Impact of 2018 EU risk minimisation measures and revised pregnancy prevention programme on utilisation and prescribing trends of medicinal products containing valproate: an interrupted time series study

Submitted to Drug Safety

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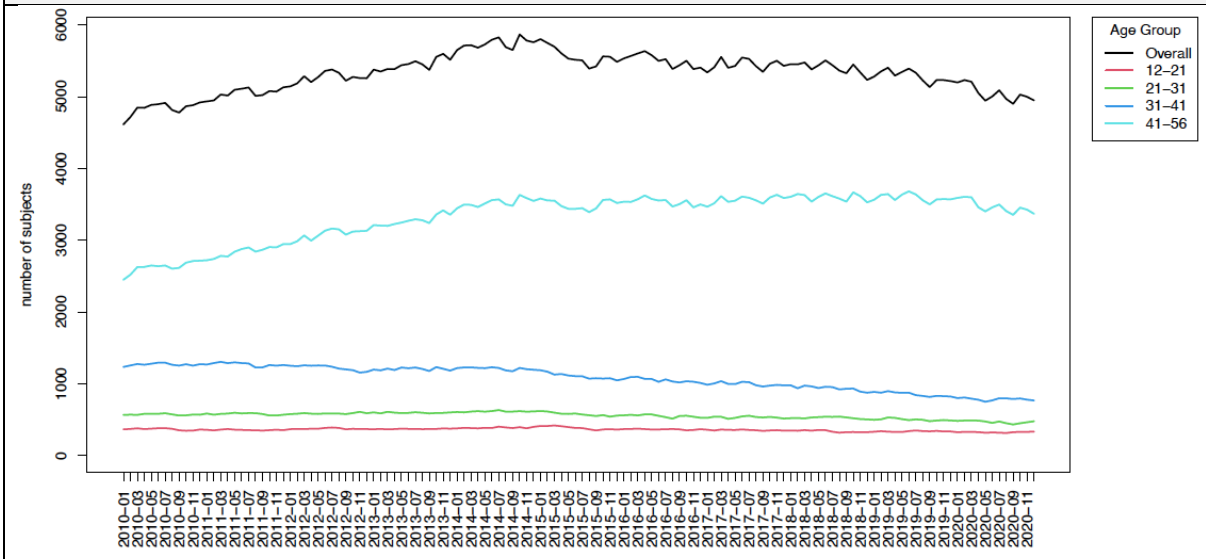
Supplementary information S.3.

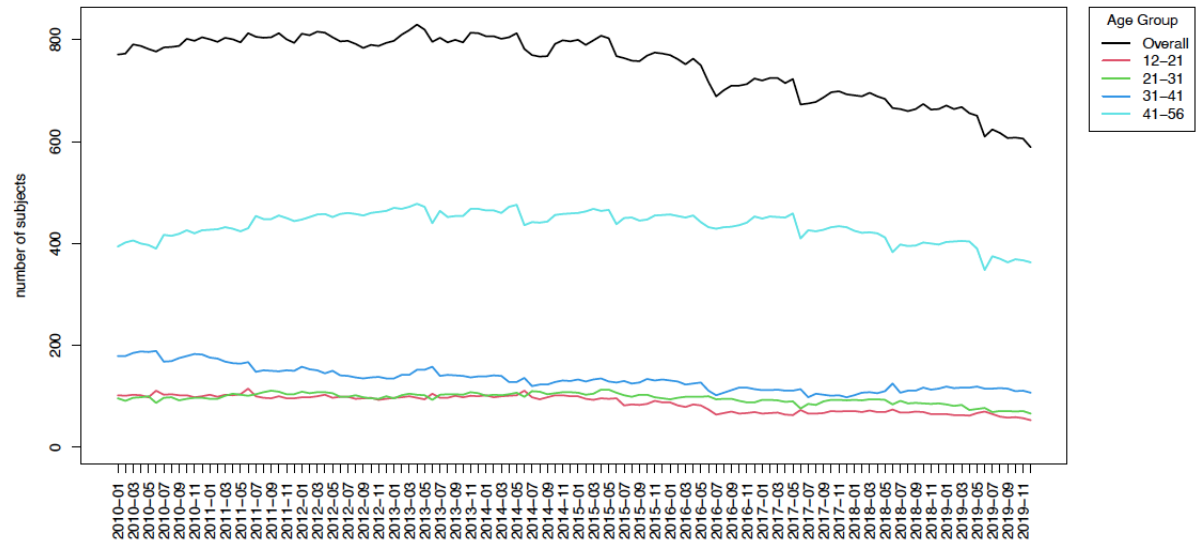
a) Stratified analyses of prevalent use of valproates and contraceptive coverage during valproate use across databases

Figure S.3.a-1 Trend in prevalent (current) use of valproates across the included databases during the study period, stratified by age group.

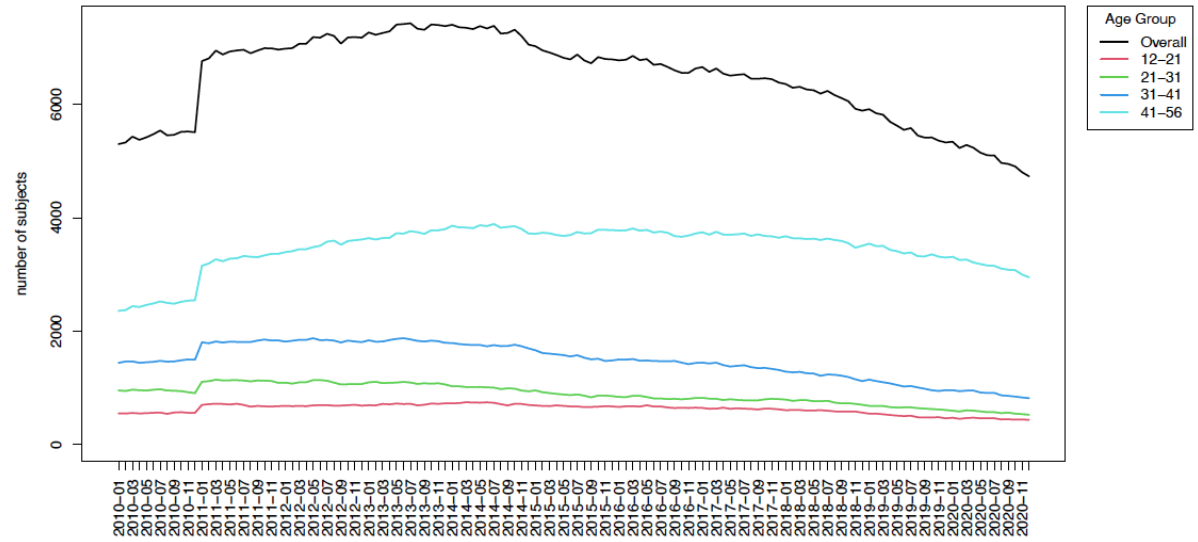
b. ARS Tuscany, IT



c. PHARMO, NL



d. BIFAP, ES



e. CPRD, UK

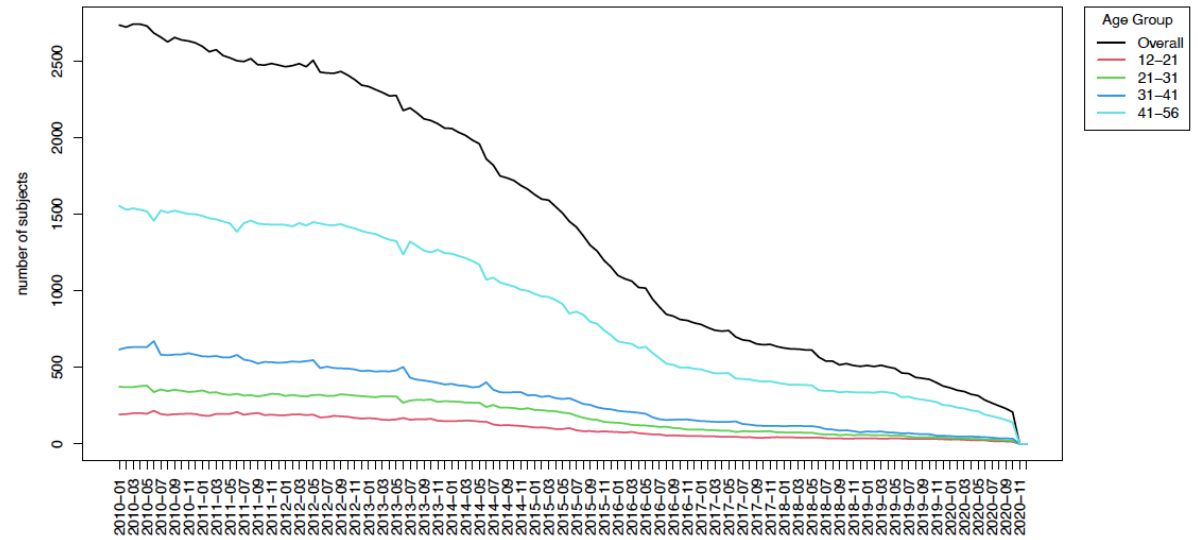
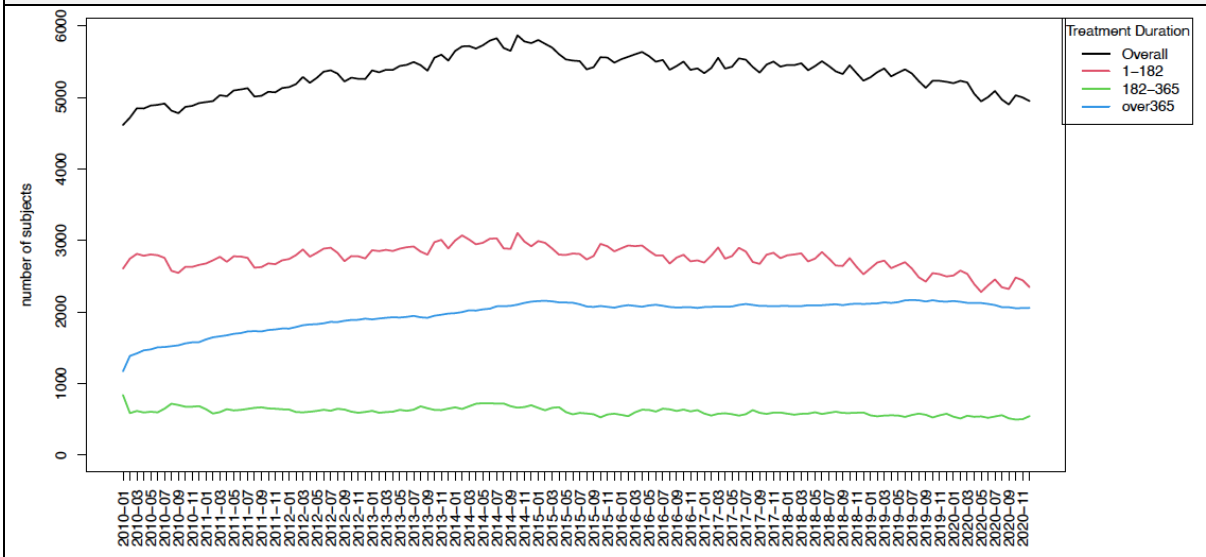
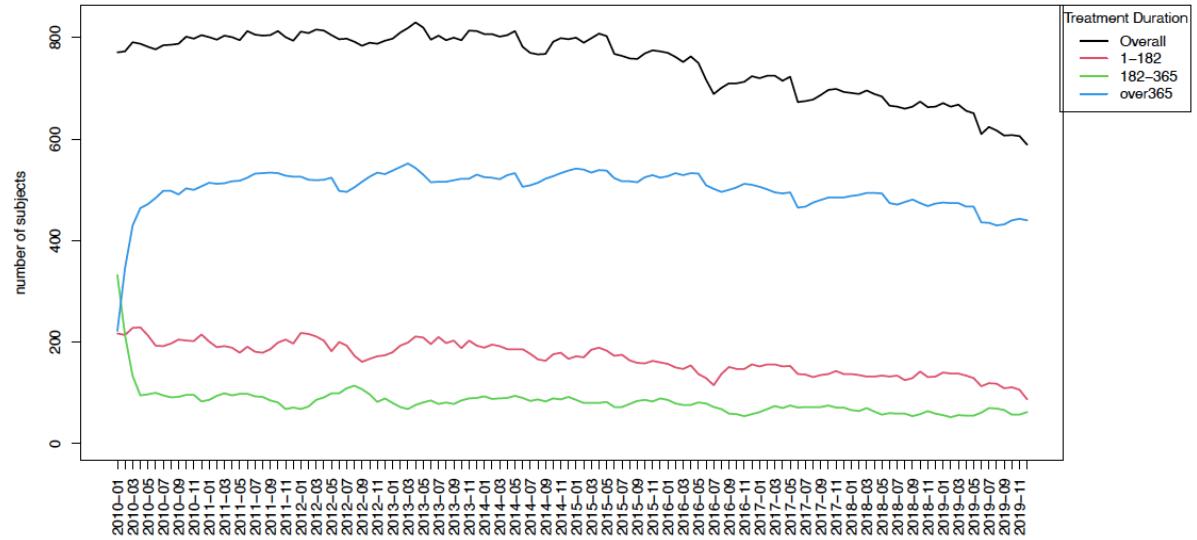


Figure S.3.a-2 Trend in prevalent (current) use of valproates across the included databases during the study period, stratified by treatment duration.

