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Fluoroquinolone-Associated Peripheral and Central Nervous System-Related Disorders: A Large German Claims-Based Cohort Study

Julia Wicherski[1] | Jonas Peltner[2] | Cornelia Becker[1] | Katrin Schüssel[3] | Gabriela Brückner[3] | Andreas Schlotmann[3] | Helmut Schröder[3] | Winfried V. Kern[4] | Britta Haenisch[1,2,5]

[1]Federal Institute for Drugs and Medical Devices (BfArM), Research Division, Pharmacoepidemiology, Bonn, Germany | [2]German Center for Neurodegenerative Diseases (DZNE), Pharmacoepidemiology in Neurodegenerative Disorders, Bonn, Germany | [3]Research Institute of AOK (WIdO), Berlin, Germany | [4]Division of Infectious Diseases, Department of Medicine II, University of Freiburg Faculty of Medicine and Medical Centre, Freiburg, Germany | [5]Center for Translational Medicine, University of Bonn, Bonn, Germany

Correspondence: Britta Haenisch (britta.haenisch@bfarm.de)

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ABSTRACT

Purpose: To examine the association between newly prescribed fluoroquinolones (FQ) and the occurrence of polyneuropathy and certain neuropsychiatric events.

Methods: German statutory health insurance-based cohort study (2013–2019) of patients exposed to FQ compared to different reference antibiotics. Patients with an incident antibiotic prescription were followed up for 365 days after initial dispensing. Outcomes were defined by incident diagnoses of polyneuropathy/other peripheral nervous system-related diseases (PNS), depression/other affective disorders (DEP), mood-related symptoms (MOOD), somnolence/stupor/coma (SSC), and consciousness-related symptoms (CONSCIOUS). Piece-wise exponential additive mixed models adjusted for person-time, age, comorbidities, year, and quarter of cohort entry were applied.

Results: The outcome-specific cohorts included 10.7–14.3 million antibiotic episodes of which 1.7% had incident PNS, 4.8% DEP, 1.5% MOOD, 0.6% SSC, 0.8% CONSCIOUS. Relative risks for these outcomes ranged from 1.04 to 1.10 for FQ versus reference antibiotics. Stratified by gender and age groups, relative risk for PNS was high in ≤39-year-old males (aHR = 1.31 [95% 1.19; 1.45]), for MOOD and CONSCIOUS in 40–69-year-old females (aHR = 1.12 [1.08; 1.15], aHR = 1.14 [1.09; 1.19]) for DEP in ≥70-year-old males (aHR = 1.16 [1.14; 1.19]), whereas relative risk for SSC was high in ≤39-year-old females (aHR = 1.24 [1.10; 1.40]). FQ-associated PNS was mainly comprised of drug-induced polyneuropathy (aHR = 1.68 [1.58; 1.79]). Relative risks for each endpoint varied by choice of active comparator.

Conclusions: FQ episodes were associated with an increased risk for neurological and neuropsychiatric events, especially within the first 92 days after initial dispensing. Risk estimates vary by age and gender subgroups.

1 | Introduction

Fluoroquinolones (FQ) are an important class of broad-spectrum antibiotics, frequently prescribed for the treatment of various gram-negative, gram-positive, atypical, and anaerobe bacteria. Therefore, FQ are applied commonly for urinary tract infections, respiratory tract infections, gastrointestinal, skin, and joint infections. There is increasing evidence for serious FQ-associated adverse drug reactions, which resulted in restrictions to authorisation in 2019 with the advice to use FQ only

in specific cases such as complicated urinary tract infection [1]. However, they are still widely used [2]. The risk of serious adverse drug reactions associated with FQ extends to nervous system-related events such as polyneuropathy, depression, or suicidal thoughts, somnolence, consciousness- or mood-affecting symptoms [1, 3]. A recent study reported an incidence of about 1% central nervous system-related side effects and 3% peripheral nervous system-related side effects in FQ users in the United States of America [4].

Fluoroquinolones can disrupt GABA receptors and alter neurotransmitter systems in the central nervous system, leading to neuropsychiatric side effects [5, 6]. FQ also interferes with sodium channels, potentially causing nervous system-related adverse effects [7]. Moreover, FQ induces oxidative stress which can result in mitochondrial damage in neurones [8, 9]. Irrespective of potential pathophysiological mechanisms of FQ, there is a lack of studies investigating risk differences for patients in different age groups, for instance, young adults, and age-gender interactions. Information on several potential reference broad-spectrum antibiotics and routine health care-based studies from European countries is also scarce.

To provide real-world evidence of FQ-associated peripheral nervous system-related diseases and neuropsychiatric disorders to describe current FQ safety, we conducted a cohort study utilising population-based claims data in Germany.

2 | Methods

2.1 | Source of Data

This population-based cohort study used administrative health claims data from the 'AOK – Die Gesundheitskasse', which is one of the largest statutory health insurances in Germany. Nearly 28 million individuals were covered by the AOK [BMG 2024]. Information on self-reported gender, date of birth, outpatient (quarterly) and inpatient (weekly) medical diagnoses (classified by the German version of ICD-10 (ICD-10-GM)), hospitalisations (with hospital procedures classified by OPS (the German adaptation of the International Classification of Procedures in Medicine)), and outpatient reimbursement information of drugs, comprising the dispensing date, the ATC code (German adaptation of WHO-ATC classification) [10], and the defined daily doses (DDD) are provided for the period from 1st January 2013 to 31st December 2019.

