ORIGINAL RESEARCH ARTICLE

Desloratadine Exposure and Incidence of Seizure: A Nordic Post-authorization Safety Study Using a New-User Cohort Study Design, 2001–2015

Annette Kjær Ersbøll[1] · Kaushik Sengupta[2,3] · Eero Pukkala[4,5] · Kristian Bolin[6] · Eline Aas[7] · Martha Emneus[8] ·
Dena Rosen Ramey[9] · Joanne E. Brady[9] · Daniel Mines[9] · Kristian Aasbjerg[10] · Christian Vestergaard[11] ·
Gunnar Gislason[1,12,13,14] · Alfred Peter Born[15] · Thora Majlund Kjærulff[1]

Abstract

Introduction A small number of adverse events of seizure in patients using desloratadine (DL) have been reported. The European Medicines Agency requested a post-authorization safety study to investigate whether there is an association between DL exposure and seizure.

Objective The aim was to study the association between DL exposure and incidence of first seizure.

Methods A new-user cohort study of individuals redeeming a first-ever prescription of DL in Denmark, Finland, Norway, and Sweden in 2001–2015 was conducted. DL exposure was defined as days' supply plus a 4-week grace period. DL unexposed periods were initiated 27 weeks after DL prescription redemption. Poisson regression was used to estimate the adjusted incidence rate and adjusted incidence rate ratio (aIRR) of incident seizure.

Results A total of 1,807,347 first-ever DL users were included in the study, with 49.3% male and a mean age of 29.5 years at inclusion; 20.3% were children aged 0–5 years. The adjusted incidence rates of seizure were 21.7 and 31.6 per 100,000 person-years during DL unexposed and exposed periods, respectively. A 46% increased incidence rate of seizure was found during DL exposed periods (aIRR = 1.46, 95% confidence interval [CI] 1.34–1.59). The aIRR ranged from 1.85 (95% CI 1.65–2.08) in children aged 0–5 years to 1.01 in adults aged 20 years or more (95% CI 0.85–1.19).

Conclusion This study found an increased incidence rate of seizure during DL exposed periods as compared to unexposed periods among individuals younger than 20 years. No difference in incidence rate of seizure was observed in adults between DL exposed and unexposed.

Key Points

In this post-authorization safety study in the Nordic countries, desloratadine (DL) exposed periods were associated with an elevated incidence rate of seizure compared to subsequent unexposed periods, with the largest effect for the exposed period following the first-ever DL prescription redemption.

In children aged 0–5 years, a marked increase in the incidence rate of febrile seizure was seen during DL exposed periods compared to unexposed periods.

Among adults, no difference in incidence rate of seizure was seen between DL exposed and unexposed periods.

✉ Annette Kjær Ersbøll
ake@sdu.dk

Extended author information available on the last page of the article

1 Introduction

A seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain [1]. Symptoms include impaired awareness, changes in muscle tone, involuntary eye movements, and loss of control of central functions such as bladder and bowel. A seizure can be a single event or recur multiple times. Seizures may be provoked or unprovoked. A provoked seizure is presumed to be a manifestation of an acute cause, such as head injury, fever, or severe metabolic derangements; however, it can also occur after a stroke or as a consequence of medication. Unprovoked seizures are defined as episodes without a clinical condition potentially responsible for the seizure. Recurrent unprovoked seizures are referred to as epilepsy [2].

Worldwide, the incidence rate (IR) of unprovoked seizures among individuals was 23–61 per 100,000 person-years based on a review including six studies [2]. In an Icelandic study, the IR of unprovoked seizures was estimated at 57 per 100,000 person-years, with highest estimates in children less than 12 months (130 per 100,000 person-years) and in adults 65 years or older (111 per 100,000 person-years) [3].

In the International Statistical Classification of Diseases and Related Health Problems (ICD) of the World Health Organization (WHO), seizures are divided into febrile and non-febrile seizures. A febrile seizure is associated with an increased body temperature and is seen in children 0–5 years old [4–6]. In this age group, febrile seizure is the most common type of seizure, affecting 2–5% of all children, and in general has a benign course [4–6].

Desloratadine (DL) is an oral antihistamine approved for use in the European Union in 2001 as a prescription medication for the relief of symptoms associated with allergic rhinitis and urticaria in adults and children. Over-the-counter (OTC) sale of DL has been available since 2013 in Denmark and Finland, and since 2014 in Norway and Sweden. DL is a second-generation H_1-antagonist; its clinical efficacy lasts for 24 h after administration, and it does not cause drowsiness [7]. Most common side effects include fatigue, dry mouth, headache, and gastrointestinal disturbances.

Studies have shown that first-generation H_1-antagonists are associated with adverse central nervous system effects, including seizures [8–10]. Preclinical and clinical trials have evaluated the effectiveness and safety of DL. No severe or serious adverse events were found in a safety study of DL syrup in children 2–5 years and 6–11 years during a 14-day trial [11]. A review of the safety profile of DL concluded that based on available data and literature, DL is safe and well tolerated, without effects on the central nervous system [12]. However, since market authorization, there have been a small number of adverse event reports of seizures in patients taking DL. This includes a clinical observation of four children who experienced epilepsy temporally associated with DL [13]. One child had no history of seizure, while the remaining three children had a seizure-free period 12–24 months before antihistamine therapy. The case reports do not permit evaluation of the association. To our knowledge, no full-scale epidemiologic studies have been performed prior to the present study on a potential link between DL exposure and incidence of seizure. In 2013, the European Medicines Agency (EMA) requested the market authorization holder (i.e., Merck & Co., Inc., Kenilworth, NJ, USA) consider options for a post-authorization safety study (PASS) (category 3 pharmacovigilance activity) to investigate whether there is an association between DL exposure and seizure. In 2016, a study protocol was approved.

We performed a PASS study using a new-user cohort study design [14, 15], including individuals with a first-ever prescription redemption of DL in the Nordic countries in the study period 2001–2015. Individual-level data from the national prescription and patient registries were combined in a joint database. In this study, we focused on the outcome of seizure overall (febrile, non-febrile, and other).

The aim of the study was to assess the association between DL exposure and incident seizure (all seizures and seizure stratified into febrile and non-febrile). The hypothesis was that the risk of seizure was highest in the first days or weeks after treatment, where we expected DL was most likely used. Furthermore, we expected that the risk of seizure was highest following the first prescription redemption.

2 Methods

A nationwide, registry-based study was conducted, including data from Denmark, Finland, Norway and Sweden and covering an underlying total population of 26 million individuals (by 2015). A new-user cohort study design was used that included all individuals with a first-ever prescription redemption of DL in the study period 2001–2015 [14, 15]. The present paper introduced some differences from the EMA PASS study. The reason was the late receipt of data from Norway, included in the present study, but not in the EMA PASS study.