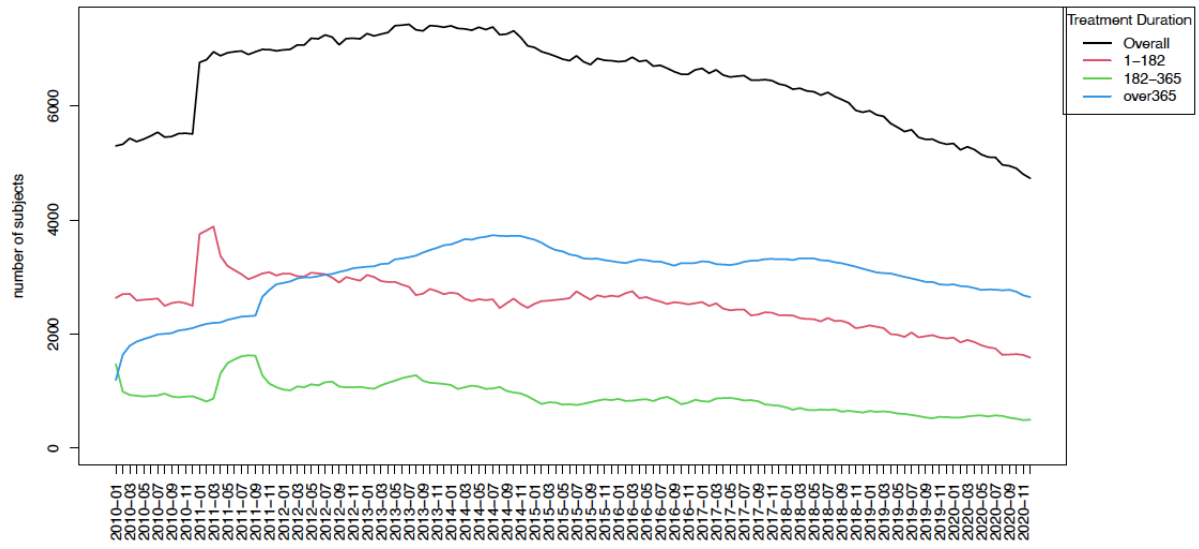
b. ARS Tuscany, IT



c. PHARMO, NL



d. BIFAP, ES



e. CPRD, UK

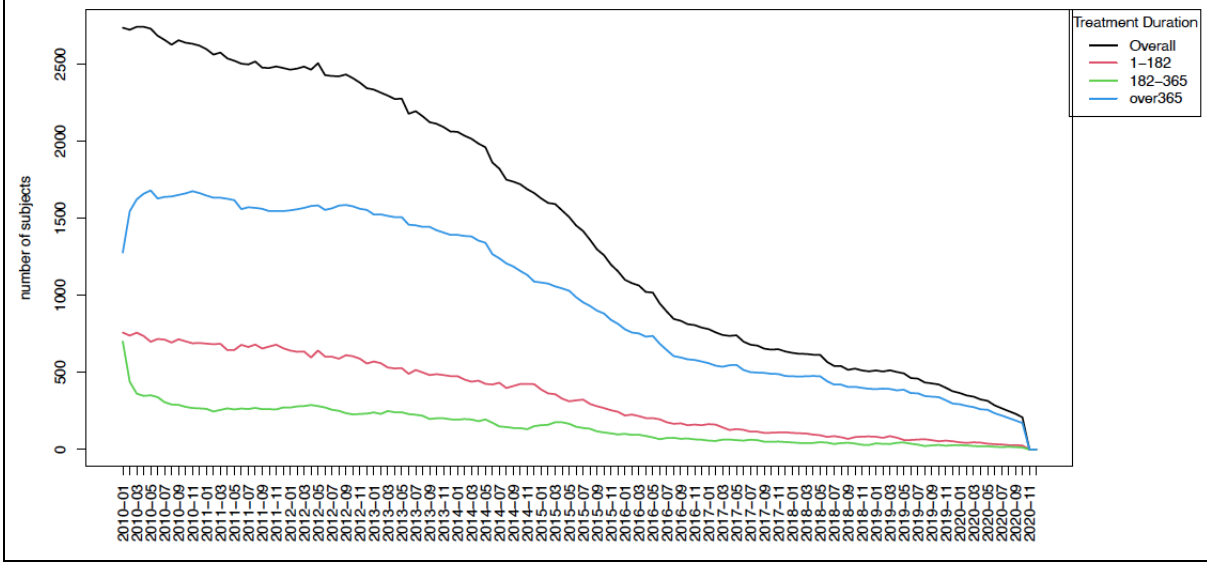
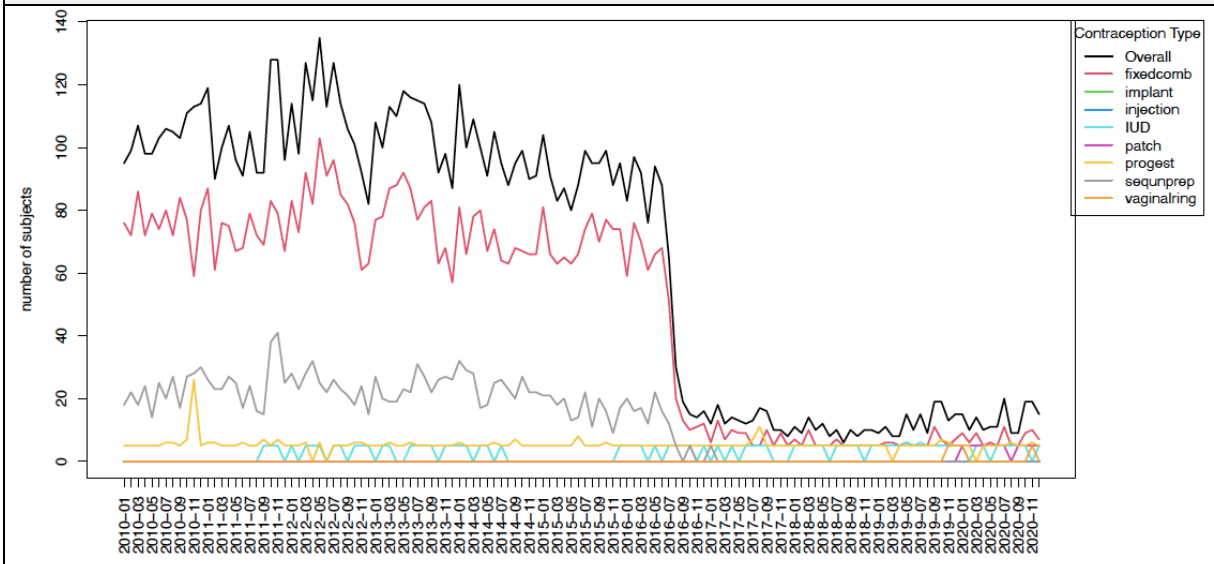
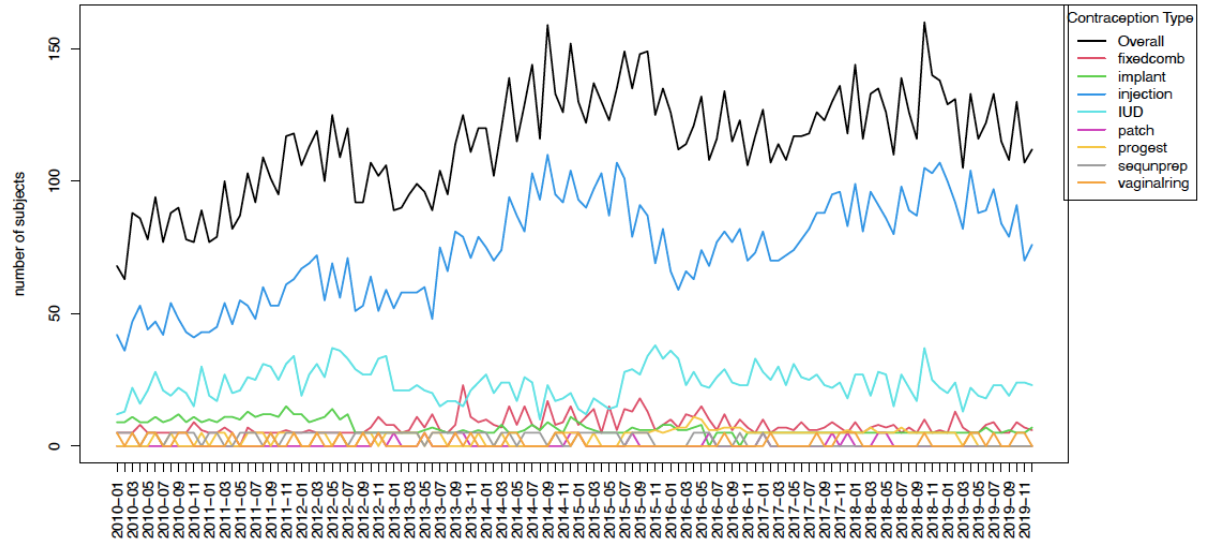


Figure S.3.a-3 Trend in contraceptive coverage during valproate use across the included databases during the study period, stratified by contraceptive type.

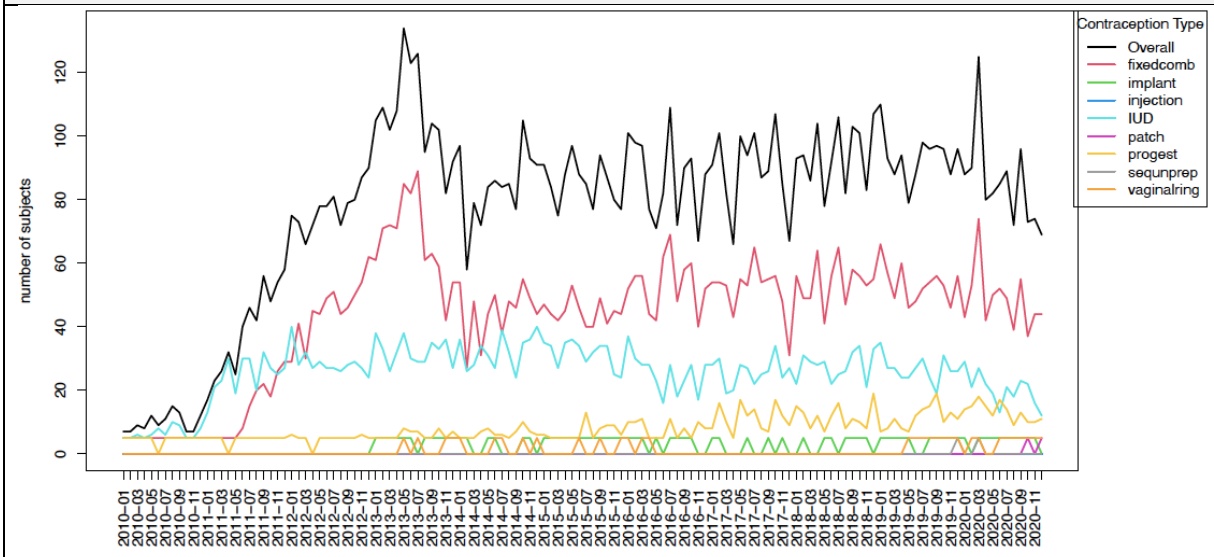
b. ARS Tuscany, IT



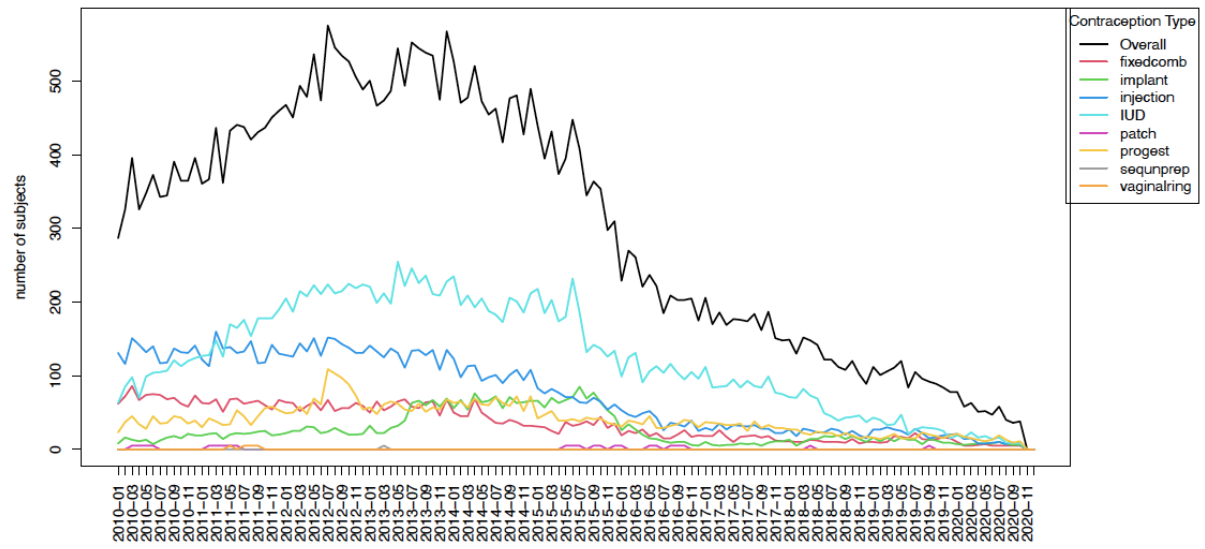
c. PHARMO, NL



d. BIFAP, ES



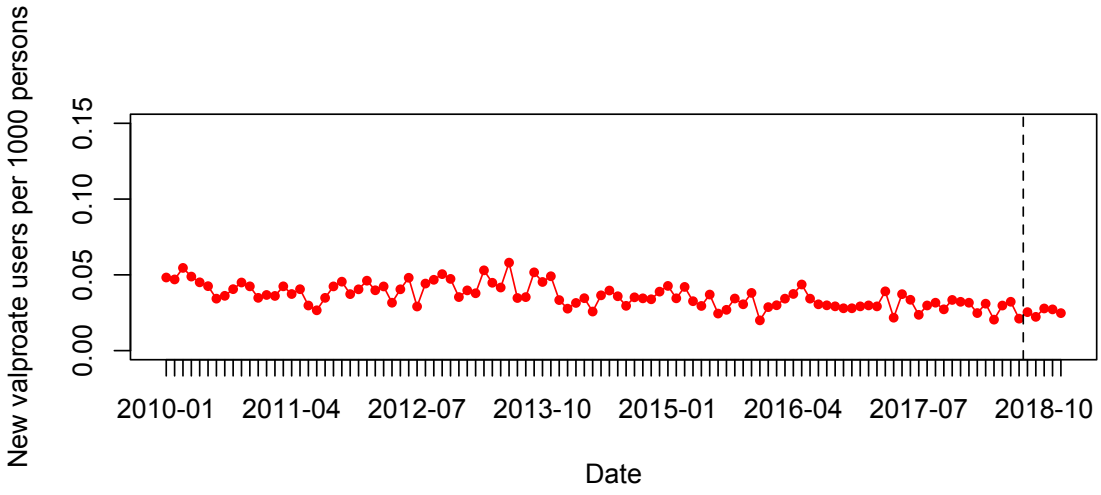
e. CPRD, UK



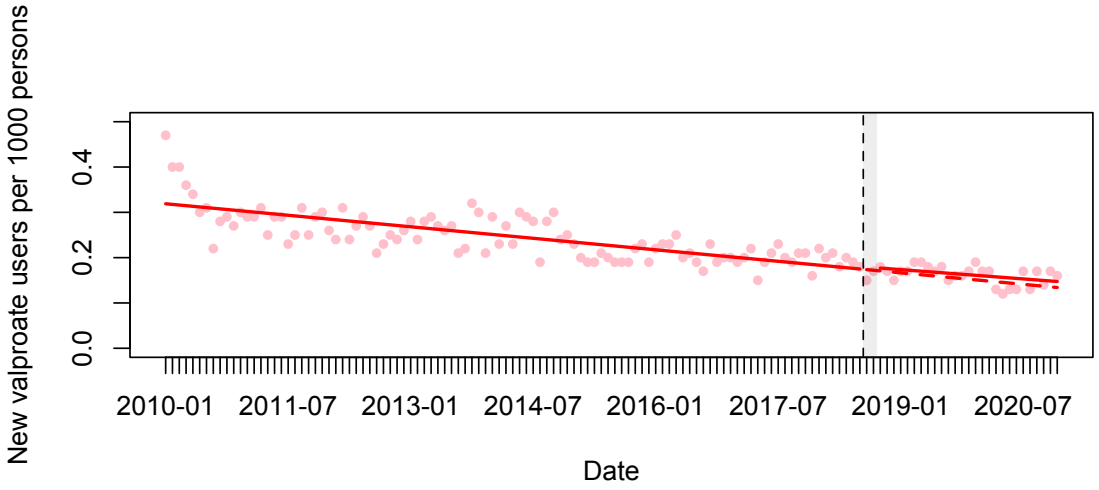
b) ITS analysis plots of incident use of valproate across databases

Figure S.3.b-1 Change in level and trend in incident use of valproates in five participating centres over the study period, modelled by interrupted time series (ITS) analysis. The time of implementation of the 2018 risk minimisation measures for valproates is shown with a light grey bar (starts with a dashed black line), and the counterfactual trend (had the intervention not occurred) is shown with the dashed red line thereafter. Note that the end of study period differs per data source. In case of DNR, the trend in incident use over time has been shown without any ITS modelling, as this was not possible due to limited time points after the 2018 intervention.

