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Li, Xinjun; Sundquist, Jan; Zöller, Bengt; Bennet, Louise; Sundquist, Kristina

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PO Box 117
221 00 Lund
+46 46-222 00 00

**Risk of hospitalization for type 2 diabetes in first- and second-generation
immigrants in Sweden: a nationwide follow-up study**

Xinjun Li^a MD, PhD, Jan Sundquist^{a,b} MD, PhD, Bengt Zöller^a MD, PhD, Louise Bennet^a
MD, PhD, Kristina Sundquist^{a,b} MD, PhD

^aCenter for Primary Health Care Research, Lund University, Sweden

^bStanford Prevention Research Center, Stanford University School of Medicine, USA

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Correspondence to:

Dr. X Li

Center for Primary Health Care Research

Lund University

Clinical Research Centre (CRC), building 28, entrance 72,

Jan Waldenströms gata 35

205 02 Malmö Sweden

Phone: +46-40-391381

Fax: +46-40-391370

E-mail: xinjun.li@med.lu.se

Abstract

Objectives. This is the first nationwide study with the aim to analyze whether there is an association between country of birth in first-generation immigrants and hospitalization for type 2 diabetes (T2D), and to study whether any such association remains in second-generation immigrants.

Design. In this follow-up study, the Swedish Hospital Discharge Register was used to identify all hospital diagnoses of T2D in first- and second-generation immigrants in Sweden between January 1, 1964 and December 31, 2007. Hospitalization rate ratios standardized with regard to gender, age, geographical region, socioeconomic status, obesity, and family history of hospitalization for T2D were estimated in first- and second-generation immigrants.

Results. Both increased and decreased risks of hospitalization for T2D were shown for several first-generation immigrant groups. However, only second-generation immigrants with Finnish or former Yugoslavian parents had higher rates of hospitalization for T2D than the reference group. No other differences remained in the second-generation immigrants.

Conclusions. The present study suggests that ethnic environmental factors may be more important than ethnic genetic factors in explaining the observed variation in hospitalization for T2D among first-generation immigrants.

Key words: Migrants, type 2 diabetes, risk factors, Sweden.

Introduction

Type 2 diabetes (T2D) is considered to be one of the major public health challenges.

Epidemiological studies have suggested that the prevalence of T2D may vary markedly across Europe and other regions, and ethnic groups (Wild *et al.*, 2004), and the rate ranges from 2 to 10% in the industrialized countries with a tendency to increase (Adeghate *et al.*, 2006; Hussain *et al.*, 2007; Ringborg *et al.*, 2008). T2D is thought to be caused by environmental and inherited factors in about equal proportions (Doria *et al.*, 2008). Many environmental risks factors are known and they include obesity, sedentary lifestyle, small or large birth weight, stress, nutritional factors, toxins (Adeghate *et al.*, 2006; Hussain *et al.*, 2007), and tobacco smoking (Willi *et al.*, 2007). Environmental changes and, more specifically, industrialization, appear to play an important role in the onset of the disease (Ershow, 2009). Family history is an important risk factor which has been shown in twins and singleton siblings (Adeghate *et al.*, 2006; Doria *et al.*, 2008; Grill *et al.*, 1999; Hemminki *et al.*, 2010; Kaprio *et al.*, 1992; Ridderstrale *et al.*, 2009; Weires *et al.*, 2007).

Previous studies have found that risk factors for T2D increase following immigration; however, in South Asian immigrants settled in United States (Kanaya *et al.*, 2010), the prevalence of T2D was decreased. In a study of Middle-eastern immigrants settled in Sweden (Glans *et al.*, 2008), the authors found an earlier onset of diagnosis of T2D, a stronger family history and a more rapid decline of pancreatic B-cell function than in Swedish patients. To the best of our knowledge, however, no earlier studies have attempted to ascertain whether or not a higher risk of developing T2D in first-generation immigrants in Sweden is associated with a higher risk of developing T2D in the next generation, i.e., in second-generation immigrants.

Sweden, like many countries, has experienced dramatic demographic changes due to increasing global migration. It has become a multicultural society in the new millennium. Today, approximately 19% of all people living in Sweden are first- or second-generation immigrants (Statistics Sweden, 2010). Careful studies of rates of hospitalization for T2D in first- and second-generation immigrants may help identify novel risk factors of hospitalization for T2D in these groups and contribute to the formulation of new preventive strategies.

