

ORIGINAL ARTICLE

Narcolepsy among first- and second-generation immigrants in Sweden: A study of the total population

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Aims: To study incident narcolepsy in first- and second-generation immigrant groups using Swedish-born individuals and native Swedes as referents.

Methods: The study population included all individuals registered and alive in Sweden at baseline. Narcolepsy was defined as having at least one registered diagnosis of narcolepsy in the Swedish National Patient Register. The incidence of narcolepsy in different immigrant groups was assessed by Cox regression, with hazard ratios (HRs) and 95% confidence intervals (CI). The models were stratified by sex and adjusted for age, geographical residence in Sweden, educational level, marital status, co-morbidities, and neighbourhood socioeconomic status.

Results: In the first-generation study, 1225 narcolepsy cases were found; 465 males and 760 females, and in the second-generation study, 1710 cases, 702 males and 1008 females. Fully adjusted HRs (95% CI) in the first-generation study was for males 0.83 (0.61–1.13) and females 0.83 (0.64–1.07), and in the second-generation study for males 0.76 (0.60–0.95) and females 0.91 (95% CI 0.76–1.09). Statistically significant excess risks of narcolepsy were found in first-generation males from North America, and second-generation males with parents from North America, and second-generation females with parents from Latin America.

Conclusions: There were only significant differences in incident narcolepsy between native Swedes and second-generation male immigrants. The observed differences can partly be explained by differences in Pandemrix® vaccinations and are probably not attributable to genetic differences between immigrants and natives.

KEYWORDS

narcolepsy, immigrants, H1N1 influenza, vaccination

1 | INTRODUCTION

Narcolepsy belongs to the group of central disorders of somnolence, and is a severe chronic neurological disease characterized by excessive daytime sleepiness, and especially with unintended daytime sleep episodes,¹ according to the ICSD-3 classification.² Narcolepsy with cataplexy, that is, sudden loss of muscle tone associated with emotions,

is categorized as type 1 narcolepsy, and considered to be an autoimmune disorder.^{3–5} Narcolepsy without cataplexy is categorized as type 2 narcolepsy.¹ Narcolepsy type 1 is also linked to disturbed sleep during nights, sleep paralysis, and with hypnagogic hallucinations at sleep onset and various occasional psychiatric symptoms.^{3–5}

A recent study focusing on the treatment of narcolepsy in Sweden identified 2508 patients from The Swedish Prescribed

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Drug Register during 2005–2017, that is, a prevalence of around 25 per 100,000 individuals.⁶ Globally, the prevalence of narcolepsy in countries where narcolepsy is well recognized and is estimated at around 30 per 100,000 individuals,⁴ with 20–50 per 100,000 in European and US populations.⁷ The highest reported rate comes from Japan with 160 per 100,000,⁸ and the lowest rate is found in Israel with only 0.23 per 100,000 according to older studies.⁹ There are, however, differences in the age strata, which could complicate direct comparisons.

Environmental factors seem to be of importance for the development of narcolepsy, but the nature of such possible factors is largely unknown.¹⁰ However, it is possible that events during early life could influence the risk of developing the disease, or the severity of it.

The findings of an increased incidence of narcolepsy after vaccination (Pandemrix®) for the H1N1 influenza in 2009–2010, with an increased risk of 5–14-fold in children and adolescents, and 2–7-fold among adults,¹¹ led to an increased interest of the disease. A cohort study found a vaccination coverage of 57% in Sweden with a total of 5.3 million inhabitants, that is, around 60% of the population, vaccinated 2009–2010.¹² The highest vaccination rates were among individuals of Nordic origin, and the lowest among foreign-born outside the Nordic countries, 37%–48%, with particularly low rates among those from Oceania, Asia, and Eastern Europe. Incident cases of narcolepsy in Sweden were estimated at 150–160 cases among children and adolescents, with a 3-fold risk for children and adolescent ≤ 20 years of age, a two-fold risk for young adults 21–30 years of age, a statistically non-significant increased risk of 1.5 in adults 31–40 years of old, and with a close to baseline level among those > 40 years of age.¹² Interestingly, an association between Pandemrix-induced narcolepsy and the non-coding RNA gene *GDNF-AS1* has been found.¹³ The *GDNF-AS1* gene regulates the expression of the essential neurotrophic factor GDNF, and changes in regulation of GDNF have been associated with neurodegenerative diseases. The association between the H1N1 vaccination and incident narcolepsy was found especially in Sweden and Finland but not in the Netherlands, the UK, and Italy according to one study,¹⁴ while in China, an association between the H1N1 influenza and narcolepsy was found.¹⁵ However, a review/meta-analysis found an increased risk of narcolepsy in countries where Pandemrix® was used (Finland, France, Ireland, the Netherlands, Norway, Sweden, and the UK) but not in other countries.¹¹