a. DNR, DK*



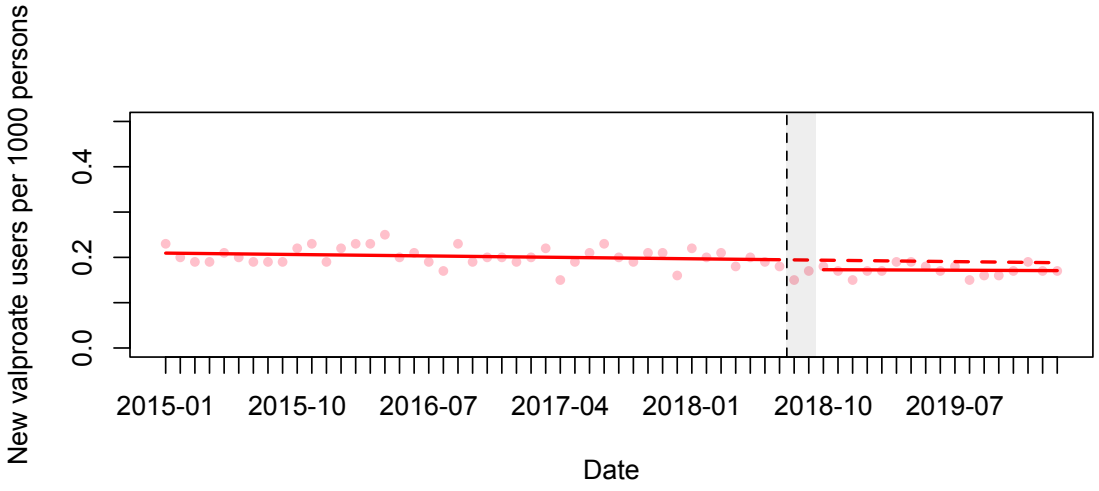
b. ARS Tuscany, IT



Level change: 0.005 new users/1000 PM, *p*=0.809

Trend change: <0.001 new users/1000 PM, *p*=0.811

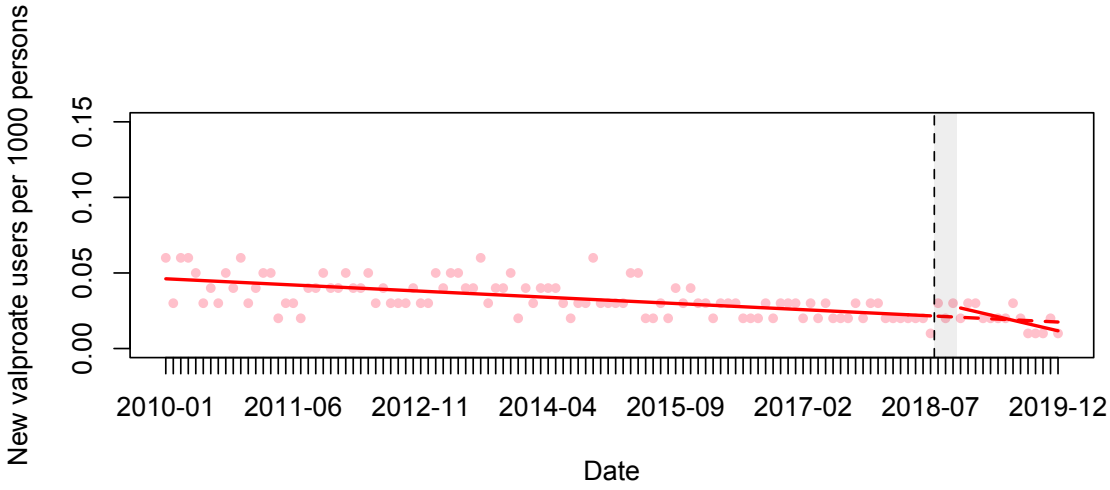
"Sensitivity analysis for the period 01.01.2015 until 29.02.2020"



Level change: -0.022 new users/1000 PM, *p*=0.090

Trend change: <0.001 new users/1000 PM, *p*=0.820

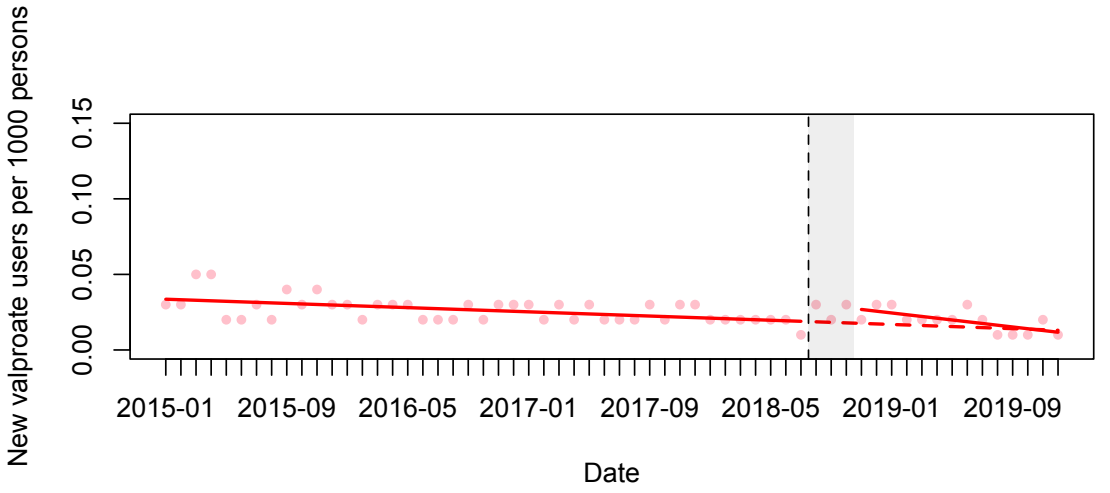
c. PHARMO, NL



Level change: 0.010 new users/1000 PM, *p*=0.167

Trend change: -0.001 new users/1000 PM, *p*=0.134

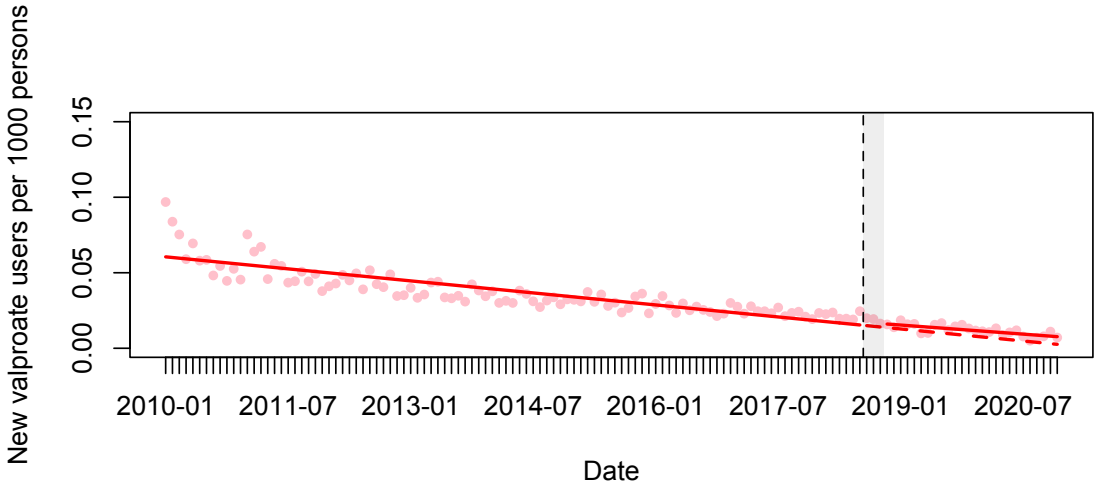
"Sensitivity analysis for the period 01.01.2015 until 31.12.2019"



Level change: 0.012 new users/1000 PM, *p*=0.029*

Trend change: -0.001 new users/1000 PM, *p*=0.087

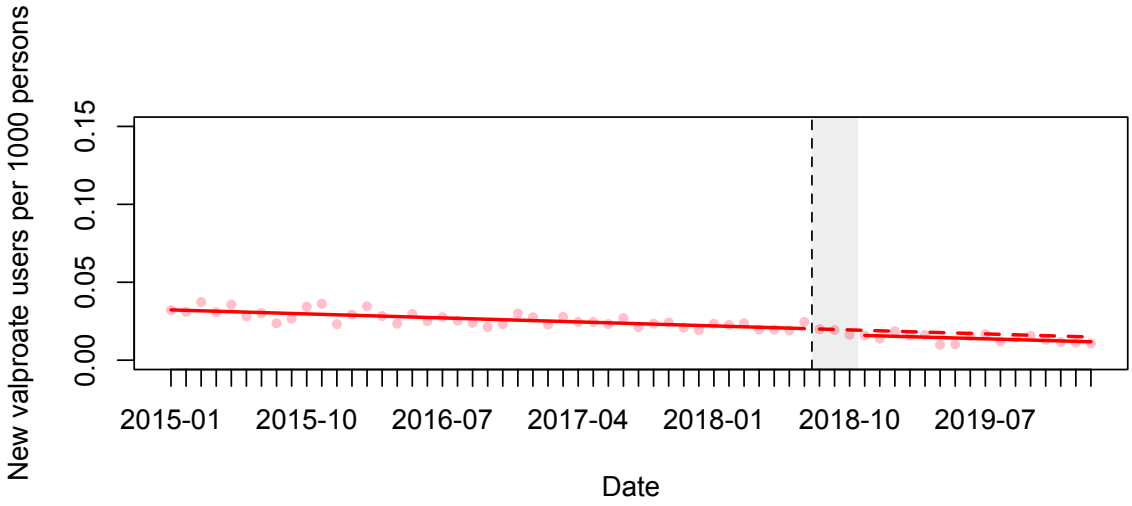
d. BIFAP, ES



Level change: 0.002 new users/1000 PM, *p*=0.745

Trend change: <0.001 new users/1000 PM, *p*=0.720

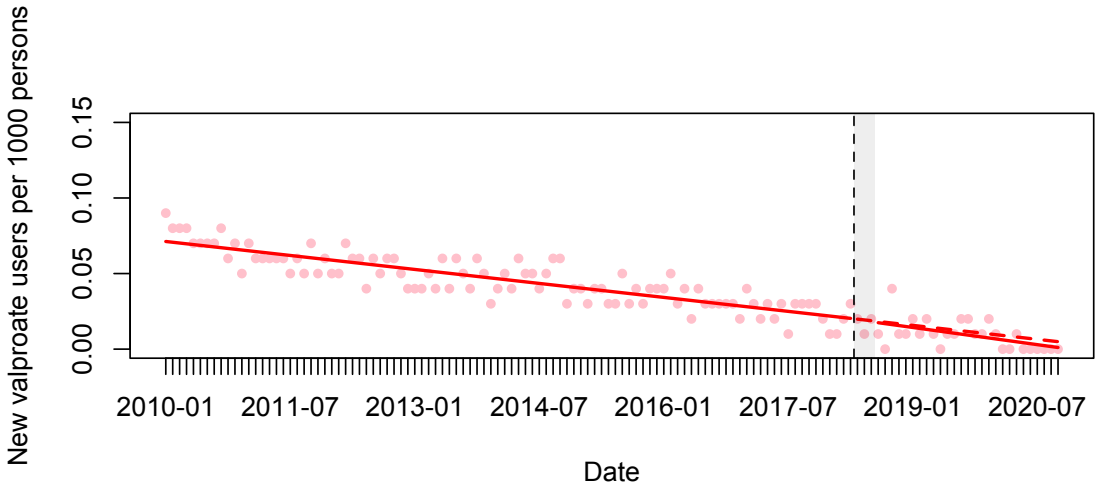
"Sensitivity analysis for the period 01.01.2015 until 29.02.2020"



Level change: -0.003 new users/1000 PM, *p*=0.124

Trend change: <0.001 new users/1000 PM, *p*=0.928

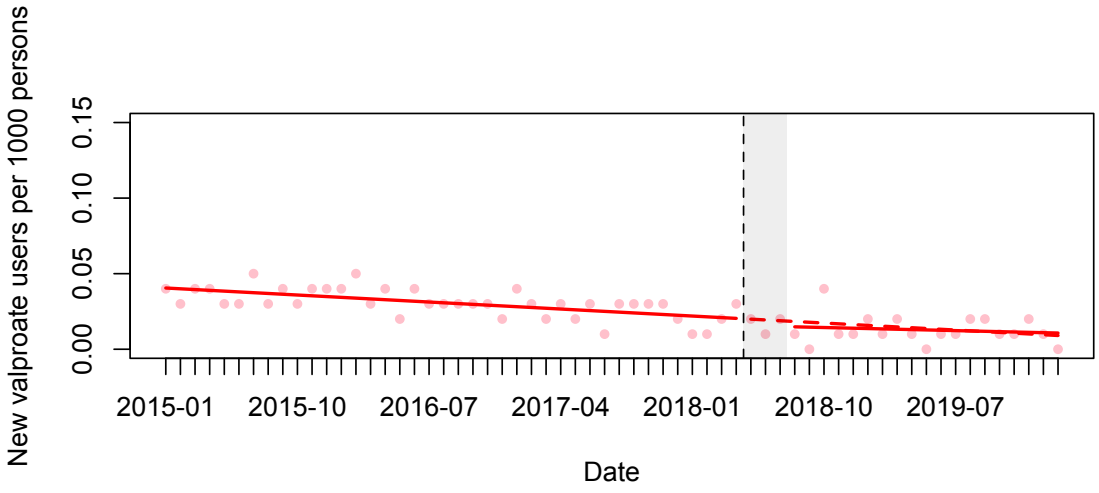
e. CPRD, UK



Level change: >-0.001 new users/1000 PM, p=0.934

Trend change: >-0.001 new users/1000 PM, p=0.564

"Sensitivity analysis for the period 01.01.2015 until 29.02.2020"



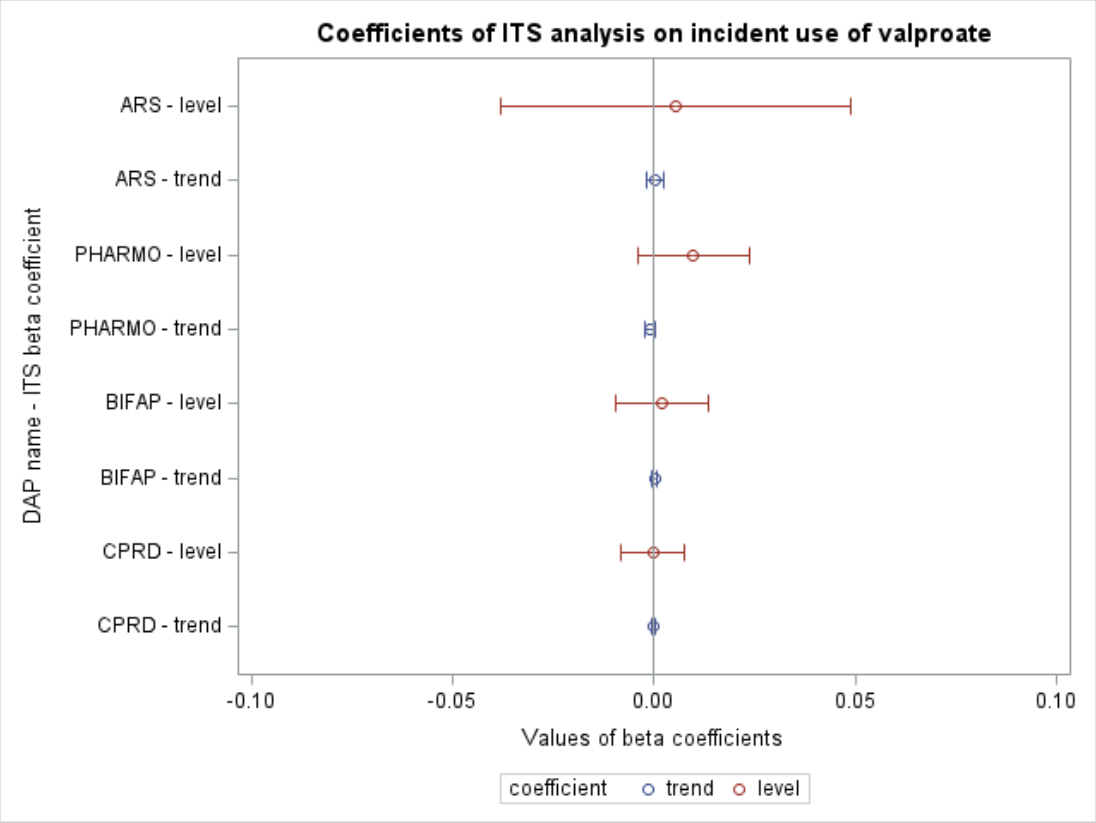
Level change: -0.005 new users/1000 PM, p=0.308

Trend change: <0.001 new users/1000 PM, p=0.345

* ITSA not conducted due to limited post-intervention data available.

Figure S.3.b-2 Forest plots showing the level and trend beta coefficients of the interrupted time series analyses of incident use of valproate after the implementation of the 2018 risk minimisation measures across centres, in the: a) main, and b) sensitivity analysis.