Our aim was to analyze whether there is an association between country of birth in first-generation immigrants and hospitalization for T2D and, further, to analyze whether this association remains in second-generation immigrants after accounting for gender, age, geographical region, socioeconomic status, hospitalization for obesity and family history of hospitalization for T2D.

Materials and methods

Data used in this study represented information on all individuals registered as residents of Sweden. It included individual-level information on age, sex, education, occupation, geographic region of residence, hospital diagnoses, and dates of hospital admissions in Sweden (1964–2007), as well as date of emigration, and date and cause of death. The datasources were several national Swedish data registers, including the Swedish National Population and Housing Census (1960–1990), the Total Population Register, the Multi-Generation register, and the Swedish Hospital Discharge register (1964–2008), provided to us

by Statistics Sweden and the National Board of Health and Welfare (Hemminki *et al.*, 2010; Ludvigsson *et al.*, 2011; Socialstyrelsen., 2000).

The dataset incorporates information on the entire national population over a period of 40 years, including all first- and second-generation immigrants registered in Sweden. It includes T2D hospitalization data for the entire population. Additionally, the dataset incorporates population-wide documentation regarding concomitant factors such as geographical region and socioeconomic status. We used the main diagnoses for T2D recorded in the register. Additional linkages were carried out to: national census data to obtain individual socioeconomic status, occupation, and geographical region of residence; the national Registry of Cause of Death to identify date of death; and the Immigration Register to identify date of emigration. All linkages were performed by the use of an individual national identification number that is assigned to each person in Sweden for his or her lifetime. This number was replaced by a serial number for each person in order to provide anonymity.

The follow-up period started on January 1, 1964 and proceeded until hospitalization for T2D, death, emigration or the end of the study period on December 31, 2007.

Outcome variable

The 7th, 8th, 9th and 10th revisions of the WHO's International Classification of Diseases (ICD-7, ICD-8, ICD-9 and ICD-10) were used to define the outcome variable, first hospitalization for T2D during the study period. ICD-7 codes 260 was used in Swedish hospitals before 1969, ICD-8 code 250 from 1969-1986, ICD-9 code 250 from 1987-1996, and ICD-10 codes E11 to E14 from 1997 onwards. The codes for T2D and type 1 diabetes

were first separated in ICD-10 (1997 onward), and we thus only included patients aged over 30 years at hospitalization in order to minimize patients with type 1 diabetes.

Individual variables

Individual variables included gender, age, geographical region, socioeconomic status, hospitalization for obesity, and family history of hospitalization for T2D.

Gender: males and females.

Age was divided into 5-year categories.

Geographical region was divided into (1) large cities (cities with a population of more than 200,000, i.e., Stockholm, Gothenburg and Malmö), (2) Southern Sweden and (3) Northern Sweden. Sweden is divided into 25 counties. The border between Northern and Southern Sweden has traditionally been drawn at the Dalälven River. Therefore, all counties north of that river were defined as part of Northern Sweden. Geographical region was included as an individual variable to adjust for possible differences between geographical regions in Sweden regarding hospital admissions for T2D.

Socioeconomic status of the men and women was thus divided into five categories: (1) farmers, (2) self-employed workers, (3) professionals, (4) middle level employees, (5) manual workers, and (6) all others. It is of great importance to account for socioeconomic factors in studies on T2D and immigrants, because even though the ethnic, cultural and social heterogeneity among immigrants is large, poor socioeconomic circumstances are more common among immigrants than among non-immigrants in Sweden (Bennet *et al.*, 2011; Sundquist, 1995).

Comorbidity of obesity was defined as the first hospital diagnosis at follow up from 1970-2008: ICD-8 277.99, ICD-9 278A, and ICD-10 E65-E68.

Family history of hospitalization for T2D was divided into two groups, one with and one

without family history of a first hospital diagnosis of T2D during the study period.

Predictor variable

The predictor variable was *first- or second-generation immigrant* status. *First-generation immigrants* were defined as all people born abroad in one of the countries and regions of parental birth included in the statistical analysis. *Second-generation immigrants* were defined as all people with at least one first-generation immigrant parent.