2.1 Data Sources

The study was conducted as a multi-database study (MDS), where individual-level national raw data were shared [16]. Raw data were extracted in each country by national coordinators from the national population, prescription, and patient registries. The national coordinators performed data control before raw data were transferred to Statistics Denmark, where a combined database was established. The Danish national coordinator derived the variables for the study and performed the statistical analyses. This MDS is described as strategy B by Gini et al. [16]. As a part of this strategy, the national coordinators obtained national approvals, and the national coordinators agreed on a study protocol, statistical analysis plan, and table shells that were approved by EMA. Individual-level linkage of data was possible due to the unique personal identification code assigned to all residents in the Nordic countries at birth or immigration and used as a registration key in all registries [17, 18]. The civil registration systems (i.e., population registries) include information on vital status, date of birth, sex, and migration [19–22]. Individuals in the study were identified in the national prescription registries, which contain data on all prescription

redemptions in retail pharmacies, including the Anatomical Therapeutic Classification (ATC) code, dose, package size, and number of packages [20, 23–26].

In addition, data were collected from the national patient registries, including information from public and private hospitals, diagnoses registered at all in- and out-patient contacts and in emergency rooms, and dates of admission and discharge and type of hospital contact (emergency, elective) [27–29]. Both primary and secondary diagnoses are registered using ICD-8, ICD-9, and ICD-10 codes; the primary diagnosis is the primary cause of hospitalization, and secondary diagnoses are contributing diagnoses. Drugs administered during hospitalization are not captured at an individual-level and therefore are not included in the study. Harmonization of the definition of diagnoses using ICD-8, ICD-9, and ICD-10 codes between countries was performed in consultation with national clinical experts.

For an overview of registries and study periods for the four countries, see Supplementary Table S1 in the electronic supplementary material.

2.2 Study Population

All individuals with a first-ever dispensing of DL in the study period (2001–2015) were included in the study. The date of study entry was the date of first DL prescription redemption. Individuals were excluded if they were not residing in Denmark, Finland, Norway, or Sweden at the date of first DL prescription redemption, had a diagnosis of seizure, epilepsy, malignant brain tumor, or head trauma, or had redeemed a prescription of antiepileptic medicine before study entry. Individuals who were diagnosed with any brain tumor or head trauma or redeemed a prescription of antiepileptic medicine after study entry (i.e., censoring events) were censored at the date of first occurrence, with the intention to exclude provoked or chronic seizures. Individuals were followed until study end (i.e., 31 December 2015) or the first occurrence of a seizure (outcome) or a censoring event, emigration, or death, whichever came first.

2.3 Desloratadine Exposure

The ATC code for DL is RO6AX27. DL exposure was a time-varying variable measured on a daily time scale. Thus, an individual could repeatedly contribute risk time both in DL exposed and unexposed periods during the study period depending on the number of DL prescription redemptions (Supplementary Figure S1, see the electronic supplementary material). A similar definition of DL exposure was used in a previous study [30].

A DL exposed period was defined for each prescription redemption as days' supply from date of DL prescription redemption plus a 4-week grace period (i.e., 28 days). A

DL unexposed period started 27 weeks beyond the date of the prior prescription redemption. If a new DL prescription redemption occurred during an exposed period, the exposed period was extended from that date, with a period equal to days' supply plus a 4-week grace period. A DL prescription redemption after the 4-week grace period and less than 27 weeks after the previous prescription redemption started a new exposed period. The selection of 27 weeks beyond the date of prior DL prescription redemption to define the start of a DL unexposed period was based on clinical judgment. We expected that a gap of more than 6 months since the prior prescription redemption likely meant that DL was not being used.

The period in between the DL exposed period (days' supply plus a 4-week grace period) and the DL unexposed period (starting 27 weeks beyond the date of prior DL prescription redemption) was considered as neither exposed nor unexposed (see Supplementary Figure S1 in the electronic supplementary material). This in-between period is not included in the main analysis.

Days' supply was calculated based on the number of tablets or amount of solution dispensed, the strength of the tablets or solution, and the standard daily dose based on the age of the individual (6–12 months: 1 mg/day; 1–5 years: 1.25 mg/day; 6–11 years: 2.5 mg/day; ≥ 12 years: 5 mg/day).

Since the prescription registry in Sweden was established after the introduction of DL, a 6-month drug-free look-back period was applied to account for truncation bias. In addition, individuals with DL prescription redemptions within 6 months after immigrating to Denmark or Sweden were excluded. Only the first migration date was collected for this study from Finland. No historic migration data were available in Norway.

2.4 Outcomes

The study outcome was incident seizure using primary diagnoses from emergency rooms or inpatient settings registered in the national patient registries. The ICD-10 code for seizure is R56; for febrile seizure, it is R56.0; and for non-febrile seizure, it is R56.8. To identify incident disease, a disease-free look-back period as long as possible for the registries in Denmark, Finland, and Sweden was applied. In Norway, the patient registry was established in 2008. There, a shorter disease-free look-back period was applied (for individuals with study entry in 2010, only a 2–year look-back period could be applied). Due to privacy concerns, Norwegian data for seizures were coded R56 and could not be further divided into febrile and non-febrile seizures.

No studies have examined the validity of the diagnosis codes for seizure in the total population. However, Vestergaard et al. [31] examined the validity of the discharge diagnosis of febrile seizure in children using the Danish National Patient Registry (ICD-10 code R56.0). The positive

predictive value (PPV) was 92.8% (95% confidence interval [CI] 88.8–95.7%). The sensitivity (defined as completeness by the authors) was 71.5% (95% CI 66.3–76.4%) [31].

2.5 Confounders

Potential confounders of the association between DL exposure and the incidence of seizure were identified in consultation with a group of clinical experts (within pharmacology, dermatology, allergy, and epidemiology) and in the literature. The directed acyclic graphs (DAGs) method was used to select the variables needed for confounder adjustment to obtain an unbiased estimate of the association [32, 33].

The minimal sufficient adjustment set included age, sex, country, calendar year, seasonality, and a history of asthma, severe rhinitis, or chronic urticaria in the past 5 years (Supplementary Figure S2, see the electronic supplementary material). Asthma, severe rhinitis, and chronic urticaria were defined as binary variables (ATC and ICD codes are given in Supplementary Table S2).

Age was divided in 5-year categories. As individuals aged during the follow-up, they could contribute observation time to more than one age category. Seasonality was a time-varying variable defined as winter (December– February), spring (March–May), summer (June–August), and autumn (September–November).