2.2 | Cohort

The first dispensed (index) prescription of a FQ or an active comparator drug (AC) administered by any route and for any indication (Figure 1) was defined as the cohort entry date (CED). A wash-out period of 365 days was used to exclude patients with pre-existing diagnoses for the outcomes of interest (prevalent cases). At the CED, individuals had to have continuous coverage by the AOK health insurance for at least 365 days and had to be ≥ 18 years old to be included in the study. Individuals with implausible drug amounts dispensed (DDDs > 100) for antibiotic indications as well as individuals with outpatient outcomes captured in the CED quarter were excluded.

All included individuals were assigned to separate cohorts as shown in Figure S1. It was possible for an individual to be included at multiple time points in and across the cohorts if all inclusion criteria were met. Individuals were represented by index episodes and followed up in a risk window of up to 365 days.

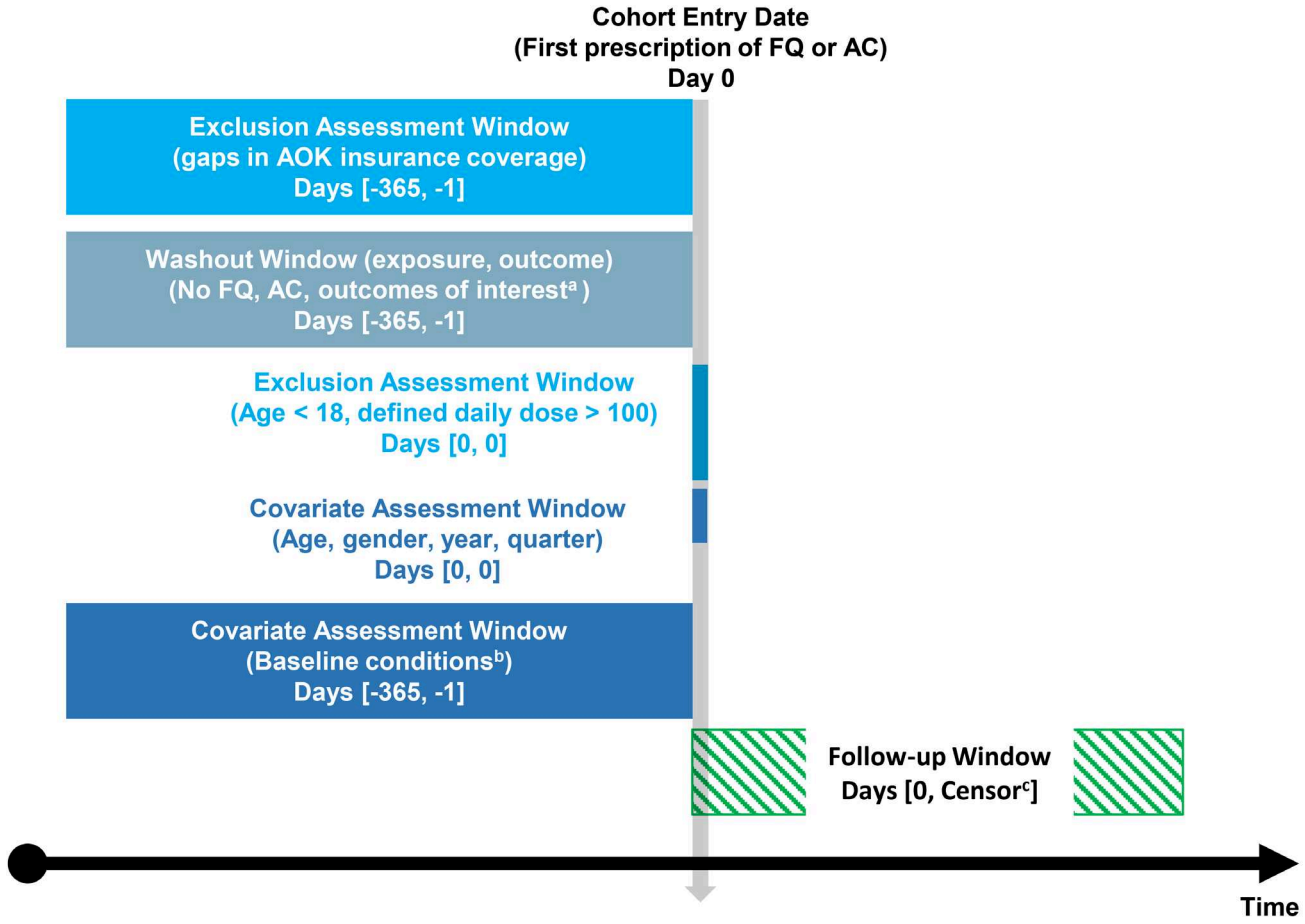
The occurrence of the five incident outcomes was identified by ICD-10-GM codes (see Table S1). Outpatient diagnoses labelled as confirmed or inpatient diagnoses labelled as discharge diagnoses were defined as outcome cases. The incident occurrence of an outcome was observed in the outcome-specific cohort. The baseline period of 365 days prior CED was used to assess all relevant covariates. General morbidity was measured by the Charlson comorbidity index (CCI) [Charlson 1987 & Quan 2011]. In addition, drug dispensings and inpatient stays were counted as measures of frailty. Outcome-specific comorbidities were captured by diagnoses and/or specific drugs dispensed with a detailed description in Table S1.

