatic increase in the incidence of T1D, predominantly in younger children (0-4 years old) worldwide. The cause of this increase is still under study.

Research motivation

This work updates the current knowledge on the global incidence of T1D across age categories and its variation over time. The increase of incidence of T1D has been associated with socioeconomic factors, such as gross domestic product (GDP). However, there have been conflicting results about the relationship between income level and the incidence of T1D.

Research objectives

We searched the global variation in the incidence of T1D in the age categories and two periods (1975-1990 and 2000-2017). We then searched to what extent these variations correlated with the GDP per capita in these countries.

Research methods

We updated through a systematic review, our previous results on the global incidence of T1D in individuals aged 0-14 years. We first retrieved the incidence of T1D data in different age categories (0-4, 5-9, 10-14, 0-14) and divided the incidence information into two periods (1975-1999 and 2000-2017). Then, we conducted an exploratory ecological analysis about the relations of population rates of T1D incidence and the average GDP of these countries. Comparisons of means, correlations, linear regression were made.

Research results

We retrieved incidence data for 84 countries, most of them are European. We observed an increase in the incidence of T1D worldwide when comparing the periods 1975-1999 and 2000-2017. We also observed an increase in the incidence of T1D in all age categories (0-4, 5-9 and 10-

14). In the period 1975-1999, the incidence increased with age, with a peak in children aged 10-14 years. For the period 2000-2017, there appeared to be an increasing number of patients in the 5-9 age group and a greater relative rise in the 0-4 age group. Also, we found that the highest incidences of the disease were reported in wealthier countries.

Research conclusions

We found a wide geographic variation in the incidence of T1D and a worldwide increase in the two periods considered in this study, especially in younger children (0-4 years old); showing an early age at onset. Also, we confirmed that there was a positive correlation between the socio-economic level and the incidence of T1D. More studies are required to elucidate the interaction between environmental, immunological and genetic factor.

Research perspectives

This study showed the enormous differences in surveillance and epidemiological reports of T1D worldwide. Most of the countries retrieved from the systematic review are European and few studies were carried out in Central and Latin America, Central Asia and Sub-Saharan Africa. It is very important that the scientific community generates more studies on the epidemiology of T1D that contribute to understanding the changes in the dynamics of the disease.

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