Asthma was defined as having redeemed at least two prescriptions of inhaled steroids within a 6-month period and/or hospital contacts with a diagnosis of asthma (including both primary and secondary diagnoses) during the 5-year period before first DL prescription redemption. To distinguish individuals treated for chronic obstructive pulmonary disease (COPD) from those treated for asthma, the first registered asthma treatment had to be redeemed when the purchaser was 45 years or younger.

Severe rhinitis was defined as having at least one prescription redemption of immunotherapy drugs (i.e., allergy shots) typically used for severe rhinitis in the 5-year period before first DL prescription redemption.

Chronic urticaria was defined as having a diagnosis of urticaria (including both primary and secondary diagnoses) during a 5-year period before first DL prescription redemption.

2.6 Statistical Analyses

A descriptive analysis of baseline characteristics of the DL users at study entry was performed by means of frequencies (*N*, %) for categorical variables and mean and standard deviation (SD) for continuous variables.

A Poisson regression of number of individuals with seizure and logarithmic transformation of follow-up time as offset was used to examine the association between DL

exposure and incidence of seizure (also called piecewise exponential model [34]).

The follow-up time was split by age (5-year age categories), calendar year (1-year categories), and season (3-month categories). Furthermore, the follow-up time was split according to DL exposure. In the main analysis, follow-up time was split according to days' supply plus a 4-week grace period (exposed period), 27 weeks or more beyond the date of prior DL prescription redemption (unexposed period), and the follow-up time in between (neither exposed nor unexposed) (see Supplementary Figure S1 in the electronic supplementary material). In the sensitivity analyses, follow-up time was split either according to prescription redemption number (1, 2, or ≥ 3, unexposed) and weeks after DL prescription redemption (0–4, 5–8, 9–16, 17–26, and ≥ 27), respectively.

IRs (unadjusted and adjusted) and incidence rate ratios (unadjusted [IRR], adjusted [aIRR]) were estimated with corresponding 95% CIs. The analyses were also stratified by country and by age group (0–5 years, 6–19 years, and ≥ 20 years). The cut-off values for age in the age-stratified analysis were selected to examine the association in children, adolescents, and adults separately (as the risk of seizure decreases with increasing age).

Six sensitivity analyses were performed to examine the robustness of the results. The first and second sensitivity analyses examined the association between DL exposure and incidence of non-febrile and febrile seizures, respectively, in children aged 0–5 years. A child can be included in both analyses with a first-ever febrile and a first-ever non-febrile seizure. The third sensitivity analysis restricted the study period to the years without OTC sale of DL (2001–2012 in Denmark and Finland, 2001–2013 in Norway and Sweden). The fourth sensitivity analysis restricted the study population to individuals with no prescription redemption of other antihistamines before the date of study entry. Finally, two sensitivity analyses were performed using alternative exposure definitions. The alternative exposure definitions included (1) periods following redemption of a number of prescriptions (1, 2, and ≥ 3 prescription redemptions vs DL unexposed periods) and (2) weeks after prescription redemption (0–4, 5–8, 9–16, and 17–26 weeks vs ≥ 27 weeks).

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

3 Results

3.1 Baseline Characteristics of the Study Population

The study identified a total of 2,300,205 DL users (Fig. 1). Prevalent DL users and individuals with illogical data were excluded (*N* = 174,962 individuals). Furthermore, we

excluded 317,896 individuals with seizure before date of first DL prescription redemption or due to other exclusion criteria (diagnosis of epilepsy, malignant brain tumor, or head trauma or prescription of antiepileptic medicine before date of first DL prescription redemption). This resulted in a study population of 1,807,347 incident DL users (246,003 in Denmark, 533,646 in Finland, 250,910 in Norway, and 776,788 in Sweden).

The study population had a mean age of 29.5 years (SD 22.3 years) at inclusion; 49.3% were male. In total, 20.3% were children aged 0–5 years (Table 1). The majority were included during spring or summer (40.9% and 30.4%). Among the study population, 14.3% had an asthma diagnosis or treatment in the 5-year period prior to the first DL prescription redemption. A total of 0.6% had treatment for severe rhinitis, and 2.1% had a diagnosis of chronic urticaria in the 5-year period prior to the first DL prescription redemption.

Some differences in population characteristics were seen between the countries. In Finland, the proportion of males was 56.5% compared to 45.3% in Denmark, 46.1%

in Norway, and 46.6% in Sweden, respectively. The proportion of children (age group 0–5 years) was larger in Finland (24.8%) than in Denmark (20.0%), Norway (14.0%), and Sweden (19.2%). The largest proportion of new DL users were included in spring (40.4–44.5%) except in Denmark, where the largest proportion of new DL users were included during summer (37.0%). Severe rhinitis was more common in the study population in Denmark and Norway (1.9%, 1.3%) than in Finland and Sweden (0.05%, 0.3%). Chronic urticaria was more frequent in Sweden (3.5%) than in the other three countries (0.7–1.1%).