2.3 | Statistical Analysis

Absolute and relative frequencies of all baseline characteristics were described and quantified by standardised differences (≤ 0.2 good balance). Incidence rates were standardised for age and gender based on the German Census 2011 [12] by applying direct standardisation with Poisson approximation [13] to estimate the corresponding 95% confidence interval (95% CI).

Adjusted hazard ratios with 95% CIs were estimated by piecewise exponential additive mixed models (PAMM) [14] which model the baseline hazard using a smooth, non-linear function. Covariates included in all models were baseline age in years and individual person-time as smooth non-linear time-constant effects. Other baseline characteristics such as the number of drugs dispensed, outcome-related comorbidities (see Table S1), CED year, and CED quarter were included as linear time-constant effects. Moreover, several pre-planned subgroup and sensitivity analyses were conducted:

Analyses were stratified by gender and age-group combinations. Since outpatient diagnoses were only available on a quarterly level, sensitivity analyses were conducted using only inpatient diagnoses which were available with higher temporal resolution (per week) and allowed for analyses of 30-, 60-, and 92-day risk windows, respectively. Propensity score matching (1:1 nearest neighbour) with a calliper of 0.1 was applied to further balance the distribution of baseline characteristics between FQ and AC groups. Variables included in the propensity score matching process are listed in Table S1. Other sensitivity analyses investigated exposure misclassification. Firstly, a 'per protocol' censoring approach was applied, and index episodes' person-time was censored if a new antibiotic drug was dispensed within the risk window. Secondly, all individuals with a hospitalisation during the baseline period were excluded because German administrative health claims data did not comprise information on inpatient antibiotic



a. Outcomes of interest: 1.) polyneuropathy and other peripheral nervous system-related diseases, 2.) depression and other affective disorders, 3.) mood-related symptoms, 4.) somnolence/ stupor/coma, 5.) consciousness-related symptoms, respectively
b. Baseline conditions included: Charlson comorbidity index, number of hospitalised days, number of drugs dispensed, outcome-specific comorbidities (1: diabetes mellitus, hypothyroidism, 2-3: ADHS, anxiety, infertility, 4-5: somnolence-inducing drugs)
c. Earliest of: outcome of interest, death, disenrollment, 365 days of follow-up, end of the study period

FQ = fluoroquinolones (ciprofloxacin, levofloxacin, enoxacin, moxifloxacin, ofloxacin, norfloxacin)
AC = active comparators (amoxicillin, amoxicillin clavulanic acid, azithromycin, cefuroxime, cephalexin, clindamycin, sulfamethoxazole-trimethoprim, doxycycline)

FIGURE 1 | Study design diagram (template by Schneeweiss et al. [11]).

exposure. Thirdly, days of hospitalisation during follow-up period were categorised into three subgroups. Furthermore, an approximation of dose effects was conducted by drug-specific dose categories (low, medium, high) based on DDDs. To investigate differences in the choice of AC agents, PAMMs for pairwise comparisons of FQ episodes and each active ingredient of the AC group were applied. Lastly, we disaggregated single ICD-10-GM codes into more specific outcome definitions (i.e., drug-induced polyneuropathy or different symptoms of loss of consciousness).

Statistical software R, version 4.1.0, was used for all analyses, except for the propensity score matching. The latter was conducted in SAS, version 9.4. All analyses were conducted from January 2023 to April 2024.

3 | Results

The five cohorts comprised between 10.7 and 14.3 million antibiotic index episodes, which fulfilled the outcome-specific selection criteria. Among these separate cohorts, the percentages of FQ episodes ranged from 18.7% to 21.5%, as shown in Figure S1.

Baseline characteristics for all cohorts are displayed in Tables S2a–e. Age differences were present across all data sets (standardised differences 0.388–0.415). The mean age of patients during FQ episodes was higher compared to the mean age of patients during AC episodes, ranging between 58.1 and 59.4 years in FQ episodes and 50.1–51.8 years in AC episodes. Males were represented in 41.9% to 46% of all FQ episodes and in 45.9% to 49.7% of all AC episodes. Differences in health status related

variables and endpoint-specific comorbidities showed more frailty and morbidity in the study population of FQ episodes, especially for the CCI (standardised differences 0.251–0.255) and drugs dispensed (standardised differences 0.303–0.318). The quarters of the CED were balanced between FQ and AC across all data sets and more antibiotics were prescribed and dispensed in the winter months (i.e., Q1 and Q4). Regarding the distribution of FQ and AC episodes across the CED years 2014–2018, there was a declining trend in dispensed FQ episodes but not in AC episodes. The former decreased from 22.4%–22.6% in 2014 to 16.5%–16.6% in 2018 across the data sets.

3.1 | Primary Outcome

During the 365-day risk window, 1.7% of all index episodes had an incident PNS, 4.8% DEP, 1.5% MOOD, 0.6% SSC, and 0.8% CONSCIOUS. The crude incidence rates of all outcomes were higher for FQ episodes compared to AC episodes even after age- and gender-standardisation (Table 1).

Looking specifically at index episodes with an outcome, it was noticeable that the proportion of FQ episodes with an outcome declined between the CED years 2014–2018. The absolute decline in FQ episodes with outcome comparing CED 2014 and CED 2018 was −8.2% for PNS, −9.5% for DEP, −6.6% for MOOD, −3.0% for SSC, and −5.9% for CONSCIOUS. The downward trend became a bit more pronounced from 2016 onwards. Among AC episodes with an outcome, the proportion for DEP also declined over time. For SSC and CONSCIOUS, a countertrend was observed in the distribution of AC episodes with outcomes in each CED year. For PNS and MOOD, the proportions remained relatively stable over the entire CED years (Table S3).