The dataset included people from 64 countries and regions of birth (or, in the case of second-generation immigrants, of parental birth). Immigration from a number of these countries and regions began relatively recently, so the number of members of the first-, and the second-generation is also relatively small. For this reason (less than 10 cases of T2D in the either generation), these countries of birth were excluded from the study. As a result, we included 10 regions (Nordic countries, Southern Europe, Western Europe, Eastern Europe, Baltic countries, Central Europe, Africa, North America, Latin America and Asia) and 25 countries (Denmark, Finland, Norway, France, Greece, Italy, Spain, Netherland, Great Britain/Ireland, Germany, Austria, former Yugoslavia, Croatia, Romania, Bulgaria, Estonia, Latvia, Poland, Hungary, Chile, Turkey, Lebanon, Iran, Iraq and Russia) in our analysis.

Statistical analysis

Age-standardised hospitalization rates were calculated for the whole follow-up period, divided into 5-year periods. Standardized hospitalization (inpatients) rate ratios (SIR) with 95% confidence intervals (95% CI) were calculated as the ratio of observed to expected number of cases (Rothman *et al.*, 1998). The expected number of cases was based on the observed number of cases in the reference category. The expected numbers of cases were

calculated from age- (in 5-year groups), gender-, period- (in 5-year categories), socioeconomic status-, geographical region-, hospitalization of obesity, and family history of hospitalization for T2D-specific standard hospitalization rates. Risks of hospitalization for T2D in first-generation immigrants were calculated separately for men and women. Person-years were calculated beginning when subjects were included in the study (in 1964 or later) until hospitalization for T2D, death, emigration or the end of the study on December 31, 2007. Risks of hospitalization for T2D in second-generation immigrants were also calculated separately for men and women according to parental birth (father and/or mother) and compatriot parents. Because the initial gender-specific analysis showed no gender-specific effects, data are given for both genders combined.

Ethical considerations

This study was approved by the Ethics Committee of Lund University, Sweden.

Results

The native-born Swedes constituted by far the largest group in our study, 6.0 million individuals, with 118 642 cases of hospitalization for T2D (Table 1). This group was the reference category in the SIR calculations in the first-generation immigrants and will not be included in subsequent tables. In the second generation, the offspring of the native-born Swedes constituted by far the largest group. They constituted about 6.4 million individuals born of both Swedish parents, of whom 25 650 had been hospitalized for T2D. This group was the reference category in the SIR calculations in second-generation immigrants and will not be included in subsequent tables. The total number of hospitalizations for T2D cases recorded was 1838 in individuals with foreign-born parents (father and/or mother) and 610 in

individuals with compatriot parents. There were 15.4% of cases with a family history of hospitalization for T2D.

Table 2 shows SIRs of hospitalization for T2D in first-generation male and female immigrants compared with persons who were born in Sweden, after accounting for age, time period, socioeconomic status, geographical region, and hospitalization for obesity. It is noteworthy that the number of male and female immigrants is quite similar for each country, suggesting immigration in families among many nationalities. The overall SIRs for immigrants were 1.04 for men and 1.12 for women, respectively. Both female and male immigrants from Finland, Hungary, Africa, Latin America (Chile), and Lebanon had increased risks of hospitalization for T2D. Female immigrants born in Yugoslavia, Italy, Romania, and Turkey had increased risks of hospitalization for T2D. Male immigrants born in Denmark, Norway, Netherlands, England-Ireland, Baltic countries (Estonia), Iran and Russia and female immigrants born in Norway, France, and Germany had decreased risks of hospitalization for T2D.

Table 3 shows SIRs of hospitalization for T2D for second-generation immigrants by parental birth country and compatriot parents, separately, compared to the reference, i.e., persons with both parents born in Sweden, after accounting for age, gender, time period, socioeconomic status, geographical region, hospitalization for obesity, and family history of hospitalization for T2D. The overall hospitalization for T2D rate was increased for the offspring of immigrants (1.06) and compatriot parents (1.13). Among specific nationalities, the risk of hospitalization for T2D was only increased in second-generation immigrants from Finland (1.15) and Yugoslavia (1.46). The risk of hospitalization for T2D remained significant in offspring whose both parents were from Finland (1.23).

Discussion

The main finding of this study is that the increased and/or decreased risks of hospitalization for T2D among certain immigrant groups mainly disappeared in the second generation. First-generation immigrants from Finland, Italy, Yugoslavia, Romania, Hungary, Africa, Latin America (Chile), Turkey, and Lebanon had higher risks of hospitalization for T2D than the reference group (people born in Sweden). First-generation immigrants from 7 countries or regions of birth had lower risks of hospitalization for T2D. In the next generation, however, significantly increased risks were only found in immigrants from Finland and Yugoslavia (i.e., people who had at least one parent from Finland and Yugoslavia). This complex picture is indicative of a combination of environmental and genetic etiology, which is the etiology suggested by previous research (Adeghate *et al.*, 2006; Doria *et al.*, 2008; Ershow, 2009; Grill *et al.*, 1999; Hemminki *et al.*, 2010; Hussain *et al.*, 2007; Kaprio *et al.*, 1992; Ridderstrale *et al.*, 2009; Weires *et al.*, 2007; Willi *et al.*, 2007).