3.2 Association Between Desloratadine Exposure and Incidence Rate of Seizure

Among the incident DL users, a total of 3372 individuals had a diagnosis of seizure during the study period. The adjusted IRs of seizure during DL unexposed and exposed periods were 21.7 and 31.6 per 100,000 person-years, respectively. The main analysis of the association between DL exposure and incident seizure adjusted for confounders showed a 46%
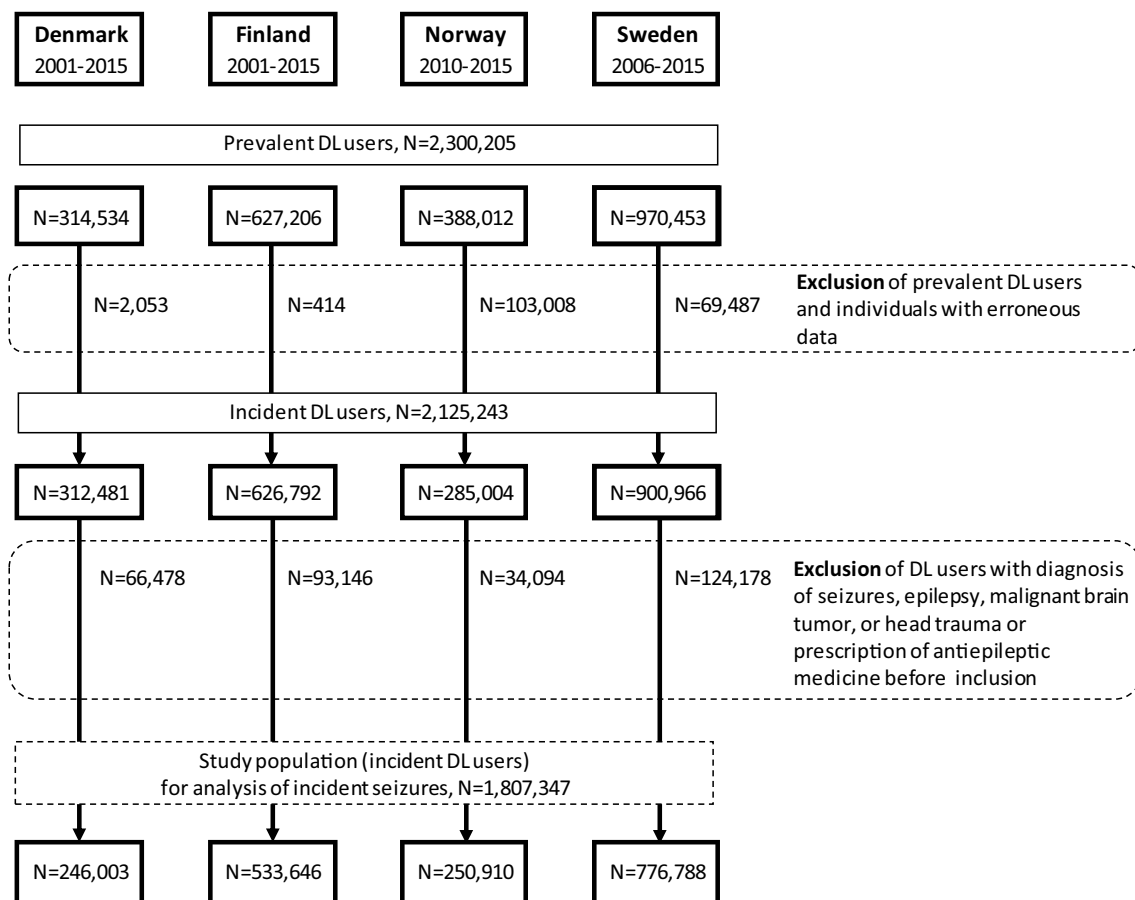

Fig. 1 Study population flow diagram. *DL* desloratadine

increased incidence of seizure during DL exposed periods (aIRR = 1.46, 95% CI 1.34–1.59) (Table 2).

Variations were seen in the IRs of seizure between the countries (Table 2). The adjusted IRs of seizure in the DL unexposed and exposed periods were lowest in Norway (6.5 and 13.0 per 100,000 person-years) and largest in Sweden (35.7 and 47.6 per 100,000 person-years). The IRR stratified by country showed an increased IR of seizure during DL exposed compared to unexposed periods for all four countries. The aIRRs were largest in Denmark and Norway,

Table 1 Baseline characteristics of the incident desloratadine users at date of first desloratadine prescription redemption, overall and stratified by country

| | Total | Denmark | Finland | Norway | Sweden |
	N = 1,807,347	N = 246,003	N = 533,646	N = 250,910	N = 776,788
Gender					
Male	890,170 (49.3)	111,376 (45.3)	301,355 (56.5)	115,731 (46.1)	361,708 (46.6)
Female	917,177 (50.7)	134,627 (54.7)	232,291 (43.5)	135,179 (53.9)	415,080 (53.4)
Age					
Mean (SD)	29.5 (22.3)	29.5 (22.4)	28.6 (22.2)	29.6 (20.6)	30.0 (22.8)
Age categories (years)					
0–5[a]	366,149 (20.3)	49,187 (20.0)	132,258 (24.8)	35,212 (14.0)	149,492 (19.2)
6–9	119,674 (6.6)	14,569 (5.9)	26,500 (5.0)	20,016 (8.0)	58,589 (7.5)
10–14	130,576 (7.2)	18,588 (7.6)	32,611 (6.1)	20,359 (8.1)	59,018 (7.6)
15–19	133,561 (7.4)	19,077 (7.8)	33,371 (6.3)	21,893 (8.7)	59,220 (7.6)
20–24	116,093 (6.4)	16,057 (6.5)	31,638 (5.9)	20,991 (8.4)	47,407 (6.1)
25–29	118,316 (6.5)	16,066 (6.5)	35,855 (6.7)	19,643 (7.8)	46,752 (6.0)
30–34	118,932 (6.6)	17,289 (7.0)	35,008 (6.6)	18,859 (7.5)	47,776 (6.2)
35–39	120,319 (6.7)	17,580 (7.1)	34,959 (6.6)	18,381 (7.3)	49,399 (6.4)
40–44	113,232 (6.3)	15,519 (6.3)	33,480 (6.3)	16,888 (6.7)	47,345 (6.1)
45–49	100,776 (5.6)	13,148 (5.3)	31,243 (5.9)	14,123 (5.6)	42,262 (5.4)
50–54	87,922 (4.9)	10,645 (4.3)	28,959 (5.4)	11,349 (4.5)	36,969 (4.8)
55–59	79,044 (4.4)	9815 (4.0)	26,176 (4.9)	9433 (3.8)	33,620 (4.3)
60–64	65,619 (3.6)	8450 (3.4)	18,177 (3.4)	7965 (3.2)	31,027 (4.0)
65–69	50,325 (2.8)	6981 (2.8)	12,106 (2.3)	6473 (2.6)	24,765 (3.2)
70–74	34,860 (1.9)	4979 (2.0)	8629 (1.6)	3871 (1.5)	17,381 (2.2)
75–79	24,518 (1.4)	3586 (1.5)	6379 (1.2)	2551 (1.0)	12,002 (1.5)
≥ 80	27,431 (1.5)	4467 (1.8)	6297 (1.2)	2903 (1.2)	13,764 (1.8)
Calendar year					
2001–2005	170,593 (9.4)	68,254 (27.7)	102,339 (19.2)	–	–
2006–2010	682,088 (37.7)	81,091 (33.0)	228,398 (42.8)	19,083 (7.6)	353,516 (45.5)
2011–2015	954,666 (52.8)	96,658 (39.3)	202,909 (38.0)	231,827 (92.4)	423,272 (54.5)
Season					
Winter	269,630 (14.9)	35,432 (14.4)	71,391 (13.4)	28,311 (11.3)	113,099 (14.6)
Spring	739,607 (40.9)	79,288 (32.2)	237,561 (44.5)	101,438 (40.4)	321,320 (41.4)
Summer	549,877 (30.4)	9,0937 (37.0)	151,408 (28.4)	87,627 (34.9)	219,905 (28.3)
Autumn	248,233 (13.7)	40,346 (16.4)	73,286 (13.7)	33,534 (13.4)	122,464 (15.8)
Diagnoses and treatments during a 5-year period prior to date of first desloratadine prescription redemption[b]					
Asthma	258,549 (14.3)	35,336 (14.4)	69,274 (13.0)	35,454 (14.1)	118,485 (15.3)
Severe rhinitis	10,096 (0.6)	4588 (1.9)	243 (0.05)	3138 (1.3)	2127 (0.3)
Chronic urticaria	37,999 (2.1)	2774 (1.1)	6093 (1.1)	1707 (0.7)	27,425 (3.5)