The covariate-adjusted hazard ratios (aHR) within the 365-day risk window each showed a small risk increase for the five FQ-associated nervous system-related endpoints (Table S4). $aHR_{PNS} = 1.04$ [1.03; 1.05], $aHR_{DEP} = 1.09$ [1.08; 1.09], $aHR_{MOOD} = 1.08$ [1.07; 1.09], $aHR_{SSC} = 1.10$ [1.08; 1.12], $aHR_{CONSCIOUS} = 1.08$ [1.06; 1.09]. Being male was a protective factor for FQ-associated DEP and MOOD ($aHR_{DEP} = 0.64$ [0.63; 0.64], $aHR_{MOOD} = 0.77$ [0.77; 0.78]), while it was a risk factor for FQ-associated SSC, CONSCIOUS, and PNS (Table S4a,b). Proxies for frailty such as the CCI, number of drugs dispensed and hospitalisation during baseline were associated with an increased risk of FQ-associated outcomes in all cohorts. Effects of CED year and quarter were negligible compared to those of other covariates. Age and individuals' person-time were relevant smoothing terms ($p < 0.001$) for all PAMM regressions as it is displayed at the end of Table S4. Regarding outcome-specific covariates, all assessed comorbid conditions increased the relative risk of the respective FQ-associated outcome, except for hypothyroidism in the PNS cohort (Table S4).

3.2 | Subgroup and Sensitivity Analyses

Figure 2 shows the results of our disaggregated analyses for gender and age groups. The highest relative risks for any of the outcomes were found for PNS in females and males ≤39 years, for DEP in males ≥70 years, for MOOD in males 40–69 years, for SSC in females of ≤39 years and 40–69 years, and for CONSCIOUS in males 40–69 years.

We restricted our analyses to inpatient outcomes and shortened the follow-up period (i.e., the risk window) in which outcomes were allowed to occur, to assess sensitivity of our results. Table 2 displays all aHRs for FQ episodes in the risk window stratified analyses. FQ exposure was associated with all inpatient outcomes in every risk window. Highest relative risk within the 30-day risk window was observed for inpatient DEP and MOOD. For PNS, SSC and CONSCIOUS relative risk does not differ between 30-, 60- and 92-day risk-window.

The results were robust after the propensity score matching (Table S5) as well as for the per-protocol censoring approach and the exclusion of individuals with baseline hospitalisation (Table S6). The risk of FQ-associated PNS, MOOD, SSC or

TABLE 1 | 365-day crude and standardised incidence rates per 10,000 index episodes.

Outcomes	Exposure	Events	IR	sIR	[95% CI]
PNS	AC	174,895	140	139	[135; 143]
	FQ	60,931	214	158	[150; 165]
DEP	AC	395,741	437	431	[423; 438]
	FQ	119,033	503	481	[464; 497]
MOOD	AC	150,848	147	124	[120; 128]
	FQ	52,827	189	137	[129; 145]
SSC	AC	56,321	49	41	[39; 43]
	FQ	26,256	84	50	[46; 54]
CONSCIOUS	AC	75,014	65	57	[54; 59]
	FQ	33,292	107	64	[60; 69]

Abbreviations: CONSCIOUS, consciousness-related symptoms; DEP, depression & other affective disorders; IR, Incidence rate per 10,000 index episodes; MOOD, mood-related symptoms; PNS, polyneuropathy & other peripheral nervous system-related diseases; sIR, age- and gender-standardised incidence rate, standardisation by German Census 2011 per 10,000 index episodes; SSC, somnolence, stupor, coma.