As regard, immigrants and narcolepsy, we could not identify any studies. However, as mentioned above, the vaccination coverage differed between different immigrant groups and by gender,¹² which might have affected the risk of narcolepsy.

The aim of this study was to study the risk of narcolepsy in first- and second-generation immigrants in Sweden with a follow-up period also including the H1N1 influenza and the Pandemrix® vaccination program in Sweden. Our hypothesis was that there may be some differences between native Swedes and different immigrant groups, as the differences between population groups in Pandemrix® vaccination coverage could affect the incidence.

2 | METHODS

2.1 | Design

The registers used in the present retrospective cohort study were the Swedish Total Population Register (TPR) and the Swedish National Patient Register (NPR). The Swedish TPR is maintained by Statistics Sweden and includes data on birth, death, marital status, family relationships, and migration within Sweden as well as emigration. The Swedish TPR is highly complete, with inclusion of 100% of births and deaths, 95% of immigrations and 91% of emigrations.¹⁶ Regarding the Swedish NPR with diagnoses reported from hospital, inpatient hospital care is complete from 1987, with a proportion of missing data of 0.9%, and where more than 99% of all somatic and psychiatric hospital discharges are registered.¹⁷ For outpatient hospital care, the missing data are estimated to be 3%.¹⁸ Subjects in all ages were included in the study. The follow-up period ran from January 1, 1998, until hospitalization/out-patient treatment of narcolepsy, death, emigration, or the end of the study period on December 31, 2018, whichever came first. In the NPR, out-patient diagnoses were included nationwide from 2001 and onward from specialist care, not primary healthcare.

2.2 | Definition of first- and second-generation immigrants

First- and second-generation immigrants were included in the study. First-generation immigrants were defined as foreign-born individuals, with the reference group defined as individuals born in Sweden. Second-generation immigrants were defined as those individuals with at least one foreign-born parent. The reference group was defined as Swedish-born individuals with two Swedish-born parents, native Swedes. Hereafter, the groups will be referred to as first-generation immigrants, second-generation immigrants, and reference groups as Swedish-born and native Swedes, respectively. Thus, second-generation immigrants, native Swedes and Swedish-born individuals could be included in both studies, with an overlapping. Potential relationships between the first- and second-generation immigrants were not considered in the analysis. We did not have access to Pandemrix® status of the individuals in the study.

2.3 | Outcome variable

Narcolepsy (G47.4).

2.4 | Co-morbidities

As co-morbidities, we used the following diagnoses (with ICD-10 code): Diabetes (E10–E14) and cancers (C00–C97). Diabetes and cancers were included in the analyses as they are related to narcolepsy.

2.5 | Demographic and socioeconomic variables

The study population was stratified by sex.

Age was used as a continuous variable in the analysis.

Educational attainment (with educational levels for parents for individuals up to 24 years of age) was categorized as ≤ 9 years (partial or complete compulsory schooling), 10–12 years (partial or complete secondary schooling), and > 12 years (attendance at college and/or university).

Marital status was set as married or not (with marital status for parents for individuals up to 24 years of age).

Geographic region of residence was included to adjust for possible regional differences in hospital admissions and was categorized as¹ large cities,² southern Sweden, and³ northern Sweden. Large cities were defined as municipalities with a population of $> 200,000$ and comprised the three largest cities in Sweden: Stockholm, Gothenburg, and Malmö.