Values are expressed as numbers (N) and percentages (%) unless stated otherwise

SD standard deviation

[a]For the first age group, children age 0–5 were combined as febrile seizure is seen in children at age 5 years or younger

[b]The look-back period was a minimum of 2 years in Norway

with a 75% and a 98% increased IR of seizure, respectively (aIRR = 1.75, 95% CI 1.44–2.14; aIRR = 1.98, 95% CI 1.36–2.89). For comparison, a 44% and 34% increased IR of seizure during DL exposed periods was seen in Finland and Sweden, respectively (aIRR = 1.44, 95% CI 1.20–1.73; aIRR = 1.34, 95% CI 1.19–1.50).

A large difference in the adjusted IR of seizure was seen between children aged 0–5 years and individuals aged 6–19 years or 20 years or older. The adjusted IRs of seizure in children aged 0–5 years were 146.5 and 270.8 per 100,000 person-years during DL unexposed and exposed periods, respectively, an absolute increase of 124.3 per 100,000 person-years (Table 2). The aIRRs showed an 85% increased IR of seizure during DL exposed periods among children aged 0–5 years (aIRR = 1.85, 95% CI 1.65–2.08). The adjusted IRs of seizure in adolescents aged 6–19 years were 25.6 and

36.3 per 100,000 person-years during DL unexposed and exposed periods, respectively, an absolute increase of 10.7 per 100,000 person-years. Among adolescents aged 6–19 years, a 42% increased IR of seizure was seen (aIRR = 1.42, 95% CI 1.17–1.71). Among adults aged 20 years or older, no difference in IR of seizure was seen between DL exposed and unexposed periods (aIRR = 1.01, 95% CI 0.85–1.19).

3.3 Sensitivity Analyses

In children aged 0–5 years, seizures were divided into febrile, non-febrile, and unspecific seizures, except for Norway (data were not available to categorize the type of seizure into febrile and non-febrile). Due to a small number of unspecified seizures in children, this type is not included in the analysis. The aIRR for Denmark, Finland, and Sweden combined

Table 2 Association between desloratadine (DL) exposure and first seizure

DL exposure	Number (N)	Follow-up time (PY)	Unadjusted			Adjusted[a]		
			IR per 100,000 PY	IRR	95% CI	IR per 100,000 PY	IRR	95% CI
Yes	745	1,166,122	63.9	1.61	(1.49–1.75)	31.6	1.46	(1.34–1.59)
No	2,627	6,634,828	39.6	1	Ref.	21.7	1	Ref.
Stratified by country								
Denmark								
Yes	129	133,806	96.4	2.38	(1.96–2.89)	42.3	1.75	(1.44–2.14)
No	503	1,242,345	40.5	1	Ref.	24.2	1	Ref.
Finland								
Yes	151	325,951	46.3	1.67	(1.40–1.98)	34.8	1.44	(1.20–1.73)
No	711	2,555,545	27.8	1	Ref.	24.1	1	Ref.
Norway								
Yes	57	173,685	32.8	1.85	(1.29–2.65)	13.0	1.98	(1.36–2.89)
No	61	343,630	17.8	1	Ref.	6.5	1	Ref.
Sweden								
Yes	408	532,679	76.6	1.41	(1.26–1.58)	47.6	1.34	(1.19–1.50)
No	1,352	2,493,308	54.2	1	Ref.	35.7	1	Ref.
Stratified by age								
0–5 years								
Yes	436	122,811	355.0	1.89	(1.69–2.11)	270.8	1.85	(1.65–2.08)
No	1,012	538,445	187.9	1	Ref.	146.5	1	Ref.
6–19 years								
Yes	143	270,274	52.9	1.36	(1.14–1.63)	36.3	1.42	(1.17–1.71)
No	655	1,685,810	38.9	1	Ref.	25.6	1	Ref.
≥ 20 years								
Yes	166	773,038	21.5	0.99	(0.84–1.16)	11.9	1.01	(0.85–1.19)
No	960	4,410,573	21.8	1	Ref.	11.8	1	Ref.

Values are expressed as numbers (N), follow-up time in PY, IR per 100,000 PY, and IRR with corresponding 95% CI for the unadjusted and adjusted analyses

CI confidence interval, *IR* incidence rate, *IRR* incidence rate ratio, *PY* person-years

[a] Adjusted for age (5-year age categories), sex, country, calendar year (1-year categories), seasonality, asthma, severe rhinitis, and chronic urticaria

was 1.46 (95% CI 1.17–1.83) for non-febrile seizure (i.e., a 46% increased IR) and 2.19 (95% CI 1.90–2.51) for febrile seizure (i.e., a 119% increased IR), respectively (Table 3).

Restricting the study period to years without OTC availability of DL did not result in any changes in the association between DL exposure and IR of seizure (aIRR = 1.47, 95% CI 1.32–1.63). Restricting the study population to individuals with no prescription redemption of other antihistamines before study entry resulted in a minor increase in the association between DL and IR of seizure (aIRR = 1.51, 95% CI 1.37–1.65).

Two alternative definitions of DL exposure were applied (exposure in relation to prescription redemption sequence and weeks after prescription redemption across all prescription redemptions). An increased IR of seizure was seen during the DL exposed periods following the first, second, and third or more prescription redemption as compared to unexposed periods. The aIRR was largest at first prescription with a 79% increased IR of seizure (aIRR = 1.79, 95% CI 1.60–1.99), and decreased at the second and third or more prescription redemptions (aIRR = 1.26, 95% CI 1.03–1.54; aIRR = 1.18, 95% CI 1.03–1.35). The second alternative DL exposure definition showed an increased IR during all four periods after a DL prescription redemption (weeks 0–4, 5–8, 9–16, and 17–26) as compared to the DL unexposed period (27 weeks or more after a DL prescription redemption). The aIRR varied irregularly from 1.57 in weeks 0–4 (95% CI 1.39–1.77), to 1.35 in weeks 5–8 (95% CI 1.17–1.55), 1.57 in weeks 9–16 (95% CI 1.41–1.74), and 1.28 in weeks 17–26 (95% CI 1.15–1.43).