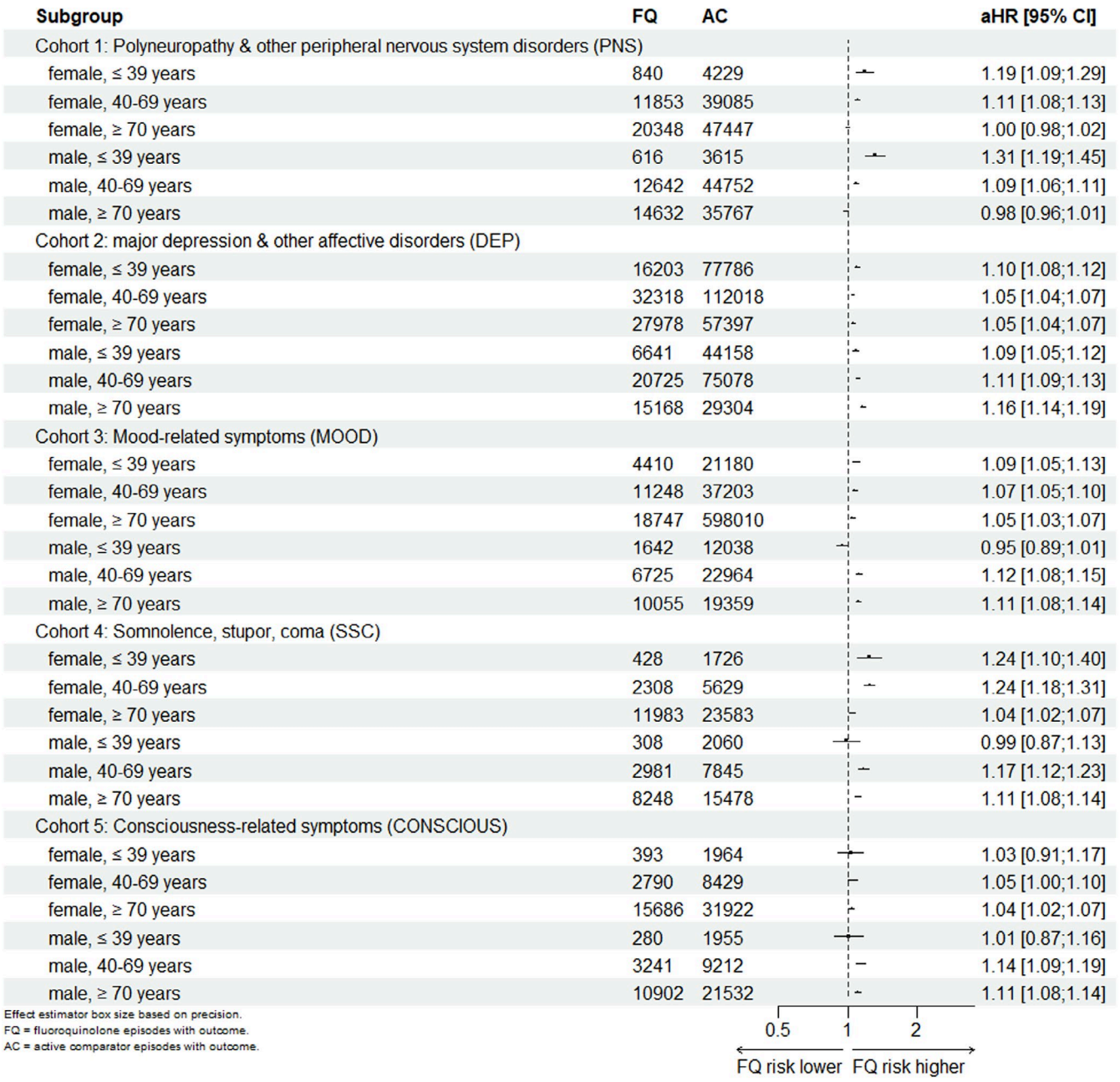


FIGURE 2 | PAMM gender- and age-stratified regressions.

TABLE 2 | PAMM inpatient outcomes only, risk window-stratified.

	aHR [95% CI]			
	Risk window (follow-up period)			
Cohort	**≤30 days**	**≤60 days**	**≤92 days**	**≤365 days**
PNS	1.10 [1.04; 1.16]	1.10 [1.06; 1.15]	1.10 [1.06; 1.14]	1.07 [1.05; 1.09]
DEP	1.24 [1.18; 1.31]	1.21 [1.16; 1.26]	1.20 [1.16; 1.24]	1.13 [1.11; 1.15]
MOOD	1.23 [1.15; 1.32]	1.20 [1.14; 1.26]	1.18 [1.13; 1.23]	1.11 [1.10; 1.13]
SSC	1.10 [1.06; 1.16]	1.13 [1.10; 1.17]	1.13 [1.10; 1.16]	1.10 [1.08; 1.12]
CONSCIOUS	1.16 [1.11; 1.22]	1.16 [1.12; 1.21]	1.17 [1.13; 1.20]	1.10 [1.08; 1.12]

Abbreviations: aHR, Adjusted hazard ratio; CI, 95% confidence interval [lower confidence level; upper confidence level] for FQ episodes; CONSCIOUS, consciousness-related symptoms; DEP, depression & other affective disorders; MOOD, mood-related symptoms; PNS, polyneuropathy & other peripheral nervous system-related diseases; SSC, somnolence, stupor, coma.

CONSCIOUS was higher in the subgroup of individuals without follow-up hospitalisation compared to individuals with hospitalisation during their follow-up period. Higher amounts of drug dispensed (i.e., DDD) were associated with higher risk of FQ-associated PNS, DEP, MOOD, SSC or CONSCIOUS. When we stratified our analyses by specific diagnoses used for the respective outcome definitions, we found several associations between the specific diagnoses and FQ episodes (Table 3). In scope of PNS, patients during FQ episodes were more likely to experience drug-induced polyneuropathy (aHR = 1.68 [1.58; 1.79]). For DEP, FQ-associated risk was more pronounced for 'other and unspecified affective disorders (incl. affective psychosis)' (aHR = 1.18 [1.06; 1.30]). Within the diagnoses for the CONSCIOUS outcomes, FQ-associated relative risk was higher for disorientation (aHR = 1.12 [1.10; 1.14]) than for other CONSCIOUS diagnoses. Table 3 displays all results of the single diagnoses codes associated with FQ-episodes compared to AC-episodes.

Furthermore, we disaggregated our AC group to the single drug agents included and further stratified this analysis for risk windows of different lengths, which is displayed in Table 4. The relative risk of all outcomes was higher in FQ episodes compared to amoxicillin, azithromycin, clindamycin, and doxycycline, especially for the subset of only inpatient diagnoses during the 92-day risk window. Contrarily, the effect estimates were decreased for FQ episodes compared to amoxicillin-clavulanic acid episodes for all outcomes in the 92-day risk window. Moreover, relative risks for FQ-associated MOOD, SSC, and CONSCIOUS were slightly decreased in comparison to sulfamethoxazole-trimethoprim. To further explore the association between FQ

TABLE 3 | PAMM sensitivity analyses, analyses stratified by diagnoses codes, cohorts 1–5.