It is reasonable to assume that socioeconomic disadvantage plays a role in the development of T2D in both first- and second-generation immigrants. This study paints a relatively complex, sometimes positive and sometimes negative role of immigrant status in hospitalization risk for T2D in immigrant populations compared with the majority population. However, the observed differences disappeared in their Swedish-born second-generation children, with few exceptions. The explanation for the higher or lower hospitalization risk for T2D found in certain immigrant groups in the current study may be a combination of genetic and environmental effects. Environmental effects may include certain risk factors for T2D (Wandell *et al.*, 2003), such as obesity, dietary fat intake, smoking, and low levels of physical activity, which may partly explain the higher risk of T2D among certain countries. Genetic

factors may also play a role. For example, in Sweden, Glans *et al.*, compared the Middle-Eastern immigrants with the Swedish-born controls and found that immigrants from the Middle-East have an earlier onset, stronger family history and a more rapid decline of pancreatic B-cell function than Swedish patients (Glans *et al.*, 2008).

In the present study, we tried to explore the genetic susceptibility of hospitalization for T2D by ethnical background. In our study, the SIRs were significantly increased for hospitalization for T2D in second-generation immigrants of Finland, and Eastern Europe (i.e., Yugoslavia), after adjustment for age, gender, time period, socioeconomic status, geographical region, hospitalization for obesity, and family history of hospitalization for T2D, which indicates that those factors alone cannot explain the increased risk of hospitalization for T2D in these immigrant groups. The rates of T2D in Finland is somewhat higher compared with Sweden, which is consistent with our results that showed that the SIRs were marginally higher for those children with one or two parents from Finland. The risk was even higher among second-generation immigrants with compatriot parents, suggesting a determining role of genetic effects.

The present study had some limitations; for example, we had no data on risk factors for T2D, such as smoking, unhealthy diets and physical inactivity. Furthermore, we had no data from the countries of origin on background T2D risk factors or morbidity. However, we did adjust for socioeconomic status, which is associated with several risk factors for T2D, such as smoking. Furthermore, because of the size of the study population, we could not confirm the validity of the diagnoses. However, the Hospital Discharge Register has high validity (almost 90%) (Ludvigsson *et al.*, 2011; Socialstyrelsen., 2000). Moreover, we only used a primary

diagnosis of T2D from the Swedish Hospital Discharge Register. This means that the included patients were hospitalized because of their T2D, thus increasing the likelihood that the diagnoses are valid. In Sweden, hospitalization for T2D may be a secondary or tertiary referral step; T2D is often diagnosed in primary care centers, which refer the patients to hospital outpatient clinics or directly to inpatient clinics. Hospital clinics are directed by specialists in internal medicine or endocrinology/diabetology (Gudbjornsdottir *et al.*, 2003). With poor diagnostic accuracy, any effects would be expected to regress toward null, which appeared not to be the case with the present results.

Another potential limitation is confounding by indication; that is, despite underlying disease, some first-generation immigrant groups may be less likely to seek medical care because of language barriers or other factors. For example, this may be true in certain immigrant groups in the United States (Taira *et al.*, 2001). However, it is important to note that caution should be exercised when comparing the results of studies on immigrants in one country with the results of studies on immigrants in another country. Immigrants to Sweden come from a wide variety of cultural, linguistic, and socioeconomic backgrounds, and studies have shown that care-seeking behavior varies on the basis of individual place of origin (Sundquist, 1993) and may even be higher in some immigrant groups. For example, among immigrants from Chile, Iran, and Turkey, care seeking is higher than among native Swedes (Hjern *et al.*, 2001). However, there was no consistent trend in the present study.

Some immigrant groups had lower risks and some immigrants groups had higher risks of hospitalization for T2DM. This argues against a selection bias in the entire group of immigrants, although it could be present in some immigrant groups. Finally, incidence rates

do not entirely correspond to hospitalization rates. Hospitalization rates may, however, be a good indicator of differences in risk between immigrant groups.

This study also has a number of strengths. For example, our study population included a well-defined open cohort of first- and second-generation immigrants. Because of the civic registration number assigned to each individual in Sweden, it was possible to trace the records of every person for the whole follow-up period. The validation (positive predictive value) of diabetes diagnosis is 99% (Ragnarson Tennvall *et al.*, 2000). Data on occupational status was nearly 100% (99.2%) complete (1980 and 1990 censuses), which enabled us to adjust our models for socioeconomic status.

CONCLUSIONS

The overall risks of hospitalization for T2D was higher or lower in some groups of first-generation immigrants than in the native-born reference group. However, these higher or lower risks disappeared in the second-generation for most immigrants groups. This suggests that ethnic environmental factors may be more important than ethnic genetic factors in the observed variation in hospitalization for T2D among first-generation immigrants. Identifying ethnic environmental factors that protects or provokes T2D will be an important issue for future research. Moreover, lifestyle interventions might be worthwhile for the prevention of T2D among specific first-generation immigrant groups known to be at higher risks of developing the disease.

Conflict of Interest Statement

There are no conflicts of interest.

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Table 1. Number of cases of hospitalized T2D in first- and second-generation individuals

Characteristics	First-generation		Second generation	
	No	%	No	%
Gender				
Men	59762	50.4	16295	63.5
Women	58880	49.6	9355	36.5
Age at diagnosis (years) ^a				
30-39	6480	2.6	6859	26.7
40-49	8330	2.5	6479	25.3
50-59	16324	5.8	7312	28.5
60-69	28197	11.2	4264	16.6
70-79	36875	16.5	736	2.9
>=80	22436	11.0		
Period				
1964-79	24147	20.4	889	3.5
1980-89	44728	37.7	3615	14.1
1990-99	32063	27.0	5819	22.7
2000-07	17704	14.9	5972	23.3
Region of residence				
Big cities	34661	29.2	7675	29.9
Southern Sweden	56905	48.0	12028	46.9
Northern Sweden	27076	22.8	5947	23.2
Socioeconomic status				
Farmers	12808	10.8	735	2.9
Self-employed workers	9245	7.8	1611	6.3
Professionals	5191	4.4	2250	8.8
Middle level employees	26446	22.3	7553	29.4
Manual workers	58898	49.6	13418	52.3
Others	6054	5.1	83	0.3
Immigrant status ^b				
Sweden	110036	92.7	23812	92.8
Immigrants	8606	7.3	1838	7.2
Hospitalization for obesity				
Yes	1098	0.9	538	2.1
No	117544	99.1	25112	97.9
Family history of T2D				
Yes			3961	15.4
No			21689	84.6

a: age at diagnosis in the second generation was limited to 75 years.

b: immigrant status in the second generation was defined by parents.

Table 2. Standardized incidence ratio for hospitalized T2D in first generation immigrants