4 Discussion

4.1 Interpretation of the Findings

The present study is to our knowledge the largest to date to investigate the safety of DL with respect to the risk of seizure. In this Nordic registry-based study conducted in a population of new DL users, we found a 46% increased incidence of seizure during DL exposed periods compared to unexposed periods. The effect was strongest in children aged 0–5 years of age (85% excess) and more modest in adolescents aged 6–19 years (42% excess). There was no effect in individuals 20 years or older. To understand the public health implications of these findings, the relative risk needs to be examined in the context of the absolute excess differences of IR of first seizure when comparing DL exposed and unexposed periods. The excess risk was modest in children aged 0–5 years (124.3 per 100,000 person-years) and small in adolescents aged 6–19 years (10.7 per 100,000 person-years).

The increased incidence of seizure was seen in all four countries. In children aged 0–5 years of age in Denmark, Finland, and Sweden, the adjusted analyses of types of seizure showed a 119% increased incidence of febrile seizure during DL exposed periods compared to unexposed periods. For comparison, a 46% increased IR of non-febrile seizure was seen in children aged 0–5 years. A plausible explanation of the higher rate of febrile seizure compared to non-febrile seizure is that for febrile seizure, an individual may have multiple stimuli that lower the seizure threshold, including DL use and fever; whereas, for non-febrile seizure, DL would be the only known stimulus. A decreasing incidence of seizure was seen with increasing prescription redemption number. This could be due to a higher likelihood of discontinuation of DL in individuals who experienced a seizure. The association between weeks after prescription redemption and IR of seizure was strongest for 0–4 and 9–16 weeks and weaker 5–8 and 17–26 weeks after prescription redemption. However, we expected a decreasing incidence with increasing number of weeks after prescription redemption.

Findings in the present study help to address the lack of epidemiologic studies on the association between DL exposure and incidence of seizure. To our knowledge, no prior full-scale epidemiologic studies have been performed on a potential link between DL exposure and incidence of seizure.

The IR of overall seizure during DL unexposed periods in the present study in Denmark, Finland, and Sweden was of similar size as the worldwide IR of unprovoked seizure [2]. In an Icelandic study, the IR of unprovoked seizure was higher than seen in the present study [3]. The IR of non-febrile seizure among children 0–5 years in the present study was slightly lower than the IR of unprovoked seizure among children 0–11 months in the Icelandic study.

The study was performed as a response to a drug safety concern regarding the potential increased risk of seizure based on case reports. In 2013, Cerminara and coauthors described four case reports of seizures in children with a family or medical history of seizure [13]. The paper indicated that some patients experienced seizures when DL was introduced that did not recur when DL was discontinued. Subsequent to the 2013 publication, but prior to the completion of the PASS, the "Special Warnings and Precautions Section" of the DL label was updated in 2017 to include convulsions. The update stated that: "Desloratadine should be administered with caution in patients with medical or familial history of seizures, and mainly young children, being more susceptible to develop new seizures under desloratadine treatment. Healthcare providers may consider discontinuing desloratadine in patients who experience a seizure while on treatment."

Table 3 Sensitivity analyses of the association between desloratadine (DL) exposure and first seizure

DL exposure	Number (N)	Follow-up time (PY)	Unadjusted			Adjusted		
			IR per 100,000 PY	IRR	95% CI	IR per 100,000 PY	IRR	95% CI
Non-febrile seizures in children aged 0–5 years[a]								
Yes	110	110,315	99.7	1.59	(1.28–1.97)	117.8	1.46	(1.17–1.83)
No	315	501,771	62.8	1	Ref.	80.7	1	Ref.
Febrile seizures in children aged 0–5 years[a]								
Yes	307	109,820	279.5	1.99	(1.74–2.28)	319.9	2.19	(1.90–2.51)
No	700	499,182	140.2	1	Ref.	145.5	1	Ref.
Restricting study period to years before OTC[b]								
Yes	503	732,684	68.7	1.73	(1.57–1.92)	42.0	1.47	(1.32–1.63)
No	1539	3,886,038	39.6	1	Ref.	28.6	1	Ref.
Restricting to individuals without other antihistamine prescription redemptions before inclusion								
Yes	595	654,147	91.0	1.84	(1.68–2.01)	42.8	1.51	(1.37–1.65)
No	2180	4,404,922	49.5	1	Ref.	28.4	1	Ref.
Alternative definition of DL exposure								
Following prescription redemption number[b]								
1	411	366,722	112.1	2.83	(2.55–3.14)	39.6	1.79	(1.60–1.99)
2	99	180,073	55.0	1.39	(1.14–1.70)	27.9	1.26	(1.03–1.54)
≥ 3	235	619,327	37.9	0.96	(0.84–1.10)	26.2	1.18	(1.03–1.35)
No	2627	6,634,828	39.6	1	Ref.	22.2	1	Ref.
Weeks after prescription redemption[b]								
0–4	298	399,940	74.5	1.88	(1.67–2.12)	31.2	1.57	(1.39–1.77)
5–8	224	353,666	63.3	1.60	(1.40–1.83)	26.9	1.35	(1.17–1.55)
9–16	448	595,249	75.3	1.90	(1.72–2.10)	31.2	1.57	(1.41–1.74)
17–26	402	597,738	67.3	1.70	(1.53–1.89)	25.6	1.28	(1.15–1.43)
≥ 27	2627	6,634,828	39.6	1	Ref	19.9	1	Ref

Values are expressed as numbers (N), follow-up time in PY, IR per 100,000 person-years, and IRR with corresponding 95% CI for the unadjusted and adjusted analyses

CI confidence interval, *IR* incidence rate, *IRR* incidence rate ratio, *OTC* over-the-counter, *PY* person-years

[a]Adjusted for sex, country, calendar year (1-year categories), seasonality, asthma, and chronic urticaria. Data from Norway are not included as seizures could not be divided into type of seizure

[b]Adjusted for age (5-year age categories), sex, country, calendar year (1-year categories), seasonality, asthma, severe rhinitis, and chronic urticaria

4.2 Strengths and Limitations

The study has several strengths, including the use of individual-level Nordic population registries covering the entire population of DL users, with limited impact of selection bias on results. Hence, the study population was representative of the population in the Nordic countries, increasing the generalizability of the findings. The national registries are of high quality, with high validity and completeness [19, 20, 23, 27, 28, 35]. Another strength is that the prescription registries cover the vast majority of redeemed prescription drugs, except for drugs dispensed at hospitals [36]. Furthermore, the study was performed using a new-user design, limiting

the risk of confounding by indication [14]. In this new-user study design, DL exposed periods are compared with DL unexposed periods among individuals with at least one DL prescription redemption. Confounding was controlled for in multivariable analyses adjusting for confounders identified prior to analyses using a causal diagram. Finally, the sensitivity analyses performed increase the robustness of the study findings. The risk of surveillance bias is considered minimal as new-onset seizures are almost always medically evaluated.