Cohort	ICD-10-GM	Diagnosis	aHR_{FQ}	[95% CI]
PNS	G60	Hereditary and idiopathic neuropathy	1.04	[0.97; 1.11]
	G60.3	Idiopathic progressive neuropathy	1.10	[0.94; 1.29]
	G61	Inflammatory polyneuropathy	1.09	[0.98; 1.20]
	G62.8/G62.9	Other and unspecified polyneuropathies	1.07	[1.05; 1.08]
	G62.0	Drug-induced polyneuropathy	1.68	[1.58; 1.79]
	G63	Polyneuropathy in diseases classified elsewhere	1.01	[1.00; 1.03]
	G64	Other disorders of peripheral nervous system	0.94	[0.84; 1.05]
DEP	F32	Depressive episode	1.09	[1.08; 1.09]
	F38.0/F38.1	Other and unspecified affective disorders (incl. affective psychosis)	1.18	[1.06; 1.30]
MOOD	R45.0	Nervousness	1.07	[1.04; 1.10]
	R45.1	Restlessness and agitation	1.09	[1.08; 1.11]
	R45.2	Unhappiness	1.03	[0.96; 1.10]
	R45.3	Demoralisation and apathy	1.05	[0.93; 1.19]
	R45.4	Irritability and anger	1.01	[0.91; 1.13]
	R45.5	Hostility	0.89	[0.75; 1.06]
	R45.6	Violent behaviour	0.90	[0.78; 1.03]
	R45.7	State of emotional shock and stress, unspecified	1.00	[0.93; 1.08]
	R45.8	Other symptoms and signs involving emotional state (incl. suicidal behaviour)	1.08	[1.04; 1.12]
SSC	R40.0	Somnolence	1.02	[1.00; 1.04]
	R40.1	Stupor	1.03	[0.98; 1.09]
	R40.2	Coma	1.02	[0.97; 1.07]
CONSCIOUS	R41.1	Disorientation	1.12	[1.10; 1.15]
	R41.2	Anterograde amnesia	0.93	[0.66; 1.29]
	R41.3	Retrograde amnesia	0.98	[0.91; 1.06]
	R41.4	Other amnesia	0.98	[0.95; 1.02]
	R41.8	Other symptoms and signs involving cognitive functions and awareness	1.02	[0.99; 1.06]

Abbreviations: aHR_{FQ}, Adjusted hazard ratio for fluoroquinolone-episode; CI, 95% confidence interval [lower confidence level; upper confidence level]; CONSCIOUS, Consciousness-related symptoms; DEP, Depression & other affective disorders; MOOD, Mood-related symptoms; PNS, Polyneuropathy & other peripheral nervous system-related diseases; SSC, Somnolence, stupor, coma.

TABLE 4 | PAMM regression, sensitivity analyses for FQ episodes compared to single agents of the AC group.

	Cohort 1: PNS		Cohort 2: DEP		Cohort 3: MOOD		Cohort 4: SSC		Cohort 5: CONSCIOUS	
AC agent	**aHR**	**[95% CI]**	**aHR**	**[95% CI]**	**aHR**	**[95% CI]**	**aHR**	**[95% CI]**	**aHR**	**[95% CI]**
365-day risk window[a]										
Amoxicillin	1.11	[1.09;1.12]	1.10	[1.09;1.11]	1.13	[1.11;1.14]	1.22	[1.19;1.25]	1.16	[1.14;1.19]
Amoxicillin-clavulanic acid	0.97	[0.96;0.99]	1.09	[1.08;1.11]	1.03	[1.01;1.05]	0.87	[0.85;0.89]	0.96	[0.93;0.98]
Azithromycin	1.19	[1.16;1.21]	1.09	[1.07;1.10]	1.09	[1.07;1.12]	1.45	[1.40;1.50]	1.24	[1.21;1.28]
Cephalexin	0.91	[0.83;1.00]	1.03	[0.97;1.10]	1.11	[1.00;1.23]	1.26	[1.07;1.49]	0.97	[0.85;1.11]
Cefuroxime	1.03	[1.01;1.04]	1.10	[1.09;1.11]	1.07	[1.05;1.08]	1.04	[1.02;1.07]	1.07	[1.04;1.09]
Clindamycin	1.01	[0.99;1.03]	1.15	[1.13;1.16]	1.19	[1.17;1.22]	1.38	[1.34;1.43]	1.16	[1.13;1.19]
Sulfamethoxazole-trimethoprim	1.01	[0.99;1.03]	0.99	[0.97;1.00]	0.91	[0.89;0.93]	0.89	[0.87;0.92]	0.91	[0.88;0.93]
Doxycycline	1.10	[1.08;1.12]	1.08	[1.07;1.10]	1.11	[1.09;1.13]	1.38	[1.34;1.43]	1.20	[1.17;1.23]
92-day risk window[b]										
Amoxicillin	1.43	[1.35;1.51]	1.38	[1.31;1.45]	1.37	[1.28;1.47]	1.25	[1.19;1.31]	1.35	[1.29;1.43]
Amoxicillin-clavulanic acid	0.75	[0.71;0.79]	0.97	[0.92;1.03]	0.83	[0.78;0.89]	0.82	[0.78;0.86]	0.88	[0.83;0.93]
Azithromycin	1.91	[1.75;2.08]	1.50	[1.40;1.61]	1.64	[1.48;1.81]	1.61	[1.50;1.72]	1.59	[1.48;1.72]
Cephalexin	0.81	[0.61;1.09]	1.10	[0.80;1.49]	1.65	[1.00;2.73]	1.24	[0.91;1.68]	1.02	[0.75;1.39]
Cefuroxime	0.98	[0.94;1.03]	1.14	[1.09;1.19]	1.11	[1.05;1.18]	1.04	[1.00;1.08]	1.13	[1.08;1.18]
Clindamycin	0.95	[0.90;1.02]	1.37	[1.29;1.46]	1.49	[1.36;1.63]	1.59	[1.48;1.70]	1.39	[1.30;1.49]
Sulfamethoxazole-trimethoprim	1.02	[0.95;1.09]	1.04	[0.98;1.11]	0.88	[0.81;0.96]	0.94	[0.89;0.99]	0.93	[0.87;0.99]
Doxycycline	1.51	[1.41;1.63]	1.41	[1.32;1.50]	1.56	[1.43;1.71]	1.49	[1.40;1.59]	1.52	[1.42;1.63]
365-day risk window[a], **excl. cancer history, only ICD G62.0 (drug-induced polyneuropathy)**										
Amoxicillin	1.65	[1.36;1.99]								
Amoxicillin-clavulanic acid	1.09	[0.87;1.35]								
Azithromycin	1.92	[1.47;2.51]								
Cephalexin	0.87	[0.32;2.37]								
Cefuroxime	1.32	[1.11;1.57]								
Clindamycin	1.39	[1.11;1.75]								
Sulfamethoxazole-trimethoprim	0.63	[0.51;0.77]								
Doxycycline	1.67	[1.32;2.11]								
92-day risk window[b], **excl. cancer history, only ICD G62.0 (drug-induced polyneuropathy)**										
Amoxicillin	2.04	[1.13;3.70]								
Amoxicillin-clavulanic acid	1.11	[0.59;2.08]								
Azithromycin	2.29	[0.99;5.32]								