2.6 | Neighbourhood deprivation

Neighborhood socioeconomic status (NSES) was derived from Small Area Market Statistics (SAMS). The neighbourhoods were derived from small area market statistics (SAMS), which were originally created for commercial purposes and pertain to small geographic areas with boundaries defined by homogenous types of buildings. The average population in each SAMS neighbourhood is approximately 2000 people for Stockholm and 1000 people for the rest of Sweden. A summary index was calculated to characterize neighbourhood-level deprivation. This index was categorized into four groups: more than one standard deviation (SD) below the mean (low deprivation level or high SES), more than one SD above the mean (high deprivation level or low SES), and within one SD of the mean (moderate SES or moderate deprivation level). The group with low deprivation level or high SES was used as reference group. Unknown neighborhood SES comprised its own group.

2.7 | Statistical analysis

Baseline data are presented with continuous variables as mean and standard deviations, and categorical variables as counts and percentages. We used Cox regression analysis to estimate the relative risk (hazard ratios (HR) with 95% confidence intervals (CI)) of incident narcolepsy in different groups of first- and second-generation immigrants compared with the reference group, that is, Swedish-born individuals or native Swedes, during the follow-up time. For immigrants, we categorized into Nordic countries, other European countries (including Russia), North America and the rest of the world, that is, Africa, Asia, and Latin America. All analyses were stratified by sex. Three models were used: Model 1 with adjustment for age and region of residence; Model 2 with adjustment for age, region of residence, educational level, marital status, and neighborhood SES,

to examine to what extent SES explained the association between country of birth and incident narcolepsy; and Model 3 as Model 2 but with the inclusion also of relevant co-morbidities (diabetes and cancer), to examine if other diagnoses explained the association between country of birth and narcolepsy. As a sensitivity analysis, we also included preterm birth (defined as < 37 gestational weeks; information from the Swedish Medical Birth Register) in the second-generation study to examine if this had an impact on the HRs. The prevalence of narcolepsy was estimated for individuals alive at 31/12/2018 and including diagnoses set 5 years earlier.

3 | RESULTS

The study population included 7,033,625 in the first-generation and 6,466,889 in the second-generation sub-study (Table 1). Altogether, 1225 cases of narcolepsy were found in the first-generation study (465 males and 760 females), and 1710 cases in the second-generation study (702 males and 1008 females). The age-distribution of cases was different in the first- and second-generation studies, with in the first-generation study 220 (18.0%) were < 20 years of age (Table S1, S2a,b), and in the second-generation study 818 (47.8%) (Table S1), with higher rates among both males (69.6%) and females (57.9%) with foreign-born parents (Tables S1a,b). The female/male ratio was 1.48 in the first-generation study, and 1.51 in the second-generation study. The prevalence of narcolepsy for individuals alive at 31/12/2018 was for Swedish-born males and females 45.7 and 83.3 per 100,000 individuals, respectively, and for foreign-born males and females 32.1 and 32.9 per 100,000 individuals, respectively. The female/male ratio was 1.82 for Swedish-born, and 1.02 for foreign-born.

The association with diabetes in the first-generation study was increased in males and females being Swedish-born, and in the second-generation study in native Swedes (Tables S1a,b, S6a,b), and in second-generation immigrant females (Table S1b). The association with cancers was increased in first-generation immigrant males (Table S1a), and in the second-generation study in native female Swedes (Table S1b).

Regarding the risk of narcolepsy among first-generation immigrant males and females, Table 2, the risk was not statistically different from Swedish-born males and females, fully adjusted HRs 0.83 (95% CI 0.61–1.13) and 0.83 (95% CI 0.64–1.07), respectively. The only group with a statistically significant excess risk was found in first-generation immigrant males from North America, fully adjusted HR 4.29 (95% CI 1.74–10.55).

Among second-generation immigrants, a statistically significant decreased risk was found overall among second-generation immigrant males, Table 3, fully adjusted HR 0.76 (95% CI 0.60–0.95), but not among females, fully adjusted HR 0.91 (95% CI 0.76–1.09). A statistically significant decreased risk was found among second-generation immigrant males and females with parents from non-Nordic European countries, HRs 0.50 (95% CI 0.31–0.81) and 0.63 (95% CI 0.43–0.93), respectively. An increased risk was found for

TABLE 1 Population in first-generation and second-generation study and the number of cases of narcolepsy

	First-generation individuals				Second-generation individuals			
	Population		Cases		Population		Cases	
	No.	%	No	%	No.	%	No	%
Total population	7,033,625		1225		6,466,889		1710	
Gender								
Males	3,337,581	47.5	465	38.0	3,311,594	51.2	702	41.1
Females	3,696,044	52.5	760	62.0	3,155,295	48.8	1008	58.9
Immigrant status								
Swedish	5,738,883	81.6	1090	89.0	5,492,315	84.9	1473	86.1
Foreign born ^a	1,294,742	18.4	135	11.0	974,574	15.1	237	13.9
Age (years)								
<20	1,052,043	15.0	220	18.0	2,074,980	32.1	818	47.8
20–29	1,077,056	15.3	234	19.1	1,023,317	15.8	272	15.9
30–39	1,113,278	15.8	150	12.2	1,060,188	16.4	160	9.4
40–49	1,042,603	14.8	165	13.5	989,510	15.3	169	9.9
50–59	1,067,662	15.2	216	17.6	956,883	14.8	216	12.6
60+	1,680,983	23.9	240	19.6	362,011	5.6	75	4.4
Educational level								
≤9	3,188,893	45.3	482	39.3	1,593,711	24.6	366	21.4
10–12	2,434,908	34.6	460	37.6	3,057,757	47.3	797	46.6
>12	1,409,824	20.0	283	23.1	1,815,421	28.1	547	32.0
Region of residence								
Large cities	3,017,207	42.9	609	49.7	3,071,851	47.5	879	51.4
Southern Sweden	2,155,318	30.6	420	34.3	2,193,678	33.9	571	33.4
Northern Sweden	1,861,100	26.5	196	16.0	1,201,360	18.6	260	15.2
Marital status								
Married	3,714,352	52.8	503	41.1	2,068,912	32.0	340	19.9
Not married	3,319,273	47.2	722	58.9	4,397,977	68.0	1370	80.1
Neighborhood deprivation								
Low	1,478,437	21.0	321	26.2	1,611,631	24.9	444	26.0
Middle	3,721,882	52.9	687	56.1	3,818,947	59.1	1016	59.4
High	1,018,693	14.5	179	14.6	953,506	14.7	244	14.3
Unknown	814,613	11.6	38	3.1	82,805	1.3	6	0.4
Diagnosis of diabetes	470,481	6.7	112	9.1	308,117	4.8	91	5.3
Diagnosis of cancer	1,128,139	16.0	211	17.2	54,413	0.8	23	1.3

^aImmigration status in the second-generation was defined according to the parental birth countries.

males with parents born in North America, fully adjusted HR 2.53 (95% CI 1.13–5.65), and females with parents from Latin America ($n = 11$), fully adjusted HR 1.86 (95% CI 1.02–3.39). When including preterm/premature birth in the analysis (Table S1) in the second-generation study, only marginal changes were found.

The incidence rates (IRs) in total and over time (Figures S1,S2) for the time periods 1998–2002, 2003–2007, 2008–2012, and 2013–2018 counted per 100,000 person-years adjusted to the European standardized population were (with IRs and 95% CIs) for all males in total was 0.72 (0.65–0.79), and for the time periods 0.88, 0.67, 0.90, and 0.60, respectively; for all females in total 1.06 (0.99–1.14), and

for the time periods 1.14, 0.92, 1.29, and 1.63, respectively; for all Swedish-born 0.95 (0.89–1.01) and for the time periods 1.08, 0.79, 1.19, and 1.44, respectively; and lastly for all foreign-born 0.55, 0.91, 0.59, and 0.48, respectively.

4 | DISCUSSION

The main findings of this study were that there was no statistically significant different risk of narcolepsy in general among first-generation immigrant males and females. Among second-generation

TABLE 2 Incidence of narcolepsy first-generation immigrant vs Swedish-born males and females expressed as hazard ratios (HR) with 95% confidence intervals (95% CI)

	Obs.	Model 1			Model 2			Model 3		
		HR	95% CI		HR	95% CI		HR	95% CI	
Males										
Sweden	407	1.00			1.00			1.00		
All foreign-born	58	0.75	0.57	0.98	0.83	0.61	1.14	0.83	0.61	1.13
Nordic countries	17	0.82	0.50	1.33	0.95	0.57	1.57	0.96	0.58	1.59
Other European countries	14	0.61	0.36	1.03	0.66	0.38	1.13	0.65	0.38	1.12
North America	5	3.58	1.48	8.64	4.20	1.70	10.34	4.25	1.72	10.47
Africa, Asia, Latin America	22	0.68	0.44	1.05	0.76	0.48	1.21	0.75	0.47	1.18
Females										
Sweden	683	1.00			1.00			1.00		
All foreign-born	77	0.61	0.48	0.78	0.83	0.65	1.07	0.83	0.64	1.06
Nordic countries	17	0.76	0.52	1.10	0.94	0.65	1.38	0.94	0.64	1.38
Other European countries	19	0.56	0.35	0.88	0.73	0.46	1.17	0.73	0.46	1.16
North America	5	1.14	0.28	4.55	1.69	0.42	6.80	1.70	0.42	6.85
Africa, Asia, Latin America	36	0.52	0.35	0.77	0.77	0.52	1.16	0.76	0.51	1.15

Note: Model 1: adjusted for age; model 2: adjusted for age, region of residence in Sweden, educational level, marital status, and neighborhood deprivations; model 3: model 2 + comorbidities. Bold values are statistically significant.

HR: Hazard ratios; CI: confidence interval.

TABLE 3 Incidence of narcolepsy in second-generation immigrant vs native Swedish males and females expressed as hazard ratios (HR) with 95% confidence intervals (95% CI)

	Obs.	Model 1			Model 2			Model 3		
		HR	95% CI		HR	95% CI		HR	95% CI	
Males										
Sweden	610	1.00			1.00			1.00		
All with foreign-born parents	92	0.76	0.61	0.94	0.75	0.60	0.94	0.75	0.60	0.95
Nordic countries	36	0.76	0.54	1.06	0.76	0.54	1.06	0.76	0.55	1.07
Other European countries	17	0.51	0.32	0.83	0.50	0.31	0.81	0.50	0.31	0.81
North America	6	2.66	1.19	5.95	2.57	1.15	5.76	2.56	1.14	5.73
Africa, Asia, Latin America	33	0.86	0.60	1.23	0.86	0.59	1.25	0.86	0.59	1.24
Females										
Sweden	863	1.00			1.00			1.00		
All with foreign-born parents	145	0.87	0.73	1.04	0.90	0.75	1.08	0.91	0.76	1.09
Nordic countries	72	1.06	0.84	1.36	1.07	0.84	1.36	1.08	0.84	1.37
Other European countries	28	0.62	0.43	0.91	0.63	0.43	0.92	0.64	0.44	0.93
North America	3	0.94	0.30	2.93	0.95	0.31	2.95	0.94	0.30	2.93
Africa, Asia, Latin America	42	0.83	0.61	1.14	0.91	0.66	1.26	0.91	0.66	1.26

Note: Model 1: adjusted for age; model 2: adjusted for age, region of residence in Sweden, educational level, marital status, and neighborhood deprivations; model 3: model 2 + comorbidities. Bold values are statistically significant.

Abbreviations: CI, confidence interval; HR, Hazard ratios.

males, a slightly lower risk was found among males with foreign-born parents, which was not found among females in general. Notably, a higher risk was found in certain subgroups, that is, among first-generation immigrant males from North America and second-generation immigrant males with parents from North America, and a

marginally higher risk among second-generation immigrant females with parents from Latin America.

In the first-generation study we found an increase in incidence rates for all Swedish-born individuals during 2008–2012, that is, the years around the H1N1 epidemic and Pandemrix® use, but not

among first-generation immigrants, and the IR also increased in Swedish-born during the years 2013–2018. Regarding males and females in general in the first-generation study, the risk increased for both genders in the years 2008–2012, with a further increase in females thereafter, but a decrease in males. The differences in Pandemrix® coverage might be responsible for these differences.

We have no good explanation to the higher risk among first- and second-generation immigrant males from North America, but the absolute number of narcolepsy cases was low suggesting that the results should be interpreted with caution. As there were many cases after the H1N1 vaccination, the coverage of the Pandemrix® vaccination in different groups is of interest. For the Pandemrix® vaccination, the coverage was highest among first-generation immigrants of Nordic origin, and lower in other groups.¹² Interestingly, these differences did not result in differences in the incident cases of narcolepsy in first-generation immigrants of non-Nordic origin. Otherwise, narcolepsy is clinically known to be under-reported, which may also explain the lower risk in some first-generation immigrant groups.

Yet, we found a higher risk of narcolepsy in the first-generation immigrant study among females, possibly explained by the vaccination coverage of Pandemrix®, which was higher among females than in males, 60.3% versus 54.2%.¹² The female predominance has also been shown in a recent Swedish study on narcolepsy treatment.⁶ The prevalence of narcolepsy was higher compared with the earlier Swedish study, and for Swedish-born females considerably higher, that is, 83.3 per 100,000, while among Swedish-born males in line with the prevalence rates in other European and North American countries.⁷ Of course, both over- and under-estimation of registered diagnoses might be at hand.

The association between the H1N1 influenza and narcolepsy in China is also of interest as narcolepsy was clearly shown to increase in mostly males in 2010, after the H1N1, and go back to normal levels in the following years.¹⁵ Such an association does not seem to have been present in Sweden in any immigrant group to a large extent.

We chose to include diabetes as a co-morbidity. However, according to earlier studies, Pandemrix® was not associated with a larger risk of type 1 diabetes neither in general¹⁹ nor among children,²⁰ even if a small excess risk could not be excluded.²¹ We found a moderately higher risk in the first- and second-generation immigrant studies in males and females being Swedish-born or native Swedish females, as well as among second-generation immigrant females. We also found cancers to be associated with narcolepsy in some groups in accordance with a review,²² possibly owing to the chance that narcolepsy was more easily detected in these individuals. We also included preterm birth as a co-factor in the second-generation study, but this did not change the HRs other than marginally.

There are certain limitations with this study, especially the relatively low number of cases in most first- and second-generation immigrant groups, which is why we chose to divide immigrants into large groups to get enough numbers in the different groups. Several cases of narcolepsy are probably not found, as this diagnosis is under-reported, and as under-reporting might be more common

in immigrants, it could have influenced our findings. Besides, over-reporting might also be at hand. However, this is the first study ever on this topic. We could not sub-divide narcolepsy cases into type 1, type 2, secondary, or non-specified cases. As pointed out earlier, the estimated magnitude of the increased risk of narcolepsy after Pandemrix® vaccination depends on the method to determine the index date of the disease.²³ However, our aim was not to determine the increased risk after the Pandemrix® vaccination, but to study the risk among first- and second-generation immigrants during a follow-up period covering the H1N1 influenza and the Pandemrix® vaccination program in Sweden. As the vaccination coverage differed between different groups, the risk of narcolepsy could be influenced by these vaccination coverage differences. The age distribution was quite different between first- and second-generation immigrants, out of whom many more were found in the second-generation immigrants in the age span <20 years.

In conclusion, there were only small differences in incident narcolepsy between second-generation male immigrants and native Swedes. The observed differences can partly be explained by differences in Pandemrix® vaccinations and are probably not attributable to genetic differences between immigrants and Swedish-born individuals.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/ane.13633>.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

ETHICS STATEMENT

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Regional Ethical Review Board in Lund (ref nr 2012/795 and later amendments).

CONSENT STATEMENT

Informed consent was not applicable, as the study was based on pseudonymized data from registers.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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