Limitations of the present study include the risk of misclassification of DL exposure due to lack of information on actual use of the redeemed DL. DL is taken on an as-needed

basis to treat symptomatic disease. It is difficult to establish when individuals were truly exposed to DL. However, it is presumed that DL is likely used immediately after a prescription redemption, especially after the first prescription redemption. Different definitions of DL exposure were applied in two sensitivity analyses to address this issue. Moreover, exposure misclassification can be due to left-truncation bias in relation to DL use due to late establishment of the prescription registry in Sweden. This was limited by applying a 6-month drug-free look-back period in Sweden. Furthermore, potential left-truncation bias for immigrations was handled by applying a similar 6-month drug-free look-back period after date of immigration. In addition, DL was available as an OTC drug in the last years of the study period. To overcome a potential underestimation of the association between DL exposure and incidence of the outcomes, a sensitivity analysis was performed restricting the study period so it ended in 2012 in Denmark and Finland and 2013 in Norway and Sweden. Finally, exposure misclassification could be seen if individuals used other antihistamines than DL such as an OTC drug.

Another limitation is a risk of misclassification of incident seizure including potential left-truncation bias due to late establishment of the patient registry in Norway. This was limited by applying a minimum of a 2-year disease-free look-back period in Norway. Furthermore, seizures were defined based solely on ICD-10 codes. The ICD-codes were introduced in the Nordic countries in 1994, 1996, and 1997 in Denmark, Finland, and Sweden, resulting in a minimum of 4–7 years for the look-back period for incident seizures.

A further limitation is the risk of misclassification of the comorbidities included as potential confounders (i.e., asthma, severe rhinitis, and chronic urticaria). The comorbidities were defined by contacts with hospital and/or prescription redemptions. Drugs used for treatment of asthma are also used for treatment of COPD. To limit misclassification in the present study, asthma was defined by the prescription registries if the individuals were younger than 45 years when asthma treatment was initiated. Severe rhinitis was measured as use of immunotherapies, and therefore rhinitis might be underreported. Chronic urticaria is a rare diagnosis given at specialized hospital wards, and the diagnosis might therefore also be underreported.

Confounding by indication could potentially affect the study results if the increased risk of seizure observed among individuals exposed to DL was caused by the underlying allergies rather than the use of DL itself. However, the evidence of an association between allergies and seizure is not well established. Strom and Silverberg (2016) conducted a cross-sectional study using survey data of the association between 1-year history of seizures and history of allergic disease [37]. They found an association between allergies

and seizures in children. However, the study design did not allow for conclusions on causality, and drug utilization was not accounted for in the analysis.

Furthermore, limitations include a short study period in Norway and lack of full migration history in Finland and Norway.

A new-user study design was used to adjust for pre-treatment characteristics and to be able to capture events occurring during follow-up. An alternative design could be an active-comparator design with comparison of DL use with another commonly used drug for allergic rhinitis and urticaria. However, guidelines for treatment of allergic rhinitis and urticaria varied during the study period and between the four Nordic countries. Therefore, we did not include an active-comparator group in the study.

Finally, a further limitation is that not all drugs that could increase the risk of seizure were taken into account (such as fluoroquinolones). These could have been used as exclusion criteria or censoring events.

5 Conclusions

A 46% increased incidence of seizure was found during DL exposed periods. The association between DL exposure and incident seizure was seen in all countries. The excess IR was most pronounced in children aged 0–5 years. No effect was seen among adults aged 20 years or older. We recommend being cautious in use of DL in patients with a personal history of seizure, as specified in the label for DL.

Declarations

Ethics statement According to the law in Denmark, Finland, Norway, and Sweden, registry-based studies can be performed without consent from the subjects if the purpose is performing statistical and scientific studies of significant public health concerns. The study was approved by the relevant national data agencies required by the four countries.

Availability of data and material The datasets generated and analyzed during the current study are not available. The researchers have access to data at servers at Statistics Denmark. According to the regulations at Statistics Denmark, it is not allowed to extract data from the servers at Statistics Denmark. Therefore, data are not available.

Code availability Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Author contributions AKE, EP, KB, ME, DRR, JEB, DM, and THK conceived the conception or design of this study. AKE, KS, and TMK conducted the statistical analyses. All authors contributed to the interpretation of the results. AKE and TMK drafted the manuscript. All authors commented on the manuscript and approved the final version of the manuscript.