Birth country	Men					Women				
	Population	O	SIR	95% CI		Population	O	SIR	95% CI	
Nordic countries	112944	1888	1.08	1.03	1.13	153977	2219	1.09	1.05	1.14
Denmark	18985	297	0.86	0.76	0.96	18080	227	0.94	0.82	1.07
Finland	74770	1321	1.22	1.16	1.29	107930	1572	1.19	1.14	1.25
Norway	17251	269	0.84	0.75	0.95	25842	418	0.89	0.80	0.98
Southern Europe	18366	194	0.93	0.81	1.07	11487	103	1.35	1.11	1.64
France	2259	13	0.63	0.33	1.08	1751	-			
Greece	6934	68	0.89	0.69	1.13	4754	37	1.37	0.97	1.90
Italy	4351	73	1.11	0.87	1.39	1839	36	1.69	1.18	2.34
Spain	2661	24	0.87	0.56	1.30	1624	14	1.41	0.77	2.38
Western Europe	30133	406	0.89	0.81	0.98	27731	330	0.89	0.79	0.99
Netherlands	2330	19	0.64	0.38	0.99	1613	11	0.79	0.39	1.43
Great Britain and Ireland	7224	36	0.67	0.47	0.93	4450	26	0.95	0.62	1.40
Germany	15850	268	0.91	0.81	1.03	18069	232	0.83	0.72	0.94
Austria	3318	61	1.02	0.78	1.31	2430	50	1.23	0.91	1.62
Eastern Europe	44900	487	0.96	0.88	1.05	43207	247	1.12	0.99	1.27
Yugoslavia	25335	322	1.09	0.98	1.22	23525	166	1.33	1.14	1.55
Croatia	1719	21	1.07	0.66	1.63	1632	-			
Romania	2923	37	1.18	0.83	1.63	3381	25	1.60	1.04	2.37
Bulgaria	942	11	1.05	0.52	1.88	1013	-			
Baltic Countries	7395	186	0.85	0.73	0.98	7278	168	0.86	0.74	1.01
Estonia	6102	155	0.84	0.72	0.99	5858	148	0.89	0.75	1.05
Latvia	1293	31	0.85	0.58	1.21	1420	20	0.71	0.43	1.10
Central Europe	18601	330	1.06	0.94	1.18	24793	238	1.19	1.05	1.36
Poland	9121	112	0.84	0.69	1.01	16163	120	1.16	0.96	1.38
Hungary	6190	142	1.24	1.04	1.46	5184	79	1.48	1.17	1.85
Africa	15663	238	2.16	1.89	2.45	13166	72	3.05	2.39	3.85
North America	7480	108	0.91	0.75	1.10	6758	96	0.82	0.67	1.01
Latin America	13546	117	1.30	1.08	1.56	15063	68	1.61	1.25	2.04
Chile	8224	82	1.59	1.27	1.98	8640	40	1.72	1.23	2.34
Asia	67315	607	1.06	0.98	1.15	71910	372	1.90	1.71	2.10
Turkey	12221	116	1.09	0.90	1.31	10913	107	2.59	2.12	3.13
Lebanon	5927	75	1.69	1.33	2.12	5486	31	2.90	1.97	4.12
Iran	15037	86	0.64	0.51	0.80	13286	33	0.93	0.64	1.31
Iraq	13877	117	0.92	0.76	1.11	12328	51	1.26	0.94	1.66
Russia	4335	58	0.63	0.48	0.82	6721	74	0.96	0.75	1.20

O = observed number of cases; SIR = standardized hospitalization rates ratio; CI = confidence interval

Bold type: 95% CI does not include 1.00.

Table 3. Standardized incidence ratio for hospitalized T2D in second-generation

Birth country	By parental birth country					Compatriots				
	Population	O	SIR	95% CI		Population	O	SIR	95% CI	
Nordic countries	479136	1225	1.09	1.03	1.16	146222	413	1.21	1.10	1.34
Denmark	73599	210	1.13	0.99	1.30	15015	47	1.10	0.81	1.47
Finland	315929	733	1.15	1.07	1.23	117966	339	1.23	1.10	1.37
Norway	83668	282	0.96	0.85	1.08	10136	27	1.22	0.80	1.77
Southern Europe	51064	41	1.06	0.76	1.44	13304	15	0.94	0.53	1.56
Italy	11156	17	1.09	0.64	1.76	1683	-			
Western Europe	106116	192	0.94	0.81	1.09	14173	29	0.72	0.48	1.03
Netherland	7438	11	1.06	0.53	1.90	1403	-			
Great Britain and Ireland	22916	13	0.91	0.48	1.56	2346	-			
Germany	60904	143	0.96	0.81	1.13	9174	23	0.69	0.44	1.04
Austria	10142	19	0.83	0.50	1.30	876	-			
Eastern Europe	116188	59	1.52	1.16	1.97	80477	38	1.42	1.00	1.95
Yugoslavia	70769	45	1.46	1.06	1.95	48987	33	1.42	0.98	2.00
Baltic Countries	21571	88	0.90	0.72	1.11	6451	41	0.89	0.64	1.21
Estonia	17795	73	0.87	0.68	1.09	5411	32	0.79	0.54	1.12
Latvia	3776	15	1.10	0.61	1.81	1040	-			
Central Europe	56348	67	0.89	0.69	1.13	21371	34	0.98	0.68	1.37
Poland	32599	29	0.84	0.56	1.20	12097	8	0.68	0.29	1.34
Hungary	15182	29	1.19	0.80	1.71	6224	19	1.28	0.77	2.01
North America	27811	78	0.86	0.68	1.07	1547	-			
Lartin America	43784	11	1.48	0.73	2.65	21741	-			
Asia	220191	29	1.14	0.76	1.64	157744	23	1.40	0.88	2.10
Turkey	43924	13	1.20	0.64	2.06	32365	11	1.22	0.60	2.18
Russia	11280	41	1.19	0.85	1.61	4651	-			

O = observed number of cases; SIR = standardized hospitalization rates ratio; CI = confidence interval

Bold type: 95% CI does not include 1.00.