(Continues)

TABLE 4 | (Continued)

	Cohort 1: PNS		Cohort 2: DEP		Cohort 3: MOOD		Cohort 4: SSC		Cohort 5: CONSCIOUS	
AC agent	**aHR**	**[95% CI]**	**aHR**	**[95% CI]**	**aHR**	**[95% CI]**	**aHR**	**[95% CI]**	**aHR**	**[95% CI]**
Cephalexin		*NA*								
Cefuroxime	1.33	[0.81;2.18]								
Clindamycin	1.40	[0.72;2.73]								
Sulfamethoxazole-trimethoprim	0.33	[0.20;0.53]								
Doxycycline	4.32	[1.50;12.40]								

Abbreviations: AC, Active comparator; aHR, adjusted hazard ratio for fluoroquinolone-episode; CI, 95% confidence interval [lower confidence level; upper confidence level].
[a]Main model, includes out- and inpatient diagnoses 1.
[b]Subgroup includes inpatient diagnoses only.

use and risk for polyneuropathy, we conducted an additional, exploratory analysis, in which we stratified the AC single agent comparison also for this diagnosis of polyneuropathy separately and restricted this subgroup to patients without a history of cancer. Drug-induced polyneuropathy in FQ episodes of this subgroup was 92% more likely compared to azithromycin, 67% more likely compared to doxycycline, and 65% more likely compared to amoxicillin, but 37% less likely compared to sulfamethoxazole-trimethoprim. Moreover, the relative risk for drug-induced polyneuropathy increased with further restriction to the shortened risk window of 92 days and inpatient diagnoses only but estimates' precision decreased except for the sulfamethoxazole-trimethoprim comparison (Table 4).

4 | Discussion

To the best of our knowledge, this is the first pharmacoepidemiological cohort study on FQ-associated DEP, MOOD, SSC, and CONSCIOUS in a European country, and the first study in an active comparator new-user design examining PNS and other nervous system and neuropsychiatric disorders in a large central European country with recent data. The FQ-associated relative risk for PNS was increased in ≤39-year-old individuals and particularly high for males. Relative risks for DEP and MOOD were increased in older males. Likewise, CONSCIOUS was more likely in older males whereas FQ-associated SSC was particularly high in young females. The 30-, 60-, and 92-day risk windows comprised high risks for inpatient outcomes of interest. Disaggregation by active comparator agent showed differences in the relative risk of FQ episodes for all outcomes. A positive dose–response relationship for all outcomes supports the causality of these associations.

There is only one previously published study by Wang et al. [15] estimating FQ's specific risk of hospital admission for suicidal ideation or suicide and self-inflicted injury by comparing FQ to azithromycin and trimethoprim-sulfamethoxazole in a cohort of individuals included in the US MarketScan database. During their 60-day risk window, no conclusive association was found in general and after disaggregating for gender and age, whereas our study displayed a 21%–22% increased risks for DEP and MOOD during 60-day risk windows, and an increased risk for ≥70-year-old males and ≤39 years-old females during FQ episodes. Another recent study based on US Optum data estimated an 8% increased risk of seizures/convulsions, intracranial hypertension, psychosis/delirium, or altered mental status/encephalopathy compared to azithromycin, amoxicillin, amoxicillin-clavulanic acid, and cefixime within a risk window of 120 days [4]. We did not analyse convulsion or seizure but detected a 12% increased relative risk for FQ-associated disorientation during 365 days of follow-up.