References

1. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, Engel J Jr, Forsgren L, French JA, Glynn M, Hesdorffer DC, Lee BI, Mathern GW, Moshe SL, Perucca E, Scheffer IE, Tomson T, Watanabe M, Wiebe S. ILAE Official Report: a practical clinical definition of epilepsy. Epilepsia. 2014;55(4):475–82.
2. Hauser WA, Beghi E. First seizure definitions and worldwide incidence and mortality. Epilepsia. 2008;49(Suppl 1):8–12.
3. Olafsson E, Ludvigsson P, Gudmundsson G, Herdorffer D, Kjartansson O, Hauser WA. Incidence of unprovoked seizures and epilepsy in Iceland and assessment of the epilepsy syndrome classification: a prospective study. Lancet Neurol. 2005;4:627–34.
4. Graves RC, Oehler K, Tingle LE. Febrile seizures: risks, evaluation, and prognosis. Am Fam Physician. 2012;85(2):149–53.
5. Forsgren L, Sidenvall R, Blomquist HK, Heijbel J. A prospective incidence study of febrile convulsions. Acta Paediatr Scand. 1990;79:550–7.
6. Hauser WA. The prevalence and incidence of convulsive disorders in children. Epilepsia. 1994;35(Suppl 2):S1-6.
7. Geha RS, Meltzer EO. Desloratadine: a new, nonsedating, oral antihistamine. J Allergy Clin Immunol. 2001;107(4):751–6.
8. Yamashita Y, Isagai T, Seki Y, Ohya T, Nagamitsu S, Matsuishi T. West syndrome associated with administration of a histamine H1 antagonist, oxatomide. Kurume Med J. 2004;51(3–4):273–5.
9. Chen Z, Li Z, Sakurai E, Mobarakeh JI, Ohtsu H, Watanabe T, Watanabe T, Linuma K, Yanai K. Chemical kindling induced by pentylenetetrazol in histamine H(1) receptor gene knockout mice (H(1)KO), histidine decarboxylase-deficient mice (HDC(-/-)) and mast cell-deficient W/W(v) mice. Brain Res. 2003;968(1):162–6.
10. Estelle F, Simons R. H1-receptor antagonists: safety issues. Ann Allergy Asthma Immunol. 1999;83(5):481–8.
11. Bloom M, Staudinger H, Herron J. Safety of desloratadine syrup in children. Curr Med Res Opin. 2004;20(12):1959–65.
12. Gonzáles-Núñez V, Valero A, Mullol L. Safety evaluation of desloratadine in allergic rhinitis. Expert Opin Drug Saf. 2013;12(3):445–53.
13. Cerminara C, El-Malhany N, Roberto D, Lo Castro A, Curatolo P. Seizures indiced by desloratadine, a second-generation antihistamine: clinical observations. Neuropediatrics. 2013. https://doi.org/10.1055/s-0033-1333871.
14. Lund JL, Richardson DB, Stürmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. Curr Epidemiol Rep. 2015;2:221–8.
15. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol. 2003;158:915–20.
16. Gini R, Sturkenboom MCJ, Sultana J, Cave A, Landi A, Pacurariu A, Roberto G, Schink T, Candore G, Slattery J, Trifirò G. Different strategies to execute multi-database studies for medicines surveillance in real-world setting: a reflection on the European model. Clin Pharmacol Ther. 2020;108:228–35.
17. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare andmedical research. Eur J Epidemiol. 2009;24:659–67.
18. Thygesen LC, Daasnes C, Thaulow I, Brønnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. Scand J Public Health. 2011;39(Suppl 7):12–6.
19. Pedersen CB. The Danish civil registration system. Scand J Public Health. 2011;39(Suppl 7):22–5.
20. Furu K, Wettermark B, Andersen M, Martikainen JE, Almarsdottir AB, Sørensen HT. The Nordic countries as a cohort for pharmacoepidemiological research. Basic Clin Pharmacol Toxicol. 2009;106:86–94.
21. Ludvigsson JF, Almqvist C, Bonamy AKE, Ljung R, Michaelsson K, Neovius M, Stephansson O, Weiman Y. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol. 2016;31:125–36.
22. Pukkala E. Biobanks and registers in epidemiological research on cancer. In: Dillner, J (ed.) Methods in biobanking. methods in molecular biology, Volume 675. Totowa, Humana Press. 2011, pp. 127–164. https://doi.org/10.1007/978-1-59745-423-0_5.
23. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. Scand J Public Health. 2011;39(Suppl 7):38–41.
24. Klaukka T. The Finnish database on drug utilization. Nor Epidemiol. 2001;11(1):19–22.
25. Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad Olausson P, Bergman U, et al. The new Swedish Prescribed Drug Register—opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf. 2007;16(7):726–35.
26. Wettermark B, Zoega H, Furu K, Korhonen M, Hallas J, Nørgaard M, et al. The Nordic prescription databases as a resource for pharmacoepidemiological research—a literature review. Pharmacoepidemiol Drug Saf. 2013;22:691–9.

27. Lynge E, Sandegaard JL, Rebolj M. The Danish national patient register. Scand J Public Health. 2011;39(7 Suppl):30–3.

28. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim J-L, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:1–16.

29. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient registry: a review of content, data quality and research opportunities. Clin Epidemiol. 2015;7:449–90.

30. Ersbøll AK, Kjærulff TM, Sengupta K, Pukkala E, Bolin K, Emneus M, Ramey DR, Brady JE, Mines D, Aasbjerg K, Vestergaard C, Gislason G. Association between desloratadine use and incidence of cardiac outcomes: a Nordic cohort study, 2001-2015. Presented at the 2020 36th ICPE international virtual conference on pharmacoepidemiology & therapeutic risk management; September 16, 2020.

31. Vestergaard M, Obel C, Henriksen TB, Christensen J, Madsen KM, Østergaard JR, et al. The Danish National Hospital Register is a valuable study base for epidemiologic research in febrile seizures. J Clin Epidemiol. 2006;59(1):61–6.

32. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology. 1999;10(1):37–48.

33. Textor J, Hardt J, Knuppel S. DAGitty: a graphical tool for analyzing causal diagrams. Epidemiology. 2011;22(5):745.

34. Laird N, Oliver D. Covariance analysis of censored survival data using log-linear analysis techniques. J Am Stat Assoc. 1981;76:231–40.

35. Sund R. Quality of the Finnish Hospital Discharge Register: a systematic review. Scand J Public Health. 2012;40(6):505–15.

36. Schmidt M, Hallas J, Laursen M, Friis S. Data resource profile: Danish online drug use statistics (MEDSTAT). Int J Epidemiol. 2016;45:1401–1402g.

37. Strom MA, Silverberg JI. Allergic disease is associated with childhood seizures: an analysis of the 1997–2013 National Health Interview Survey. J Allergy Clin Immunol. 2016;137:951-3.e2.

Authors and Affiliations

Annette Kjær Ersbøll[1] · **Kaushik Sengupta**[2,3] · **Eero Pukkala**[4,5] · **Kristian Bolin**[6] · **Eline Aas**[7] · **Martha Emneus**[8] · **Dena Rosen Ramey**[9] · **Joanne E. Brady**[9] · **Daniel Mines**[9] · **Kristian Aasbjerg**[10] · **Christian Vestergaard**[11] · **Gunnar Gislason**[1,12,13,14] · **Alfred Peter Born**[15] · **Thora Majlund Kjærulff**[1]

[1]   National Institute of Public Health, University of Southern Denmark, Studiestræde 6, 1455 Copenhagen, Denmark

[2]   Drug Development Consulting, Pharma IT APS, Hvidovre, Denmark

[3]   Department of Public Health, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

[4]   Finnish Cancer Registry-Institute for Statistical and Epidemiological Cancer Research, Helsinki, Finland

[5]   Faculty of Social Sciences, Tampere University, Tampere, Finland

[6]   Centre for Health Economics and Department of Economics, University of Gothenburg, Gothenburg, Sweden

[7]   Department of Health Management and Health Economics, University of Oslo, Oslo, Norway

[8]   Applied Economic and Health Research (ApHER), Copenhagen, Denmark

[9]   Merck & Co., Inc., Kenilworth, NJ, USA

[10] Department of Ophthalmology, Aalborg University Hospital, Aalborg, Denmark

[11] Department of Dermatology, Aarhus University, Aarhus, Denmark

[12] Department of Cardiology, The Cardiovascular Research Centre, Copenhagen University Hospital Herlev and Gentofte, Gentofte, Denmark

[13] Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

[14] The Danish Heart Foundation, Copenhagen, Denmark

[15] Department of Paediatrics and Adolescents Medicine, Juliane Marie Centre, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark