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TITLE: Impact of recommendations on sodium valproate prescription among women with epilepsy: an interrupted time-series study

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ABSTRACT

Background: The European Medicines Agency (EMA) has developed risk minimisation measures (RMMs) to reduce the use of the teratogenic drug, sodium valproate (VPA). The objective was to assess the impact of these RMMs among females with epilepsy in France.

Methods: We used data from the French National Health Insurance Database (SNDS), including 114,936 females aged under 50, with a reimbursement claim for an antiepileptic drug from January 2011 to December 2017, and identified as epileptic. We used a controlled interrupted time series stratifying on age: girls (0-14 years old) and women of childbearing age (15-49 years), and with 129,917 males as controls.

Results: VPA prevalent use among girls and women of childbearing age with epilepsy decreased significantly after the issue of the RMMs (trend changes of respectively -5 and -4 users per 1000 females at-risk per quarter in comparison to the control group). We did not detect any significant change in VPA incident use.

Conclusions: VPA use decreased over the study period among females with epilepsy but there were still 317 women and 206 girls initiating VPA in 2017 (8 per 1000 at-risk and 18 per 1000 respectively). This suggests that either the measures should be strengthened or that the lowest level of VPA use has been reached. In this context, the introduction of a new RMM (in 2018) need to be evaluated.

KEY WORDS: Interrupted time series, Trend, Valproate, Epilepsy, Regulatory actions.

1 Introduction

Sodium valproate (VPA) is an effective anticonvulsant for most epileptic syndromes. 1,2 VPA and its derivatives are the most frequently prescribed antiepileptic drugs (AEDs) to adults and children.[3] Since 1980, in-utero exposure to VPA has been associated with a risk of major congenital malformations (10%) in comparison with the general population (2-3%). [4,5] Recent studies on preschool children exposed in utero to VPA suggested early development delays (30-40%) [6,7] and pervasive developmental disorders (syndromes belonging to the autism spectrum) [8,9].

In Europe, in late 2013, the European Medicines Agency (EMA) reassessed the risk/benefit ratio integrating the emergence of new signals on the association between in-utero exposure to VPA and autism spectrum disorders. This reassessment led the EMA to reinforce warnings on VPA use among women of childbearing age. [10] These warnings were sent as a 'Dear Doctor letter' to healthcare professionals in Europe, and in France in December 2014: VPA and its derivatives should not be prescribed to women of childbearing age, except in case of intolerance or ineffectiveness of alternatives. Other risk minimisation measures (RMMs) were implemented in France: in May 2015, the French Medicines Agency (ANSM) informed health professionals about the stricter conditions for VPA prescriptions for young girls, adolescent girls, women of childbearing age and pregnant women. New prescription conditions were applied from January 2016 [11]: a specialist should do the initiation of VPA and the renewal could be done by a general practitioner (GP) within the year.

Measuring the impact of regulatory interventions is important to assess whether they achieve their intended objectives, and to identify areas where performance could be improved. [12] Medico-administrative data are increasingly used in healthcare research, and are particularly suited to

evaluating the impact of health policies. [13–18] In France, the national health insurance database (SNDS), which covers almost all the French population, can be used for this purpose [19].

The objective of this study was to assess whether there was a change in VPA prescription among females with epilepsy following the RMMs: a change in VPA use (prevalent and incident) and a change in VPA prescribers.

2 Material and methods

2.1 Data source

We performed this nationwide study using the SNDS. This is a medico-administrative database that includes almost all the French population (more than 60 million inhabitants). It records i) socio-demographic data such as gender, age, place of residence, type of medical insurance cover, access to free medical care and the presence of chronic disease (through the ‘*ALD*’ status), ii) healthcare dispensation data such as medical visits to health professionals, drug or medical device claims, and iii) hospital discharges in private and public health facilities. [20] This database has previously been used to describe prescription trends with respect to recommendations [21] in the context of epilepsy management [22] and VPA exposure [23].

2.2 Study Population

All females aged under 50 “at-risk” to receive VPA in a context of epilepsy between January 1, 2011 and December 31, 2017 were included. Females “at-risk” to receive valproate were defined as females with at least one reimbursement claim for an AED (ATC class N03A and some benzodiazepines: clobazam and diazepam). Considering that most drugs of interest have several indications, we used the algorithm proposed by Charlton et al. [24] (including *ALD* status, hospitalisation, and drugs co-prescriptions) to identify the use of AEDs in epilepsy. Females which were included formed the intervention group. A control group was defined as males aged under 50,

with at least one claim for an AED between January 1, 2011 to December 31, 2017, and identified as epileptic (using the Charlton et al algorithm).

The patients were followed from the first drug claim until December 31, 2017 or death, whichever came first.

2.3 Study design

An interrupted time-series (ITS) design was used to evaluate changes in VPA use (prevalent and incident) before and after the different warnings. To classify patients as incident user of VPA during a given quarter, we used one year history without any VPA claim. Otherwise, patients were classified as prevalent users.

The ITS design is suitable for evaluating the impact of population-level health interventions occurring at a well-defined point in time. Data was collected over time at equal intervals, and regression techniques were used to establish an underlying trend, 'interrupted' by an intervention at a known time point.

Over the study period, two interventions were defined: i/ In December 2014, at the time of the 'Dear Doctor' letter sending to healthcare professionals, and ii/ In January 2016, when prescribing conditions were restricted. Thus, three periods of time were defined: i/ Period 0 (pre-intervention), from 2011 first quarter to 2014 last quarter ii/ Period 1 (after the EMA warnings), from 2015 first quarter to 2015 last quarter and iii/ Period 2 (after the ANSM restrictions), from 2016 first quarter to 2017 last quarter.

To evaluate changes in VPA prescribers, we studied the annual distribution of the prescribers over the study period, using a before/after design (2011 versus 2017).

2.4 Statistical analysis

Each quarter over the study period, we determined person-time exposed to VPA (prevalent or incident use) and person-time at-risk to receive VPA assuming that one claim corresponds to 30 days of treatment. We then determined the quarterly rate of VPA users over the study period by dividing these two values.

Segmented regression analyses were used to calculate a trend (degree of change) in each segment of the time series. [25] A step function was used to determine whether there was a change in VPA use levels directly after the intervention compared to before (level effect), on the assumption of an underlying linear relationship between time and the level of use in each quarter. [14] We used regression model with autoregressive error correction. [26]. To minimize confounding from simultaneous events we added a control series so that there is both a before-after comparison and an intervention-control group comparison. [27] We conducted segmented regression models according to age category: i/ among girls (0-14) (control group = boys under 15) and ii/ among women of childbearing age (15-49) (control group= men aged 15-49), firstly on VPA use and secondly on VPA incident use. Results are expressed as trend change of VPA users per 1000 persons at-risk per quarter and level effect of VPA users per 1000 persons at-risk and as difference-in-difference (DID) of trend change and level effect among females compared to males.

Regarding the secondary objective about the change in speciality of VPA prescribers, we studied: i/ the distribution of prescribers' speciality in relation to the total number of VPA claims as treatment initiations by calculating the number of VPA initiations from the given prescriber speciality divided by the number of VPA initiations from all prescribers' speciality, and ii/ the distribution of prescribers' speciality in relation to the total number of VPA claims by calculating the number of VPA claims from the given prescriber speciality divided by the number of VPA claims from all prescribers' speciality). Prescribers' specialities could be i/ hospital doctors, who we considered as

specialist (without information on the medical speciality), or ii/ private-practice physicians whose medical speciality was categorized as neurologists, paediatricians, general practitioners and 'Other' for any other prescribers.

We used SAS Version 9.4 (PROC AUTOREG).

2.5 Data availability Statement

SNDS data is not freely available. Permanent access to French healthcare databases is automatically granted to certain government agencies, public institutions and public service authorities. Temporary access for studies and research is possible on request.

3 Results

Between January 1, 2011 and December 31, 2017, 114, 936 females under 50 had at least one claim for an AED, in a context of epilepsy; 129, 917 males formed the control group (cf. Figure 1). Males and females characteristics were similar (cf. Table 1). The median age of the population at inclusion was 31 years old. Patients had been followed for 4.6 years on average. Most patients were receiving monotherapy at inclusion (72%). One third of the population was VPA users.

3.1 Time trends and interrupted time-series.

3.1.1 VPA prevalent use

Figure 2 shows trends over the study period for VPA prevalent use among females and males according to age category. Estimates from the interrupted time-series modeling are available in the Supplementary Materials (Supp1).

Before interventions, we observed a significant decrease in trend of VPA use among girls and women of childbearing age (trend changes of -2 and -1 users per 1000 at-risk per quarter respectively, $p < 0.001$). Following EMA warnings, there was not any significant change (nor level or trend) among girls compared to boys and a significant decrease in trend among women of

childbearing age compared to men (difference in difference (DID) of -4‰, $p < 0.001$). Following ANSM recommendations, there was an immediate change in level of VPA use among both age categories compared to the control group (DID of -20‰, $p = 0.001$ among girls ; DID of -6‰, $p = 0.006$ among women).

3.1.2 VPA incident use

Figure 3 shows trends over the study period for VPA incident use among females and males according to age category. Estimates from the interrupted time-series modeling are available in the Supplementary Materials (Supp1).

Before interventions, we did not observe any significant change in incident use of VPA among women of childbearing age, however there was a decline in trend of VPA incident use among girls, but it was not significant compared to boys. Following EMA warnings, there was not any significant change (nor level or trend) among women of childbearing age compared to men and a significant decrease in trend among girls (DID of -6‰ compared to boys, $p < 0.01$). Following ANSM recommendations, there was a stabilization trend of VPA incident use among both age categories (+4‰, $p < 0.01$ among girls ; +1‰, $p < 0.0001$ among women of childbearing age). This change was significant compared to the control group only for girls. The VPA incident use was low after the interventions: around 8 women incident users per 1000 at risk and 18 girls incident users per 1000 at-risk. At the end of the study period, 87% of the women received an alternative drug before VPA initiation, and 80% of the girls.

3.2 VPA prescribers

The annual distribution of prescriber specialties among all VPA claims and among VPA claims as incident use are presented in the Supplementary materials (Supp2).

Among girls with epilepsy, the proportion of hospital practitioners increased over the study period (+7 points) but there were no change for paediatricians and neurologists (private practice). The proportion of general practitioners (GPs) however decreased (-7 points). Initiation of VPA among girls with epilepsy was mainly done by specialists in 2011 (66.8%), and in 2017 (72.6%).

Among women with epilepsy, the proportion of GPs among VPA prescriptions decreased over the study period (64% in 2011 versus 51.5% in 2017). At the same time, the proportion of specialists (hospital practitioners, neurologists) increased (+9 points and +3 points respectively over the study period). In 2011, 46.9% of VPA initiation among women with epilepsy were issued by GPs. This proportion decreased over the study period (-12 points) whereas the proportion of specialists increased but without any impact on non-hospital specialists physicians (+11 points for hospital practitioners; +0.3 for neurologists and for paediatricians).

4 Discussion

Through this French population-based study, we showed that the European RMMs were associated with a change in VPA prescriptions among females compared to males: an overall decrease in the use of VPA among girls and women of childbearing age, with prescriptions more frequently initiated by specialists rather than by GPs.

4.1 Main results, with regards to the literature

For several years there have been reports on the association between in-utero exposure to VPA and the occurrence of congenital malformations (6) and they were mostly intended for neurologists [7,29]. Thus, no major change in VPA use was expected among females with epilepsy. In fact, neurologists seem to have integrated the risk of using VPA in their prescription practice, as several authors have observed a decrease in VPA use among girls, women of childbearing age and pregnant women with epilepsy before the European interventions. [30–32]. However, GPs may have become

aware more recently of the risk associated with the use of VPA during pregnancy. Besides, according to our study, before interventions, VPA prescription by GPs were widespread (64% among women with epilepsy in 2011). What is more, women of childbearing age may also become more aware of the risk of VPA because of media coverage of EMA recommendations, and requested physicians to prescribe another drug for pregnancy prospect. Hence, despite expectations, our study showed delayed effect of the EMA intervention with a decrease in trend of VPA use among women with epilepsy and not surprisingly, an immediate effect of the ANSM intervention with a drop in the level of VPA use among girls and women with epilepsy. Simultaneously, there was a shift from primary prescription by a GP to primary prescription by a specialist. A decrease in VPA initiation was also observed among girls but not among women of childbearing age. Other authors showed similar results. In Lithuania, Puteikis *et al.* also studied the impact of the EMA risk minimisation procedures [33] and did not show any significant impact of the 2013-2014 procedure on absolute numbers of females patients (under 50) using the drug, but showed a delayed effect among girls under 15. In Sweden, Karlsson Lind *et al.* studied the impact of the Dear Doctor Letter in late 2014 and observed no post-intervention change (neither slope nor level) in VPA initiations among women with epilepsy. Of note, we observed a stabilisation trend of VPA incident use among women with epilepsy after the interventions, which was also showed by Puteikis *et al.* among females with epilepsy under 50. This result suggests that the lowest level of VPA use is reached in this population. In fact, VPA can be the only effective treatment in some epileptic syndromes [1] and is useful for many females patients of younger age (for example, those with intellectual disability or not wishing to conceive). Thus, a sharp and radical decrease in VPA prescriptions is probably not feasible or might even be unnecessary among women with epilepsy. [34] In this context, the last RMMs, implemented in Europe in 2018 should be evaluated. These RMMs recommended that VPA should only be used for women of childbearing age if they have epilepsy failing to respond to other antiepileptic drugs, and only if they are enrolled in a pregnancy prevention programme. In our study,

we showed that a majority of women initiating VPA was previously exposed to an alternative drug but we did not measure the impact of the pregnancy prevention program. This could be performed through different indicators: the incidence of VPA exposed pregnancies, or the number of women having beta-HCG laboratory analyses.

4.2 Strengths and limitations

The principal strength of our study was the use of a national database (with more than 60 million people), enabling for the first time in France the evaluation of the impact of the RMMs from European and French health authorities, on prevalent and incident use of VPA, in a large population of girls and women of childbearing age, including a control group not targeted by these RMMs.

Despite this major strength, four limitations are acknowledged.

Firstly, the actual indication for which VPA was prescribed was not recorded. Because SNDS does not include information about the underlying clinical diagnoses for drug prescriptions, we estimated the potential indications from the approved indications of AED, from chronic diseases and from hospitalisations. Therefore, the association between diagnoses and prescriptions is uncertain. However, the algorithm we used had already been used by other teams studying VPA prescription among women of childbearing age through medico-administrative database. Of note, in France, VPA could be used in the prevention of maniac episodes in bipolar disorder and off-label in the treatment of migraine and schizophrenia. We did not study VPA prescription in these cases as we were not able to identify the at-risk population.

Secondly, prescription of VPA was measured on the basis of SNDS-documented deliveries. We hypothesized that decrease in VPA deliveries means decrease in VPA prescription. However, the prescription of VPA could persist without any issue: the patient do not go to the pharmacist to get the prescribed drug. The target of the RMMs should be the prescribers and the patients with a good understanding of the benefit/risk ratio of VPA exposition or withdrawal.

Thirdly, the decrease in the use of VPA should be in parallel with an increase of alternatives treatment. In France, the French Health Authority (HAS) worked with the ANSM to propose drug alternatives in the treatment of epilepsy in girls, women of childbearing age and pregnant women. We did not study VPA alternatives in this study. Our team has previously studied trends for AEDs prescription among girls over the period from 2010 to 2016 [23] and we also studied trends for AEDs prescription among pregnant women (Under Review in Neurology).

Fourthly, it is difficult to associate the decrease in VPA use with a specific regulatory intervention (EMA or ANSM) or only to these interventions. Furthermore, the study period was divided according to the intervention dates. In this respect, the number of time-points measured between the EMA intervention and the ANSM intervention are barely sufficient to observe any effect of the EMA intervention. Thus, the observed effect cannot be attributed to an intervention time-point but rather to the set of RMMs progressively implemented. The important thing is that RMMs led the level of VPA use to be reduced.

5 Conclusions

Our results provide evidence that messaging appears to be effective in changing prescription practice and thus reducing the risk of exposure to VPA among women with epilepsy that could become pregnant. The low and stable level of VPA use observed at the end of the study period suggests that the lowest prescription rate has been reached in this population, since VPA might remain the only appropriate therapy for some girls and women. This lowest level should be sustained over time to ensure that VPA is only used in particular cases where there is no other choice and that the patient follows the pregnancy prevention program, as recommended by the last RMM (2018).

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Table 1: Patient characteristics at inclusion.

		Males		Females	
Number of Subjects	N,%	129, 917	53.1	114, 936	46.9
Age	Median, IQR	32	[17-42]	31	[17-42]
0-14 years	N,%	27, 666	21.3	24, 380	21.2
	0-10	21, 569	16.6	18, 251	15.9
	11-14	6, 097	4.7	6, 129	5.3
15-49 years	N,%	102, 251	78.7	90, 556	78.8
	15-24	20, 322	15.6	20, 336	17.7
	25-34	24, 041	18.5	21, 576	18.8
	35-44	35, 001	26.9	29, 890	26.0
	≥45	22, 887	17.6	18, 754	16.3
Duration of follow-up (years)	Mean, Sd	4.5	2.3	4.6	2.3
Monotherapy at inclusion	N,%	93, 082	71.6	83, 778	72.9
VPA users	N,%	44, 649	34.4	34, 250	29.8
	as incident use	10, 125	22.7	7, 499	21.9

IQR = Inter-Quartile Range; Sd = Standard deviation

FIGURE CAPTION

Figure 1: Flowchart for patient selection.

Figure 2: Trends for VPA prevalent use over the study period, expressed as rate per 1000 person at-risk, according to the age category: 0-14 years (A) and 15-49 (B) among females (grey) and males (black).

Figure 3: Trends for VPA incident use over the study period, expressed as rate per 1000 person at-risk, according to the age category: 0-14 years (A) and 15-49 (B) among females (grey) and males (black).

Source population

Subjects under 50 years of age with at least one reimbursement claim for an antiepileptic drug (AED) or a mood stabilizer between 2008 to 2017

N= 4,733,713

Exclusion of subjects without any claim of AED between 2011 to 2017
N= 569 233

Subjects under 50 years of age with at least one claim for an AED over the study period (from 2011 to 2017)

N=3,009,589

Exclusion of subjects without epilepsy
N = 143 134 with alcohol disorder
N = 1 378 709 with anxiety
N = 201 052 with neuropathic pain
N = 7 028 with migraine
N = 270 556 with bipolar disorder
N = 764 257 with unclassified disease

Study population

Subjects under 50 at-risk to receive valproate over the study period (from 2011 to 2017) in a context of epilepsy

N= 244,853

Intervention group

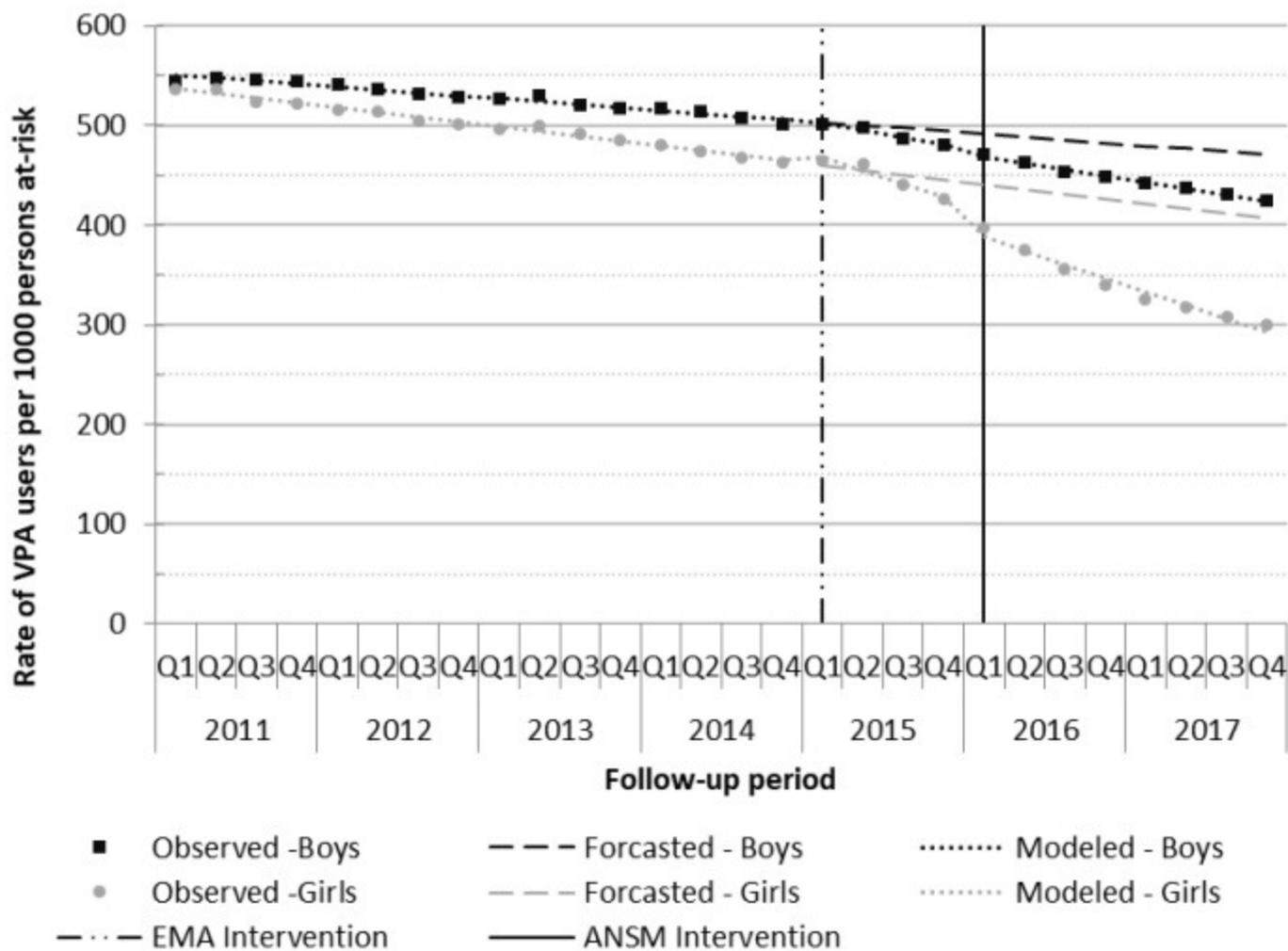
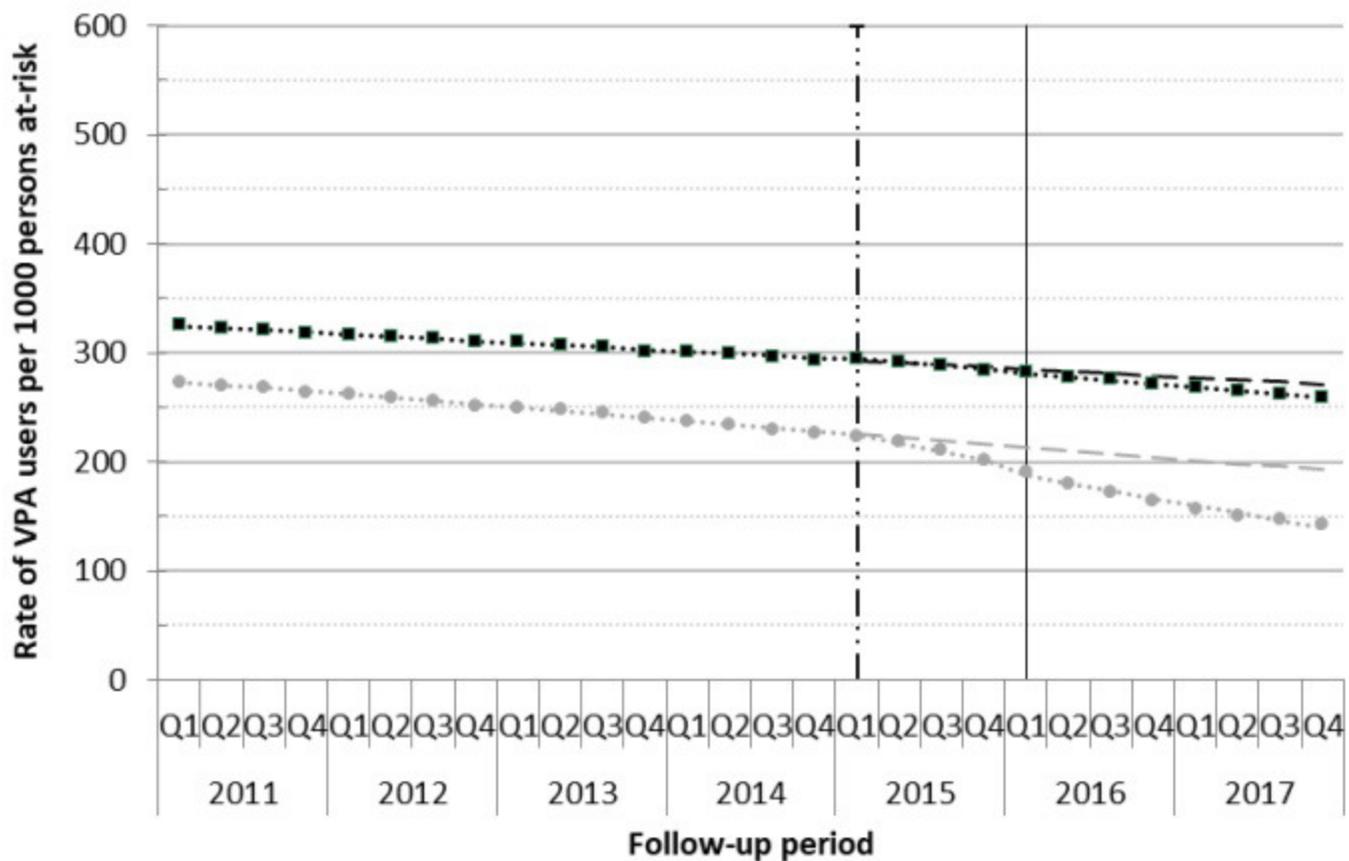
Females

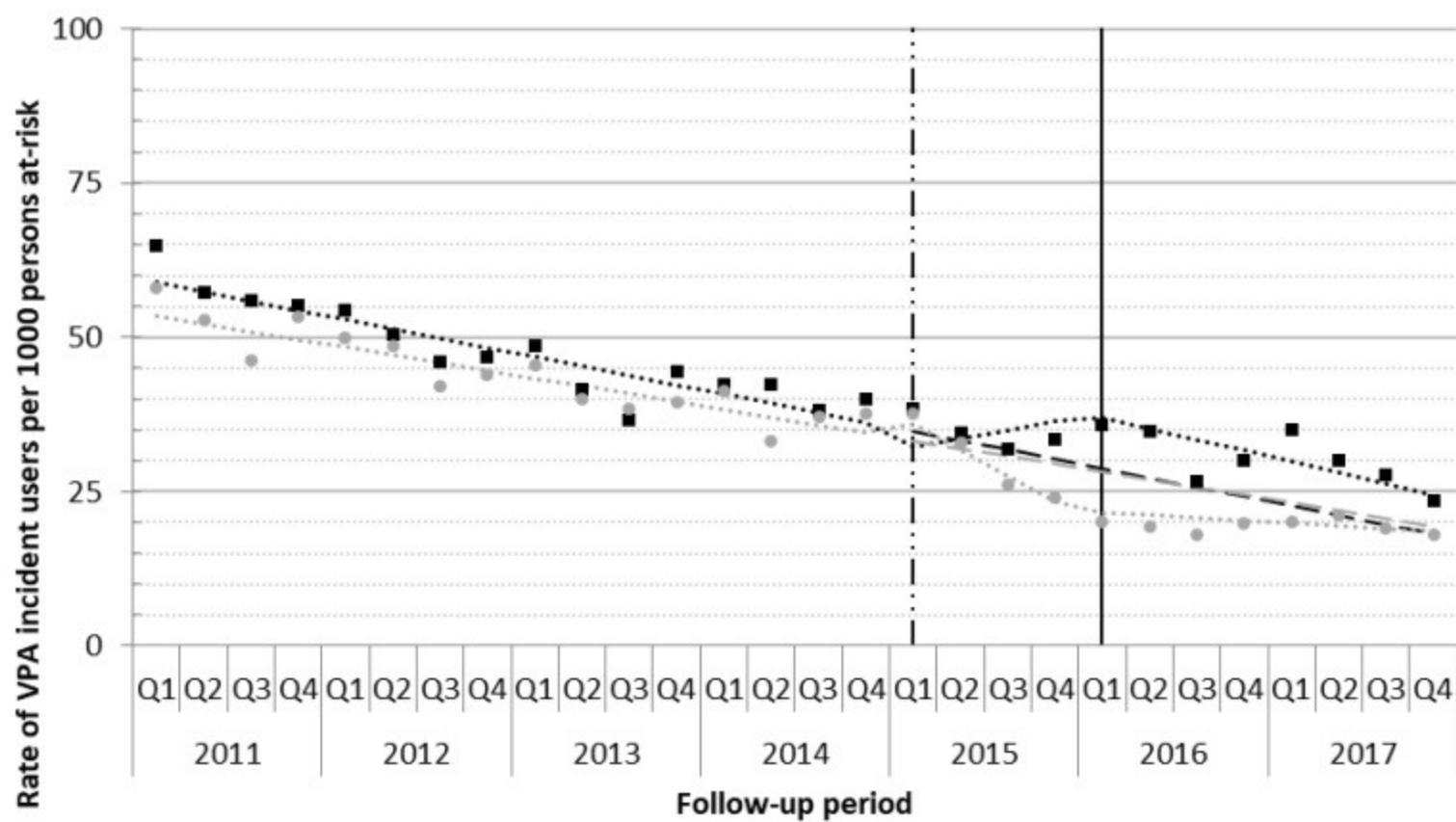
N= 114,936

Control group

Males

N= 129,917

A)**B)**

A)**B)**