Regarding FQ-associated PNS, the US Optum data-based cohort [4] that investigated FQ compared to azithromycin, amoxicillin, amoxicillin-clavulanic acid, and cefixime was most comparable to our applied study design. During their 120-day risk window, FQ episodes were associated with a 25% increased risk of peripheral neuropathy. Looking at the same comparators, our results also show increased risks for FQ in comparison to amoxicillin and azithromycin but not compared to amoxicillin-clavulanic acid. Furthermore, a nested case–control study from the UK reported a 47% higher risk for peripheral neuropathy that persisted for up to a 180-day risk window [16]. However, the UK study only used one active comparator and analysed a more selective and older study population (e.g., excluding individuals with diabetes mellitus). Lastly, there is one case–control study analysing drug-induced polyneuropathy in 45–80-year-old men using US health claims which estimated an 83% increased risk for FQ episodes [17]. In our study, a 31% increased risk for males aged ≤39 years was estimated but our findings for males ≥40 years, for which we did not find an increased risk, do not match in comparison to the study from the US. There might be relevant differences between US men of that age group and the German population. Moreover, differences in prescribing patterns, comorbidities and further confounders may be present in the specific settings.

The decline in the proportion of FQ episodes with outcomes over time shown in Table S3 requires cautious interpretation. Our data do not contain information to reliably identify factors underlying prescribing behaviour or information that would allow the observed trends to be directly linked to specific warnings. However, one possible explanation of the results displayed in Table S3 could be increasing awareness of FQ-associated adverse events among clinicians. Since 2008, there have been several warnings from drug regulatory authorities, including 'dear-doctor-letters' in Germany and international warnings

from the EMA and FDA, for example. These risk communications may have contributed to more cautious prescribing practices, so that patients with an increased baseline risk for the respective adverse events of PNS, DEP, MOOD, SSC, or CONSCIOUS were not prescribed FQs in the first place. This interpretation is also supported by the observation of the general prescribing trend (see Table S1), which showed a slight decline in total prescriptions of FQs during the CED years 2014–2018. It is conceivable that, beyond a general reduction in prescribing volume of FQs, physicians increasingly refrained from prescribing FQs to patients with known risk factors for these adverse events. However, this analysis is only descriptive and does not allow conclusions to be drawn about the association between regulatory warnings and changes in prescribing behaviour and the occurrence of adverse events.

Moreover, our data source has some limitations, which we aimed to address by applying an appropriate study design. The risk of confounding by indication was reduced by applying an active comparator new-user design. Confounding by baseline conditions and non-random treatment allocation are two further typical limitations in observational studies. In order to appropriately minimise both, we provided adjustments of relevant covariates and applied a propensity score matching approach as a sensitivity analysis. Sensitivity analyses for the single AC agents are indicative of the potential for residual confounding by indication, which must be taken into account as the bacterial infection itself may increase the likelihood of the development of the outcomes of interest. Potential exposure misclassification in our 365-day risk window analysis main model was controlled for by sensitivity analyses with shorter risk windows. Additionally, we used drug dispensing information as a proxy of exposure. Therefore, non-adherence or missing compliance in administration of our study drugs is another factor introducing a bias towards null in terms of exposure misclassification. The limited granularity of outpatient diagnoses introduced uncertainty in individuals' person-time, but the PAMM regression model is an adequate method to address such interval-censored data. Moreover, we addressed this limitation by a sensitivity analysis based on inpatient diagnoses only, thereby allowing a more precise assessment of person-time by calendar weeks. Lastly, this is an observational study design, and the data source does not contain information on important life-style factors such as body weight or alcohol consumption. However, the data set of the German statutory health insurance provider, AOK, offers a population-based insight into the real-world health care situation of patients in Germany and is a highly complete data set in terms of the billing-relevant data itself. Our data set comprises a meaningful number of patients which allows us to report precise effect estimates even for rare outcomes and for patient subgroups by age and gender. Moreover, we consider German health claims as an appropriate and worthwhile source of data since we successfully investigated also other adverse outcomes associated with FQ exposure with the present study design and data source [18].

5 | Conclusion

In this active comparator new user-designed large German cohort study, FQ episodes are associated with increased relative risks for PNS, DEP, MOOD, SSC, CONSCIOUS. The relevant risk window seemed to be about 92 days after exposure. For each outcome, differential effects were observed in subsets by gender and age groups.

Author Contributions

All authors conceived and designed the study. K.S., G.B., A.S., and H.S. had full access to all the data in the study and take full responsibility for the integrity of the data set provided for the statistical analysis. J.W., J.P., C.B., and B.H. had full access to the statistical analysis data set and carried out the statistical analysis. J.W. and J.P. analysed the data. All authors interpreted the data and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript. J.W. drafted the manuscript. J.W. and B.H. are the guarantors.

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Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

No additional data available. Statistical code available on request. The manuscript's guarantors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Definition of study variables. **Figure S1:** Cohort attrition. **Table S2a:** Study population characteristics, cohort 1: peripheral (poly-) neuropathies and other diseases of the peripheral nervous system (PNS). **Table S2b:** Study population characteristics, cohort 2: depressive episode and other affective disorders (DEP). **Table S2c:** Study population characteristics, cohort 3: symptoms and signs involving emotional state (MOOD). **Table S2d:** Study population characteristics, cohort 4: somnolence, stupor, coma (SSC). **Table S2e:** Study population characteristics, cohort 5: other symptoms and signs involving cognitive functions and awareness (CONSCIOUS). **Table S3:** Index episodes with outcome of interest, stratified by CED year, cohorts 1–5. **Table S4:** PAMM main models, cohorts 1–5. **Table S5:** PAMM main regressions, PS-matched cohorts 1–5. **Table S6:** PAMM sensitivity analyses, cohorts 1–5.