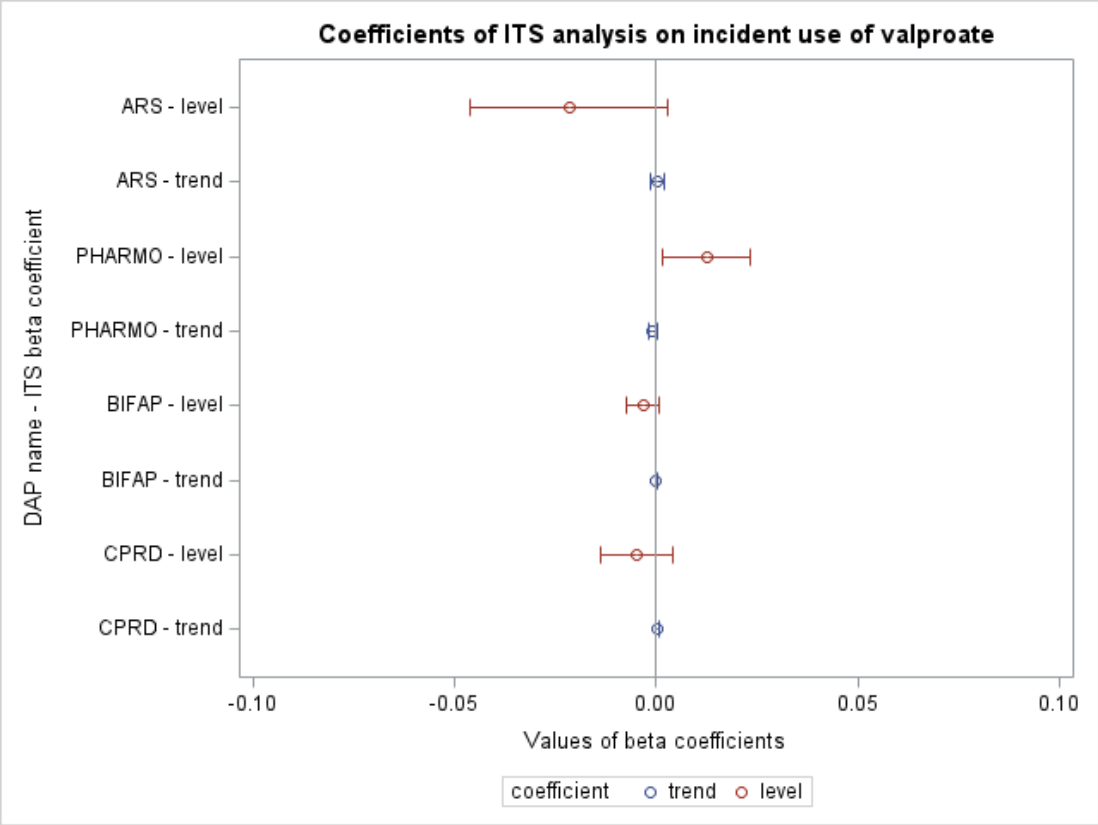
a) Main analysis (01.2010-12.2020)*



Abbreviations, DAP: Data Access Partner, ITS: interrupted time series.

* The end of study period was 12.2019 for PHARMO and 10.2020 for CPRD.

b) Sensitivity analysis (01.2015-02.2020)*

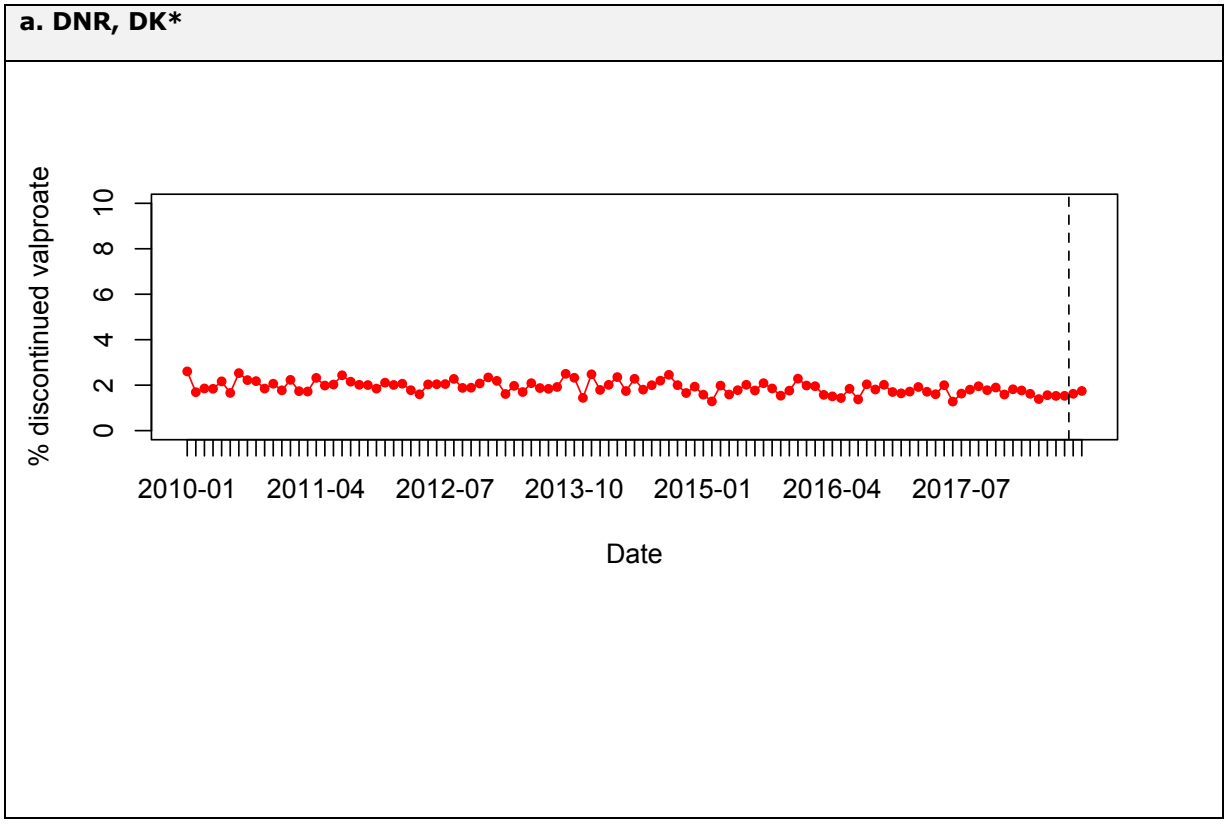


Abbreviations, DAP: Data Access Partner, ITS: interrupted time series.

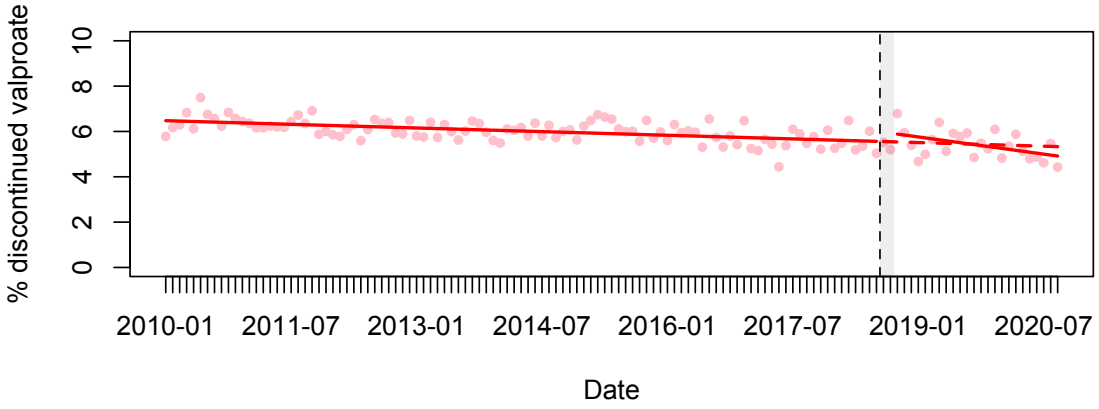
* The end of study period was 12.2019 for PHARMO.

c) ITS analysis plots of valproate discontinuation across databases

Figure S.3.c-1. Change in level and trend in proportion of valproate discontinuers in five participating centres over the study period. The time of implementation of the 2018 risk minimisation measures for valproates is shown with a light grey bar (starts with a dashed black line), and the counterfactual trend (had the intervention not occurred) is shown with the dashed red line thereafter. Note that the end of study period differs per data source. In case of DNR, the trend in incident use over time has been shown without any ITS modelling, as this was not possible due to limited time points after the 2018 intervention.



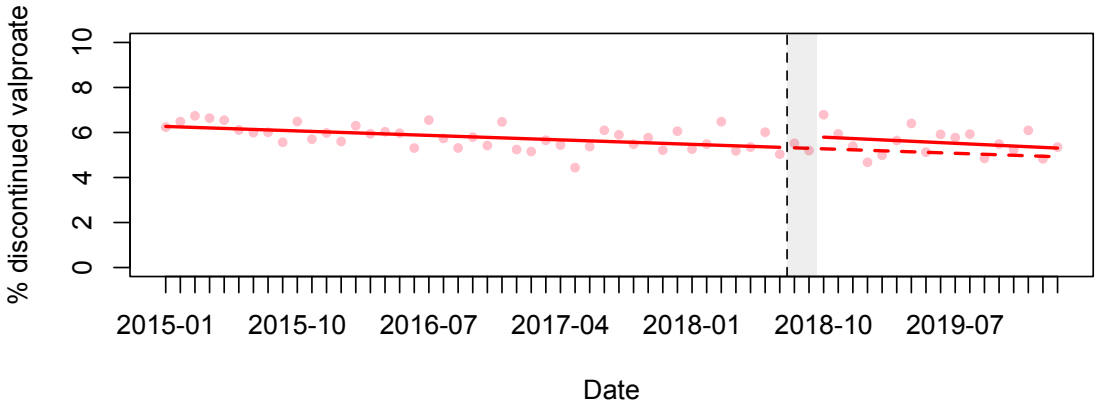
b. ARS Tuscany, IT



Level change: 0.447 discontinuers/100 valproate user, p=0.046*

Trend change: -0.033 discontinuers/100 valproate user, p=0.011*

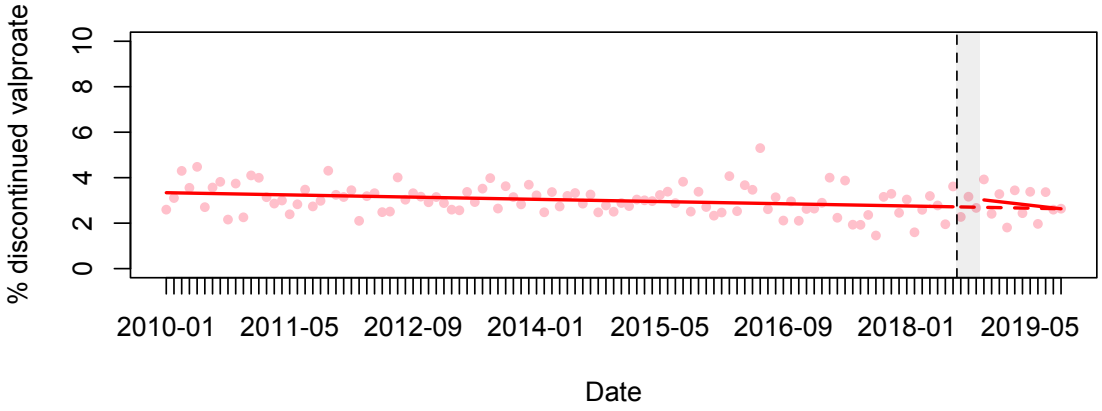
"Sensitivity analysis for the period 01.01.2015 until 29.02.2020"



Level change: 0.543 discontinuers/100 valproate user, p=0.079

Trend change: -0.008 discontinuers/100 valproate user, p=0.723

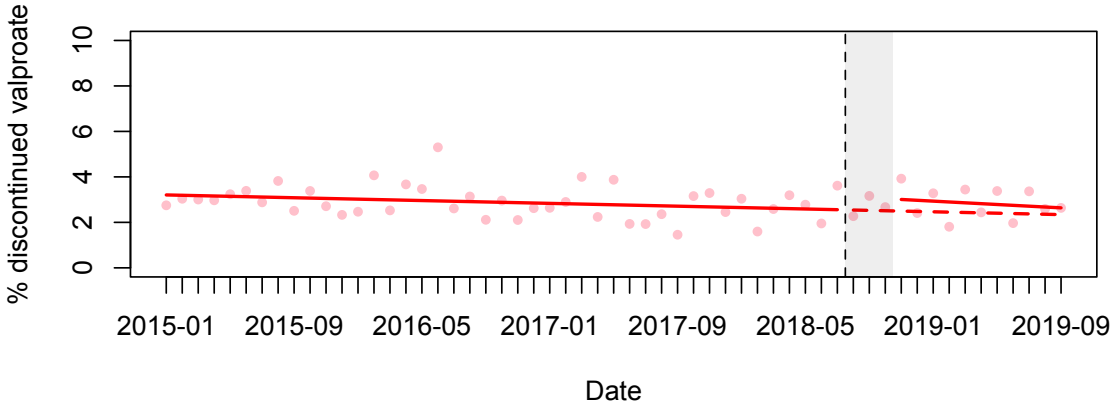
c. PHARMO, NL



Level change: 0.459 discontinuers/100 valproate user, p=0.355

Trend change: -0.033 discontinuers/100 valproate user, p=0.518

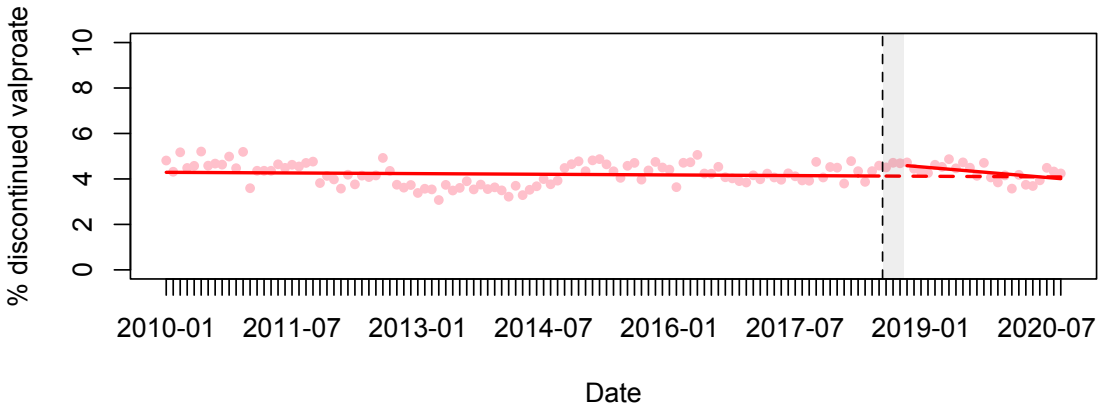
"Sensitivity analysis for the period 01.01.2015 until 30.09.2019"



Level change: 0.597 discontinuers/100 valproate user, p=0.282

Trend change: -0.021 discontinuers/100 valproate user, p=0.701

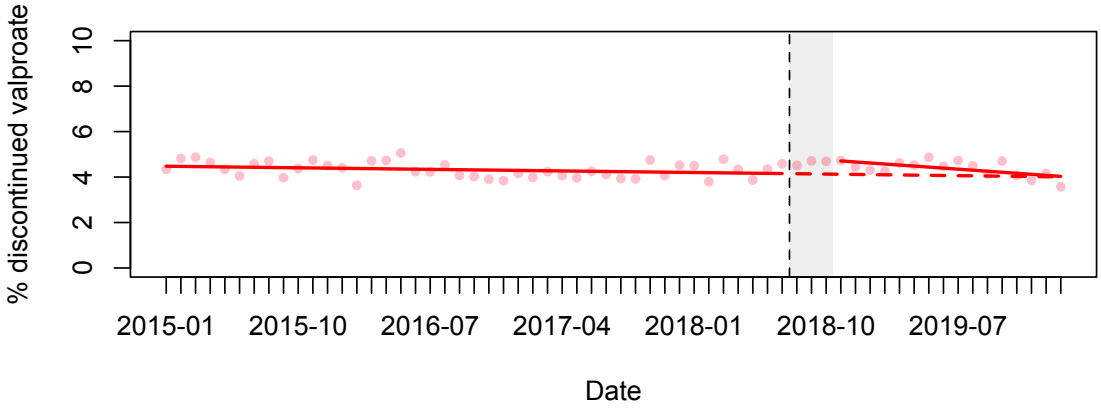
d. BIFAP, ES



Level change: 0.560 discontinuers/100 valproate user, p=0.167

Trend change: -0.024 discontinuers/100 valproate user, p=0.283

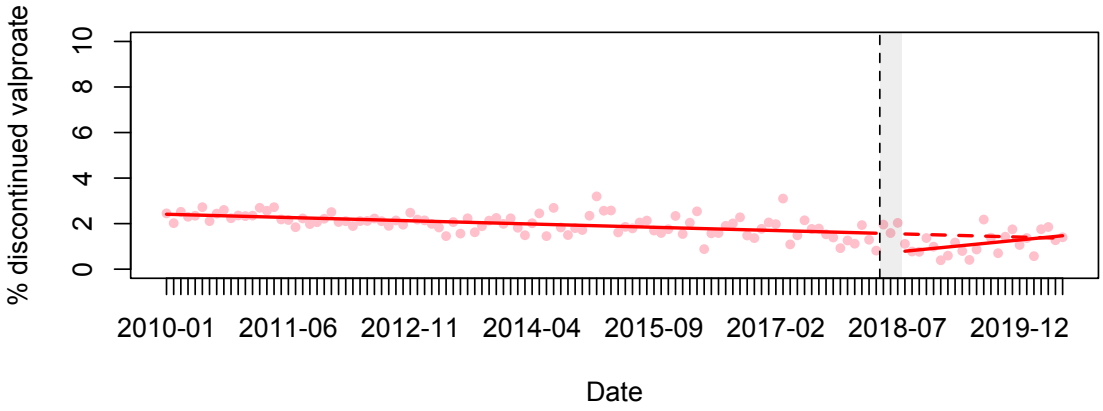
"Sensitivity analysis for the period 01.01.2015 until 29.02.2020"



Level change: 0.737 discontinuers/100 valproate user, p=0.005*

Trend change: -0.038 discontinuers/100 valproate user, p=0.055

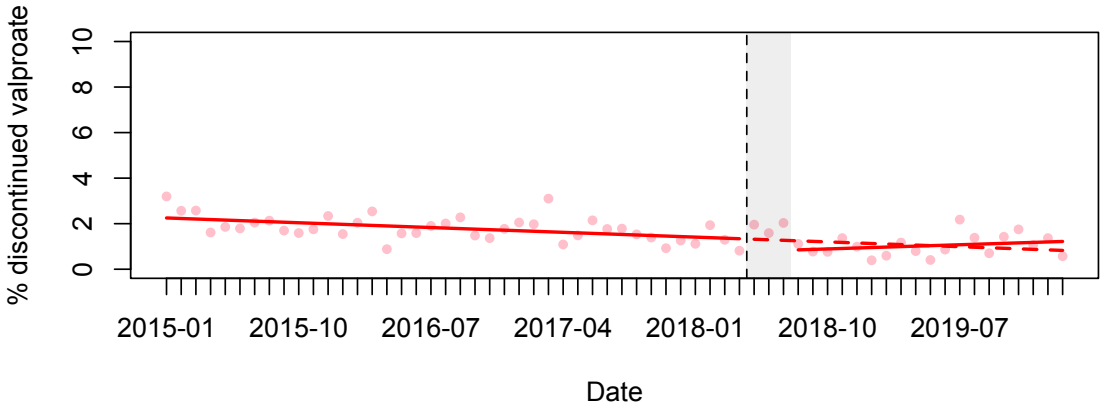
e. CPRD, UK



Level change: -0.913 discontinuers/100 valproate user, $p<0.001$*

Trend change: 0.039 discontinuers/100 valproate user, $p=0.003$*

"Sensitivity analysis for the period 01.01.2015 until 29.02.2020"



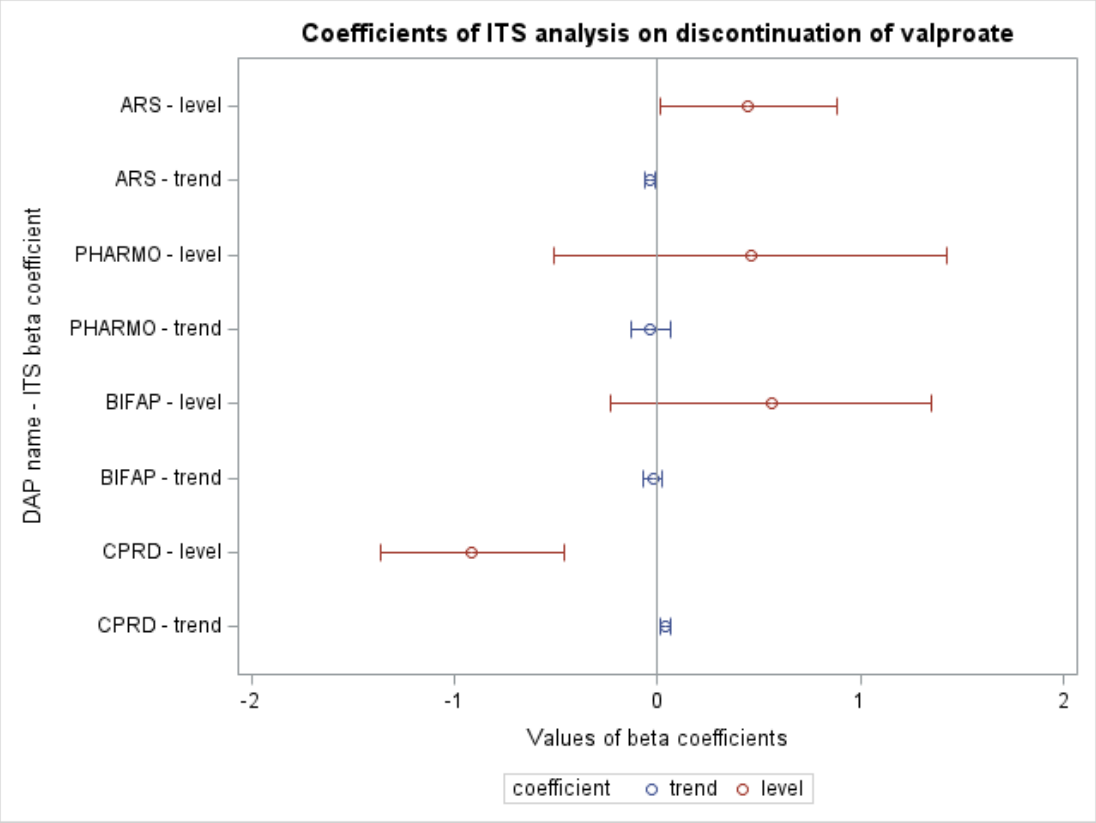
Level change: -0.572 discontinuers/100 valproate user, $p=0.087$

Trend change: 0.044 discontinuers/100 valproate user, $p=0.047$*

* ITSA not conducted due to limited post-intervention data available.

Figure S.3.c-2. Forest plots showing the level and trend beta coefficients of the interrupted time series analyses of discontinuation rates of valproate after the implementation of the 2018 risk minimisation measures across centres, in the: a) main, and b) sensitivity analysis.

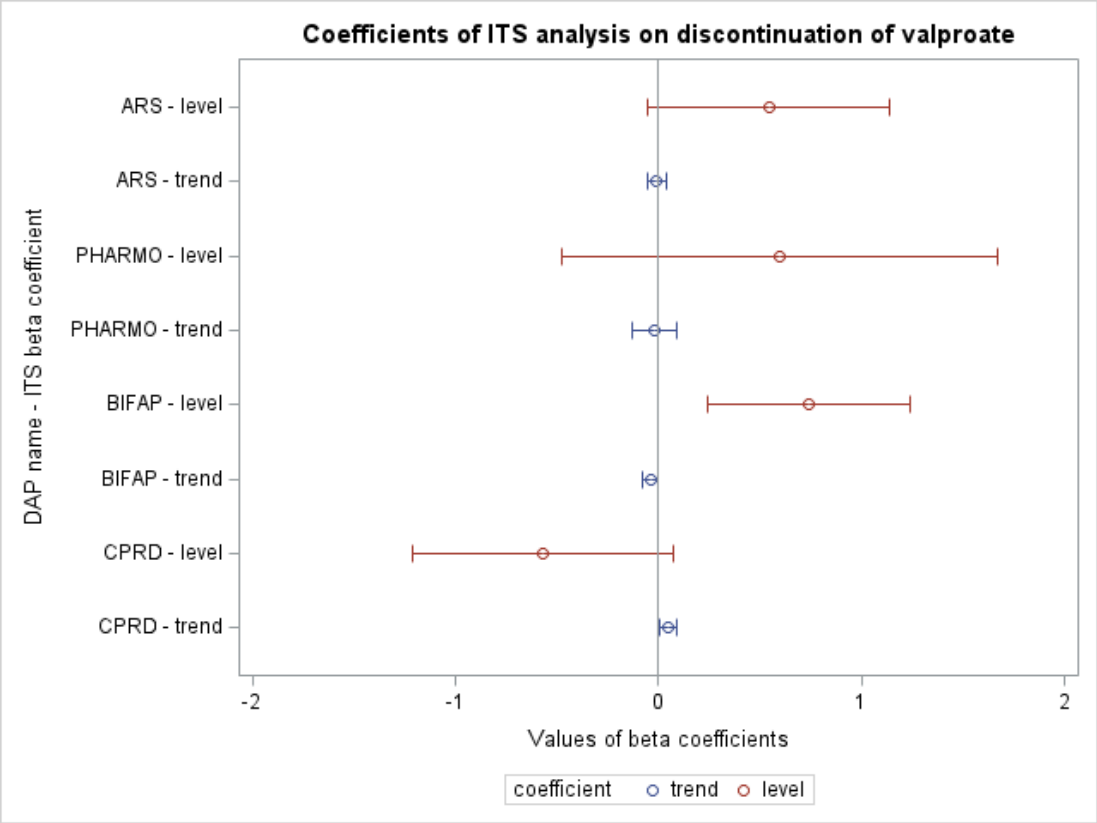
a) Main analysis (01.2010-09.2020)*



Abbreviations, DAP: Data Access Partner, ITS: interrupted time series.

* The end of study period was 09.2019 for PHARMO and 06.2020 for CPRD.

b) Sensitivity analysis (01.2015-02.2020)*

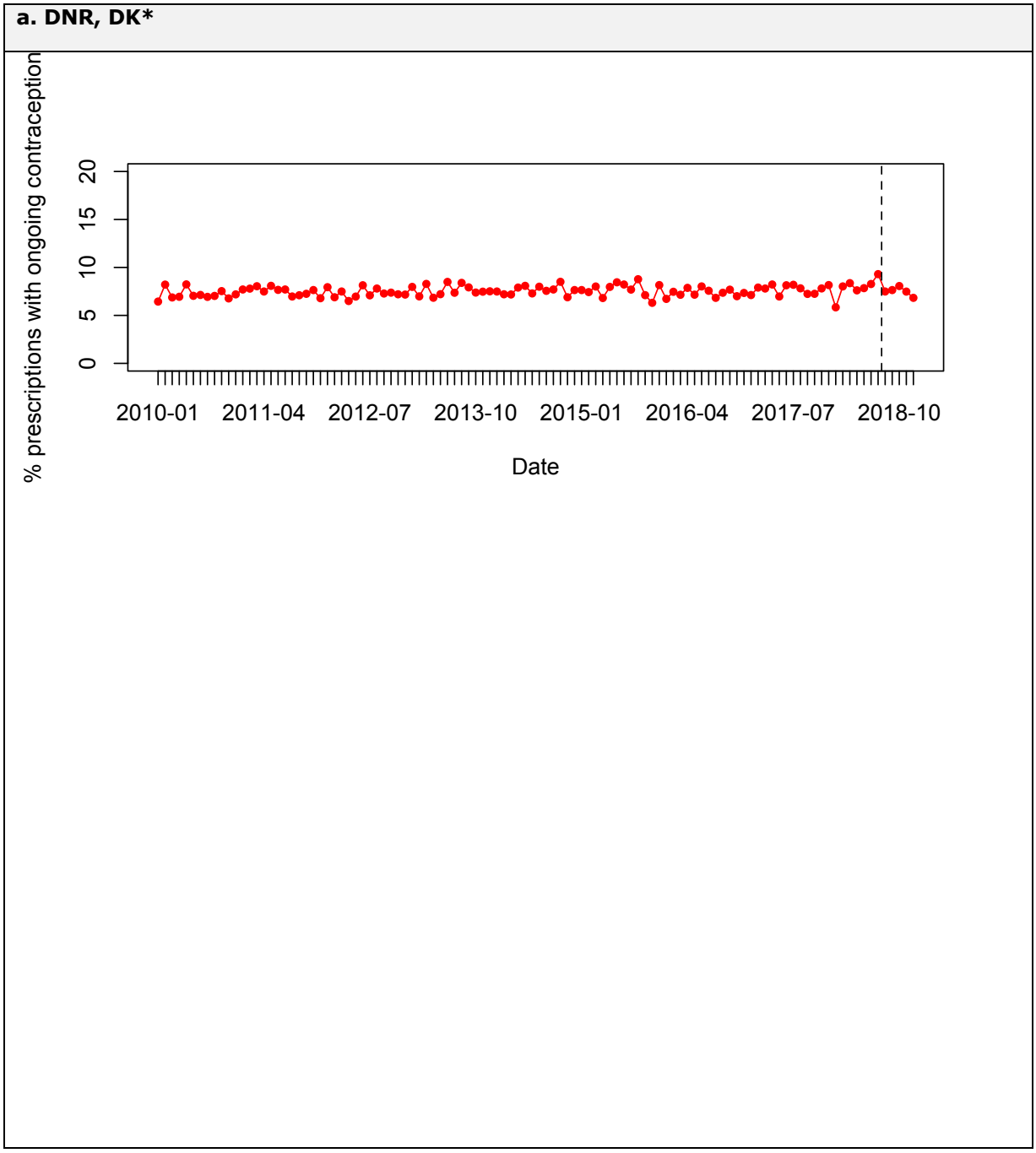


Abbreviations, DAP: Data Access Partner, ITS: interrupted time series.

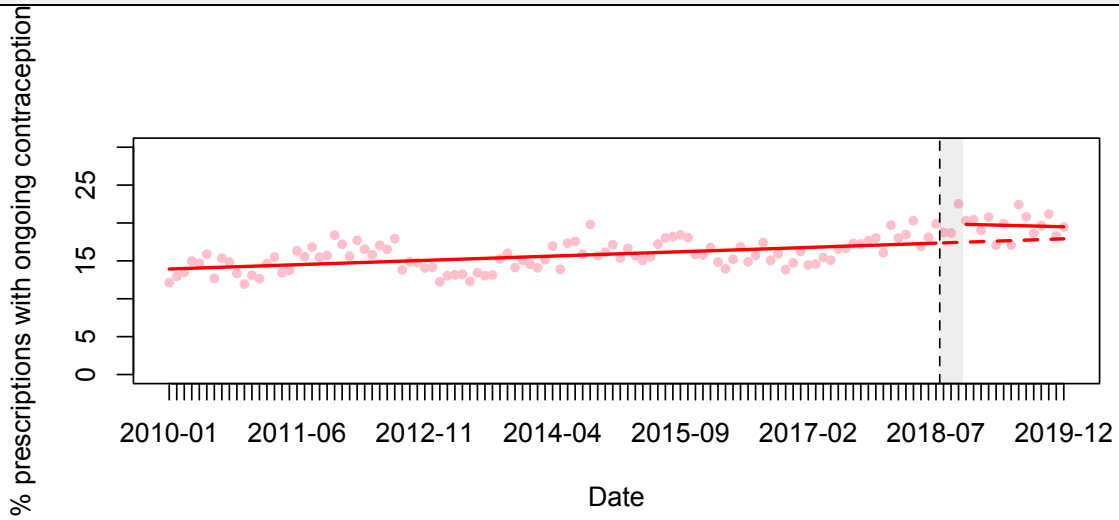
* The end of study period was 09.2019 for PHARMO.

d) ITS analysis plots of contraceptive coverage during valproate use across databases

Figure S.3.d-1. Change in trend in proportion of compliant valproate prescriptions/dispensings with a contraceptive coverage in participating centres over the study period, modelled by interrupted time series (ITS) analysis. The time of implementation of the 2018 risk minimisation measures for valproates is shown with a light grey bar (starts with a dashed black line), and the counterfactual trend (had the intervention not occurred) is shown with the dashed red line thereafter. Note that the end of study period differs per data source. There is no output produced for ARS Tuscany, as there was limited information on contraceptive use from this database. For DNR, the trend over time has been shown instead, as an ITS modelling was not possible due to limited time points after the 2018 intervention.



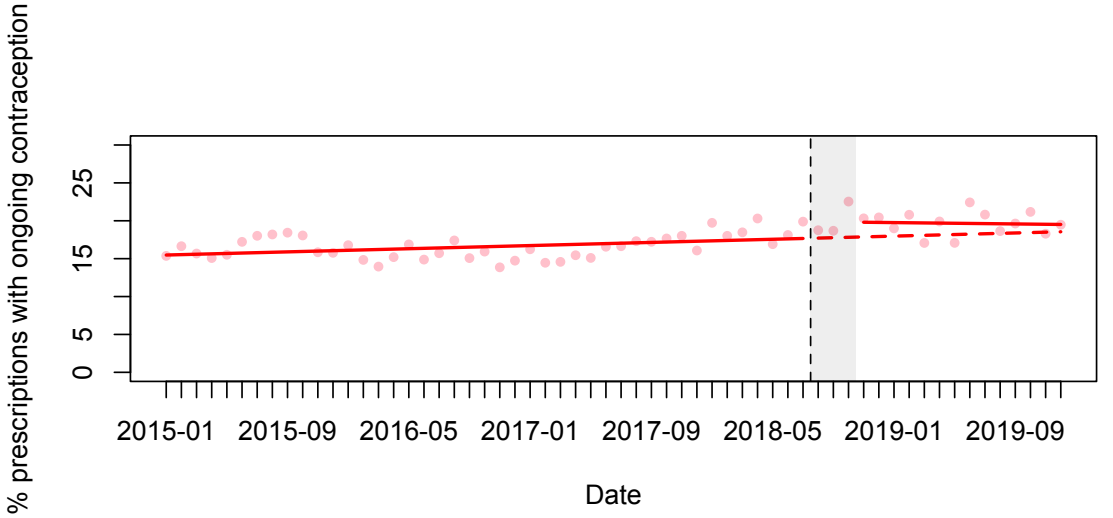
b. PHARMO, NL



Level change: 2.575 contraceptive coverage/100 valproate users, p=0.130

Trend change: -0.058 contraceptive coverage/100 valproate users, p=0.687

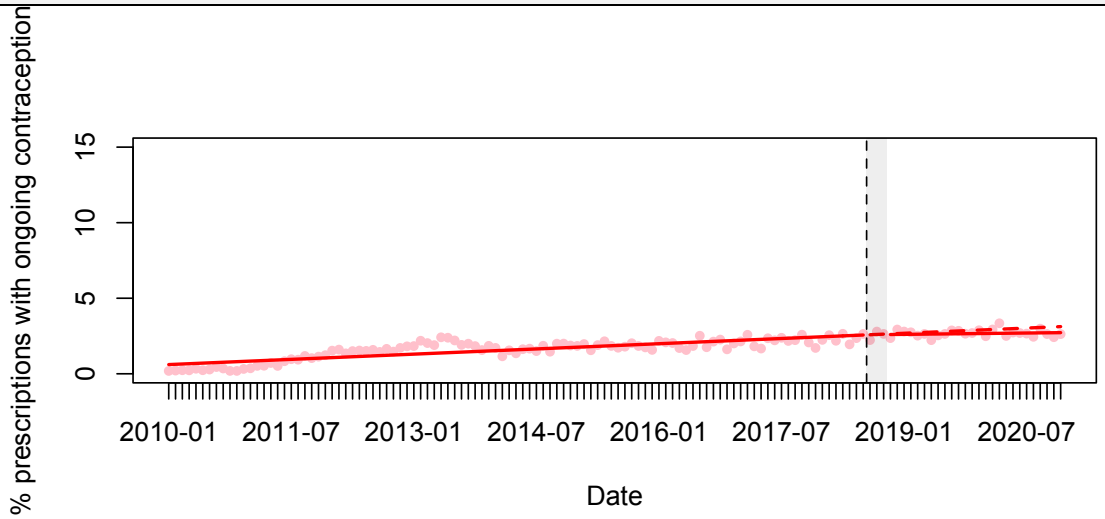
"Sensitivity analysis for the period 01.01.2015 until 31.12.2019"



Level change: 2.231 contraceptive coverage/100 valproate users, p=0.142

Trend change: -0.074 contraceptive coverage/100 valproate users, p= 0.552

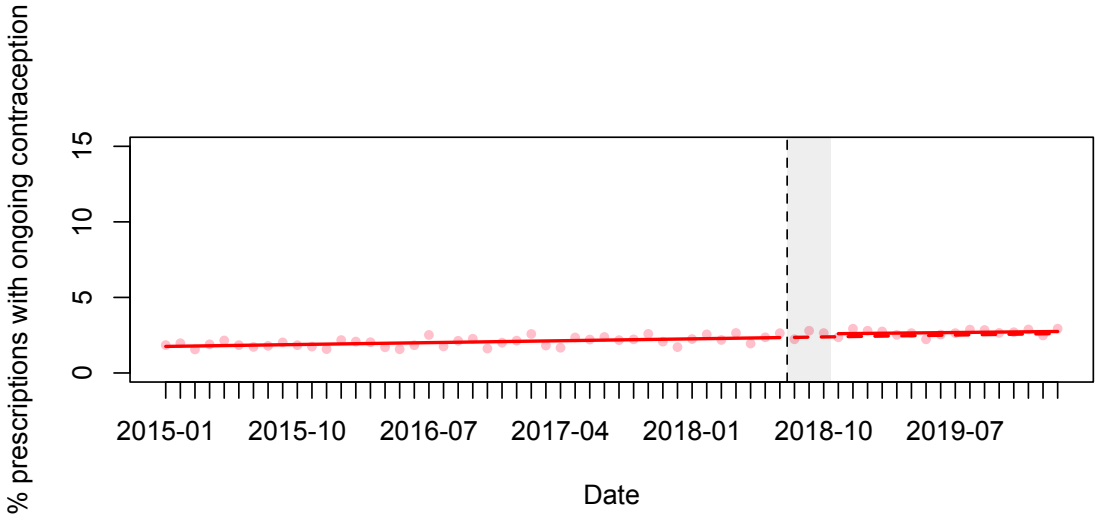
c. BIFAP, ES



Level change: 0.014 contraceptive coverage/100 valproate users, p=0.966

Trend change: -0.014 contraceptive coverage/100 valproate users, p=0.384

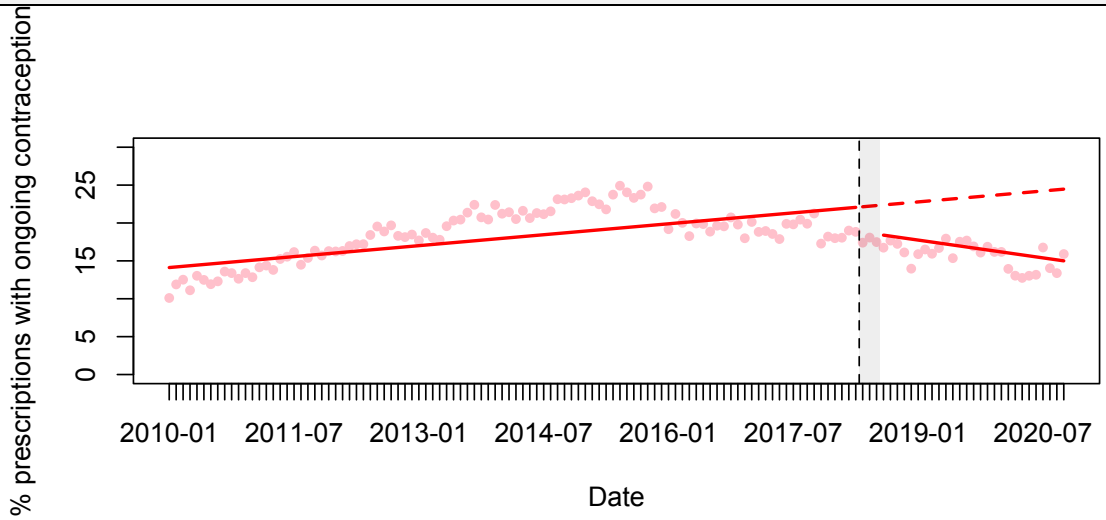
"Sensitivity analysis for the period 01.01.2015 until 29.02.2020"



Level change: 0.221 contraceptive coverage/100 valproate users, p=0.192

Trend change: -0.004 contraceptive coverage/100 valproate users, p=0.735

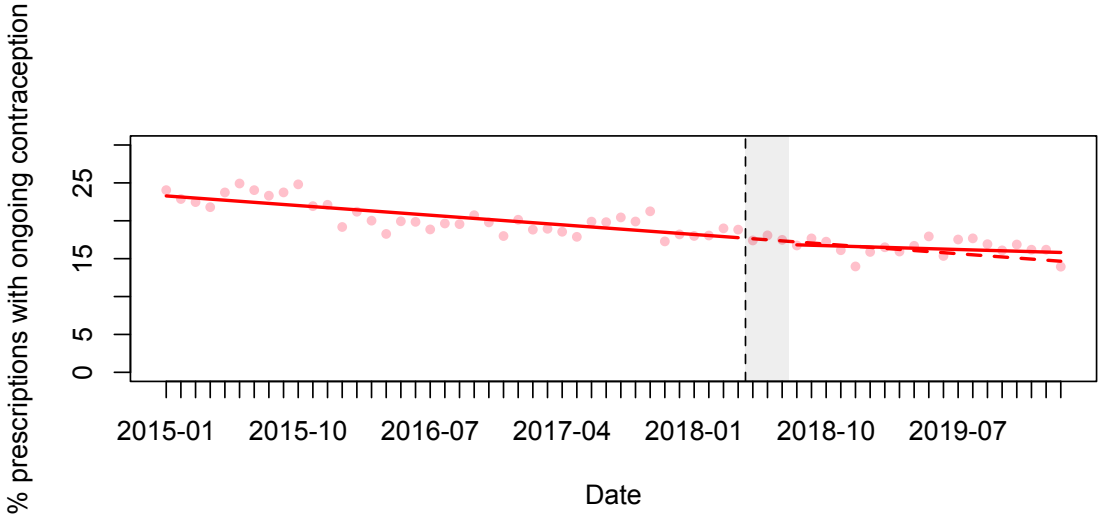
d. CPRD, UK



Level change: -3.141 contraceptive coverage/100 valproate users, p=0.185

Trend change: -0.211 contraceptive coverage/100 valproate users, p=0.125

"Sensitivity analysis for the period 01.01.2015 until 29.02.2020"



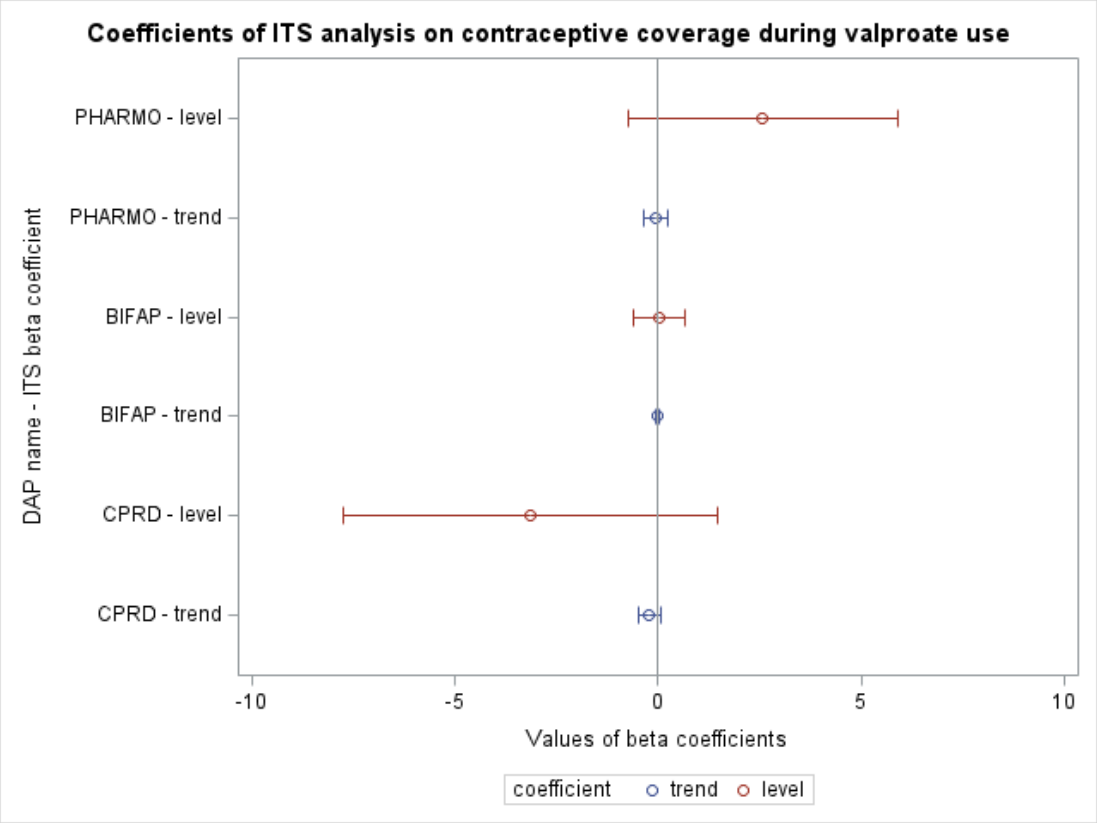
Level change: -0.719 contraceptive coverage/100 valproate users, p=0.555

Trend change: 0.085 contraceptive coverage/100 valproate users, p=0.286

* ITSA not conducted due to limited post-intervention data available.

Figure S.3.d-2. Forest plots showing the level and trend beta coefficients of the interrupted time series analyses of contraceptive coverage during valproate use after the implementation of the 2018 risk minimisation measures across centres, in the: a) main, and b) sensitivity analysis.

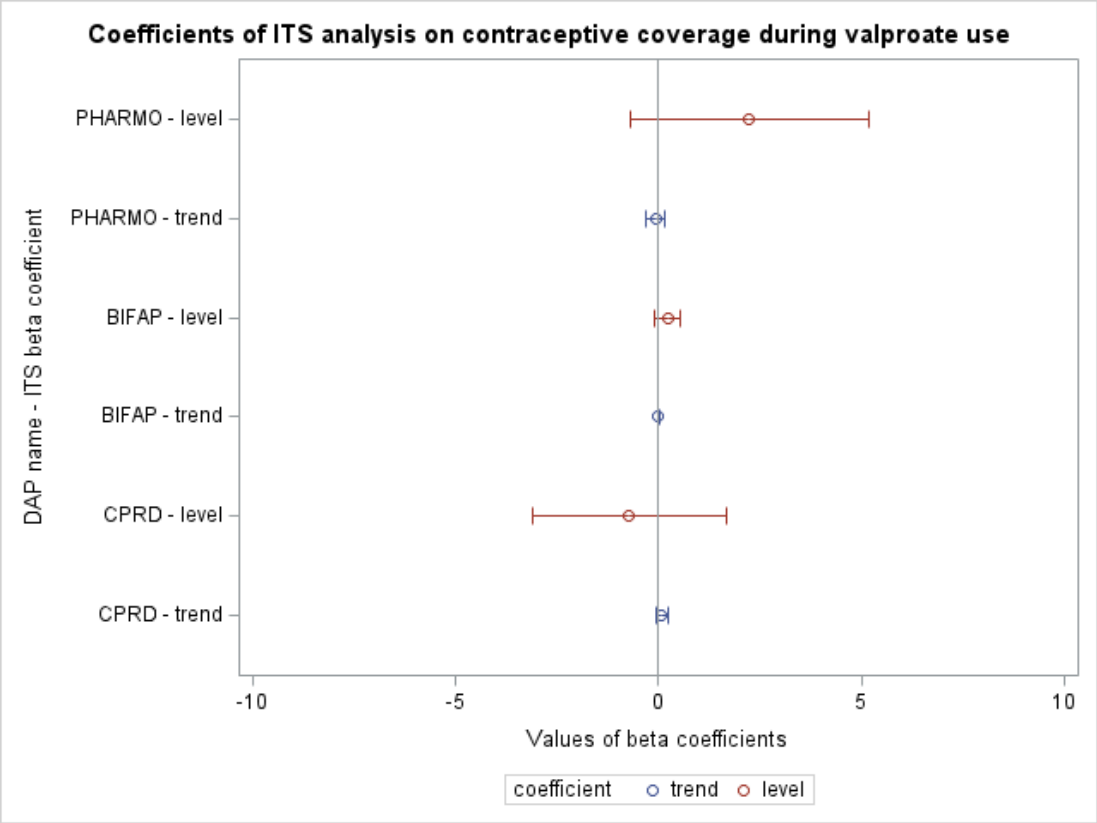
a) Main analysis (01.2010-12.2020)*



Abbreviations, DAP: Data Access Partner, ITS: interrupted time series.

* The end of study period was 09.2019 for PHARMO and 10.2020 for CPRD.

b) Sensitivity analysis (01.2015-02.2020)*



Abbreviations, DAP: Data Access Partner, ITS: interrupted time series.

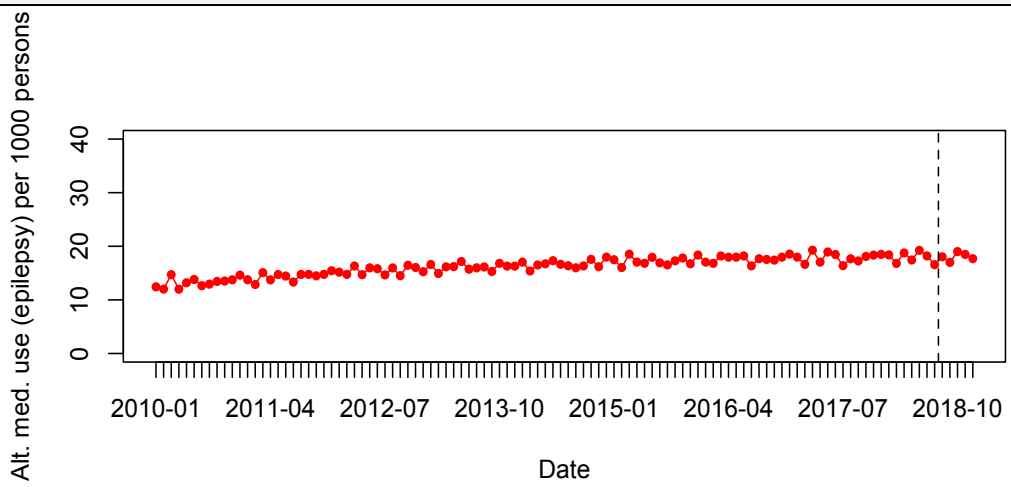
* The end of study period was 09.2019 for PHARMO.

e) Trends in alternative medication use per indication across databases

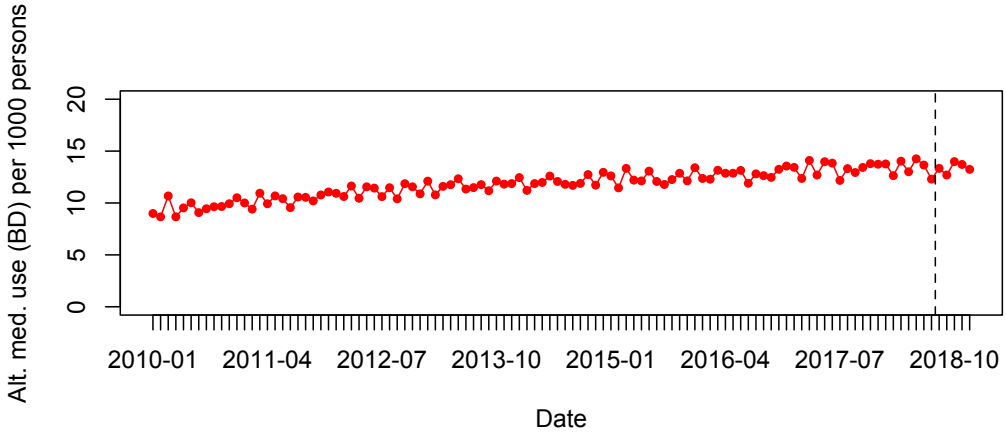
Figure S.3.d-1 Monthly rates of prescribing/dispensing of alternative medications to valproates in the overall study population per indication across databases. The time of implementation of the 2018 risk minimisation measures for valproates is shown with a black dashed line. Note that the end of study period differs per data source.

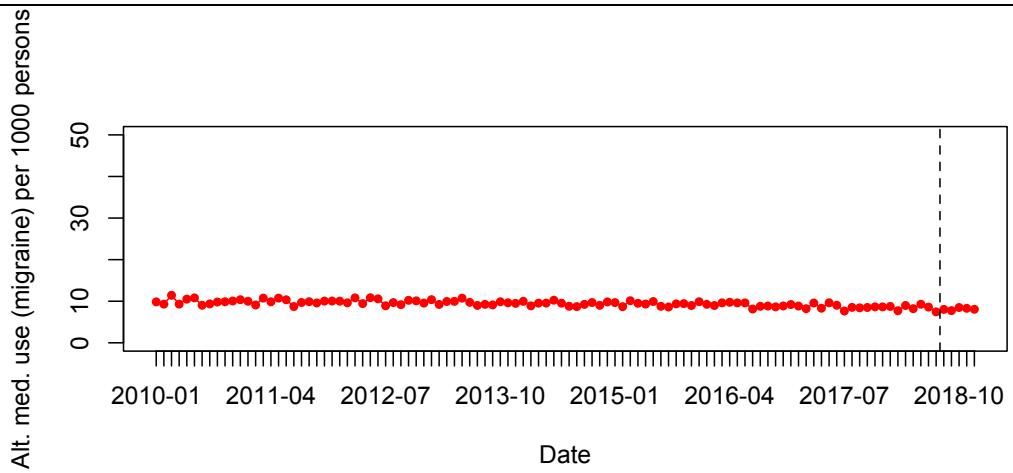
a. DNR, DK

Epilepsy



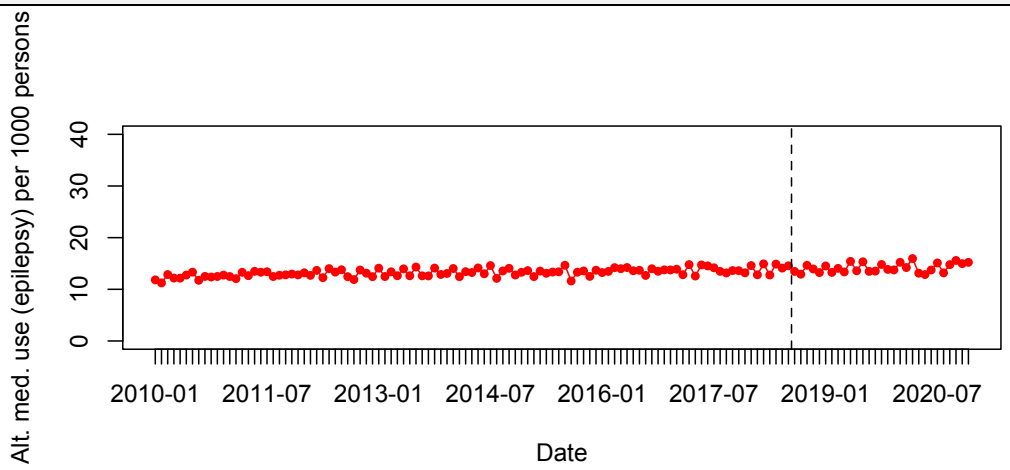
Bipolar dis.



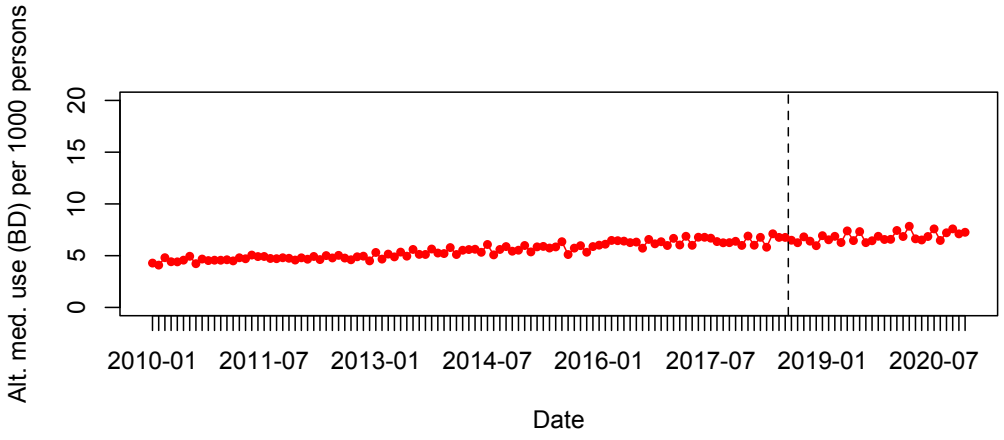
Migraine	 Alt. med. use (migraine) per 1000 persons 0 10 30 50 2010-01 2011-04 2012-07 2013-10 2015-01 2016-04 2017-07 2018-10 Date

b. ARS Tuscany, IT

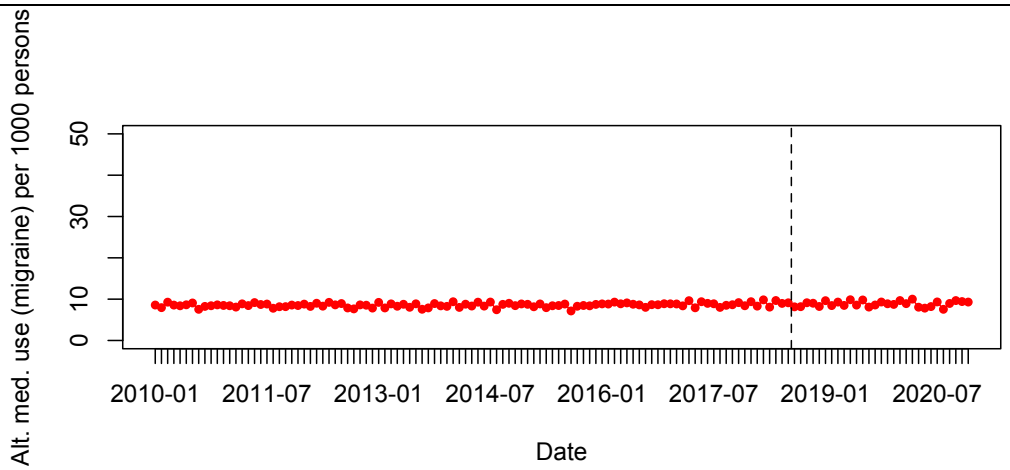
Epilepsy



Bipolar dis.

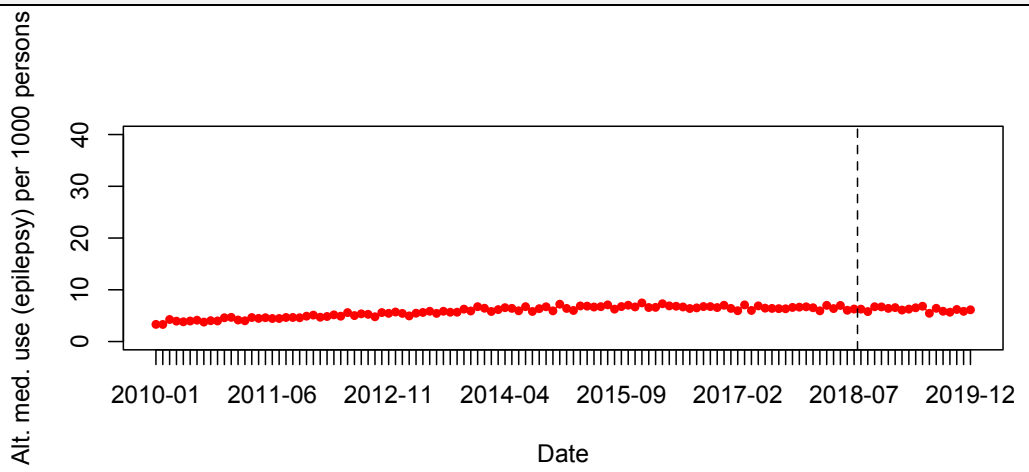


Migraine

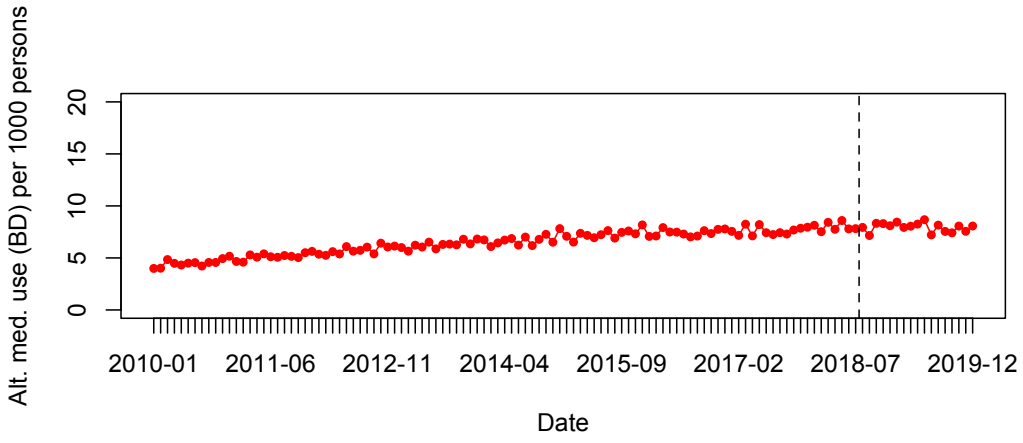


c. PHARMO, NL

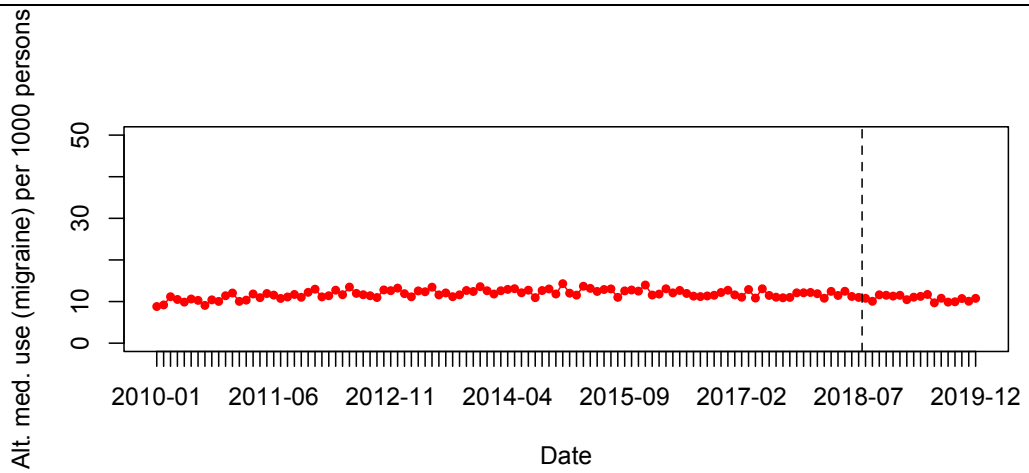
Epilepsy



Bipolar dis.

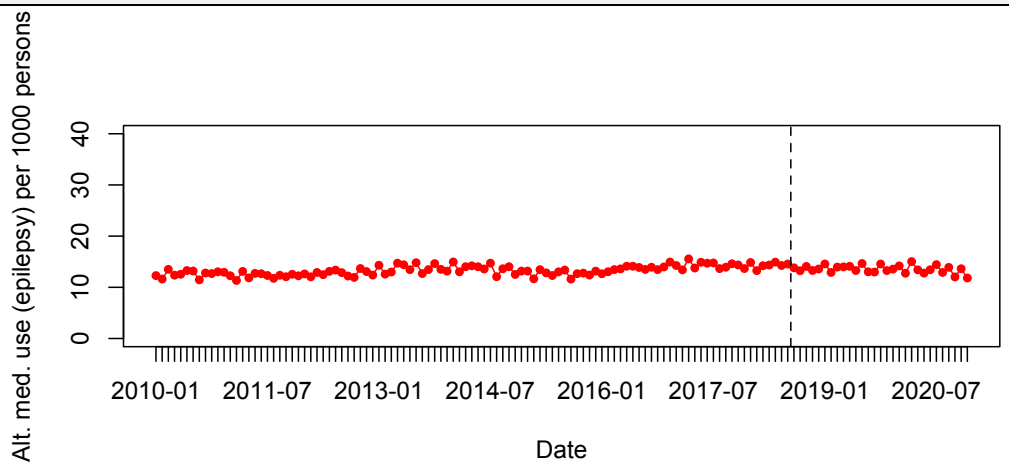


Migraine

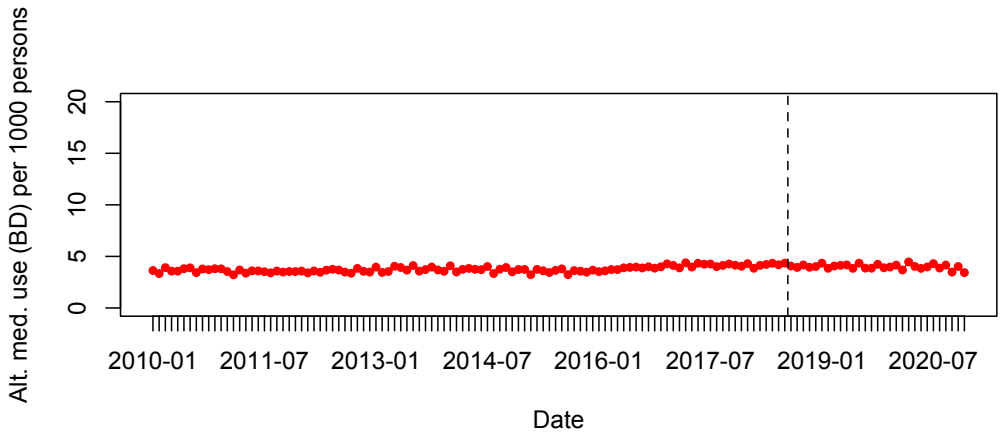


d. BIFAP, ES

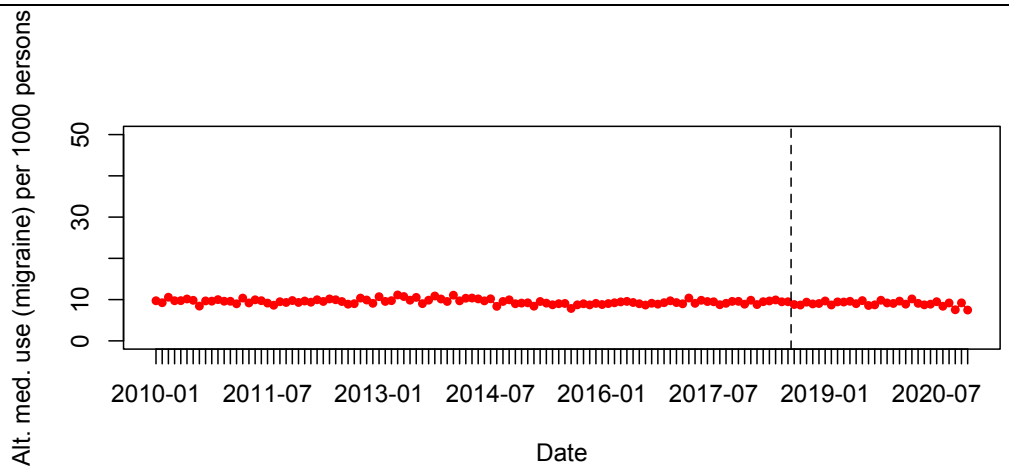
Epilepsy



Bipolar dis.

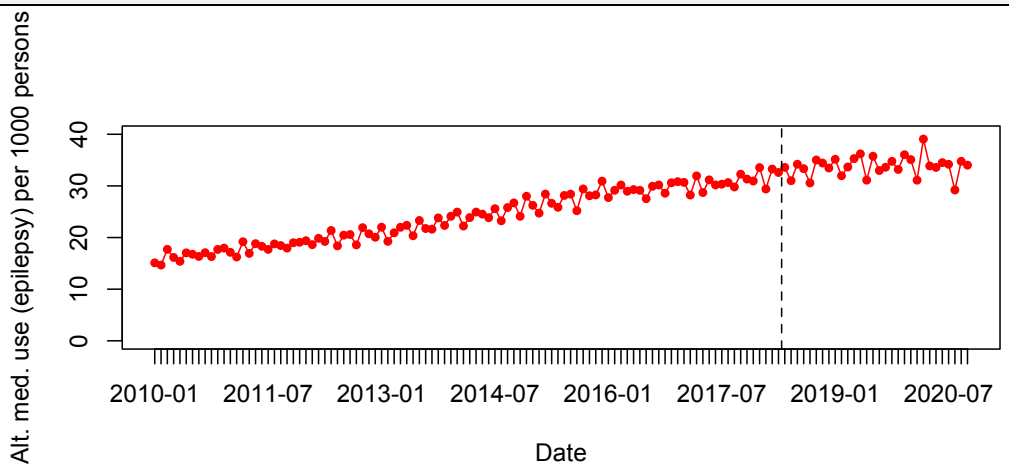


Migraine

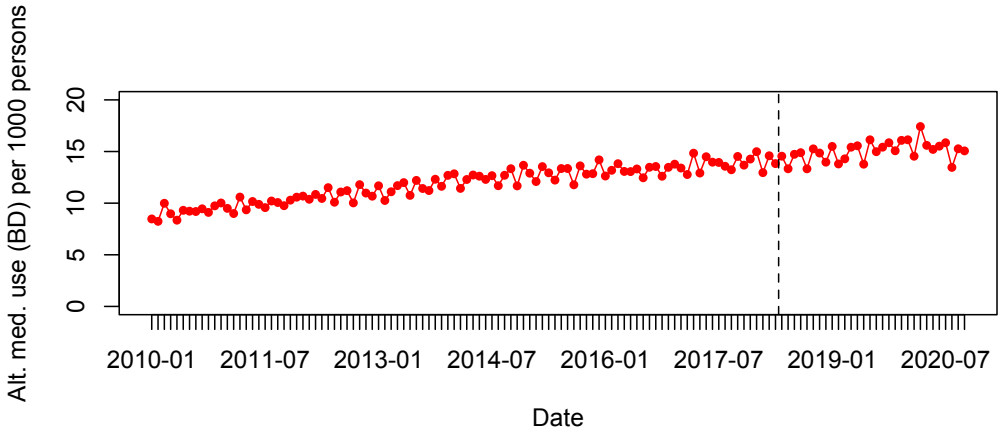


e. CPRD, UK

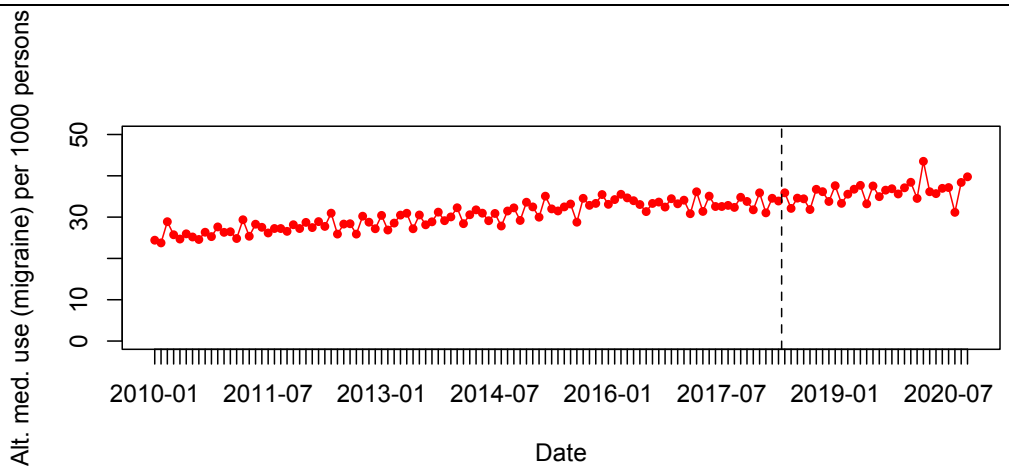
Epilepsy



Bipolar dis.



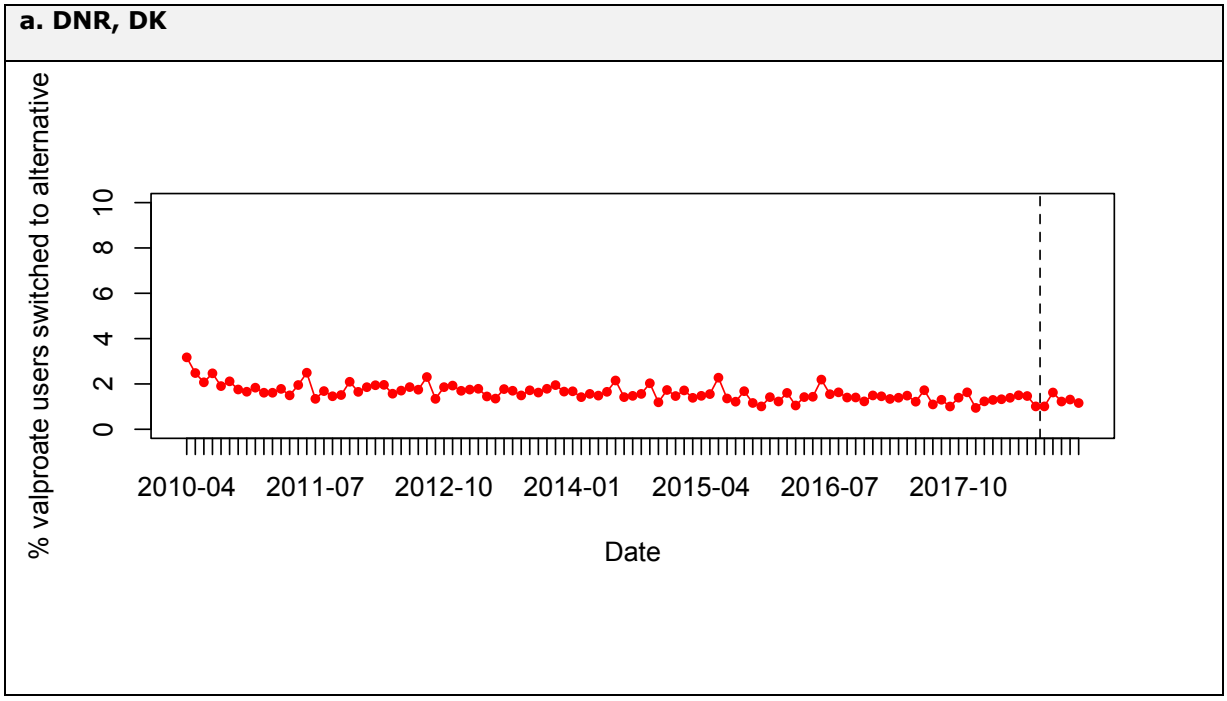
Migraine



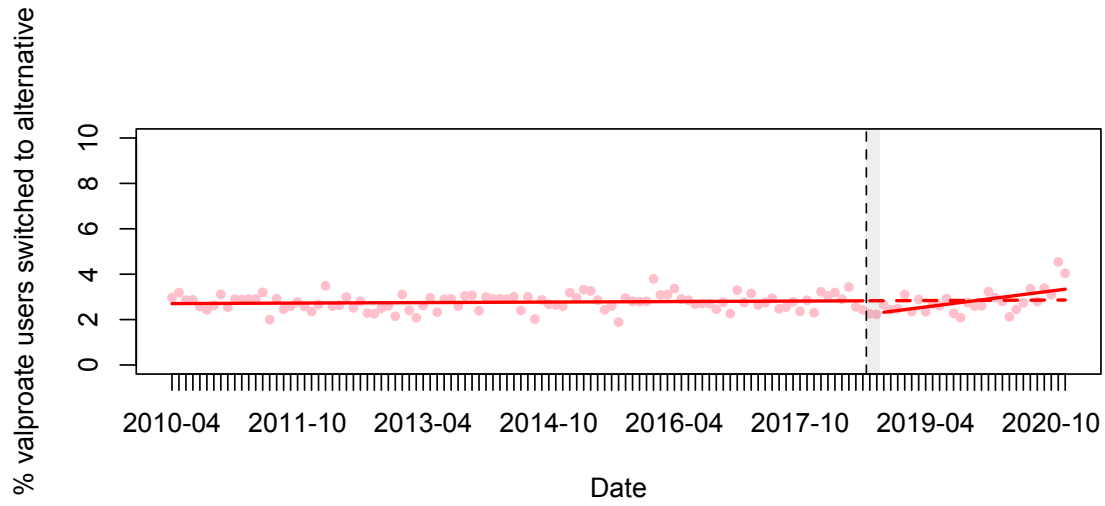
Abbreviations, Alt. med.: alternative medication.

f) ITS analysis plots of switching from valproate to alternative medications across databases

Figure S.3.d-1 Change in trend in rate of switchers from valproates to alternative medications from the participating centres over the study period, modelled by interrupted time series (ITS) analysis. The time of implementation of the 2018 risk minimisation measures for valproates is shown with a light grey bar (starts with a dashed black line), and the counterfactual trend (had the intervention not occurred) is shown with the dashed red line thereafter. Note that the end of study period differs per data source. ITS analysis was not possible in PHARMO and CPRD because the counts of switchers after 2018 were too small (often <5) to fit a stable model. For DNR, there were too few data points after the 2018 RMMs to conduct an ITS analysis. For these data sources, the trend over time has been shown instead.



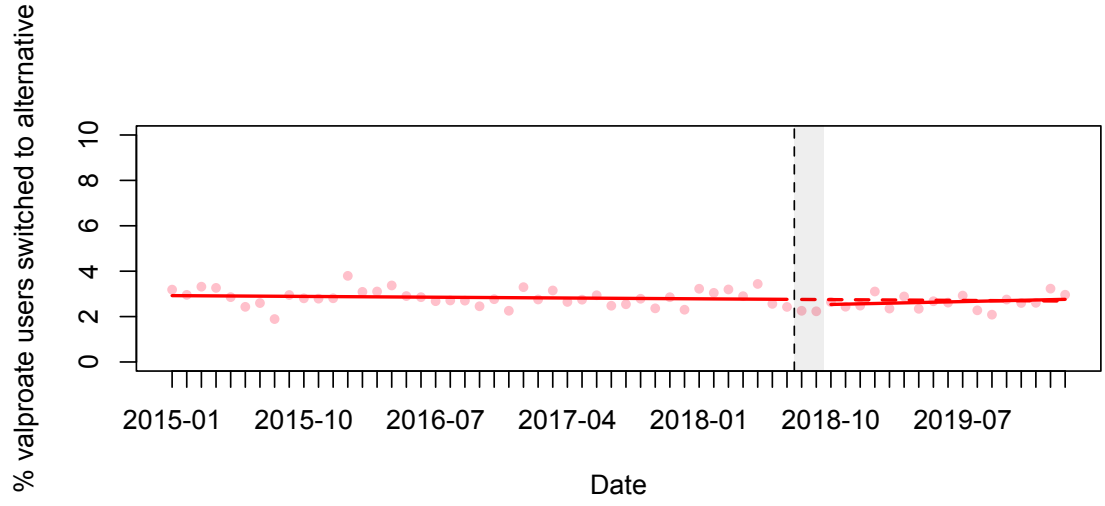
b. ARS Tuscany, IT



Level change: -0.623 switchers to alternative medications/100 valproate users, p=0.002*

Trend change: 0.038 switchers to alternative medications/100 valproate users, p<0.001*

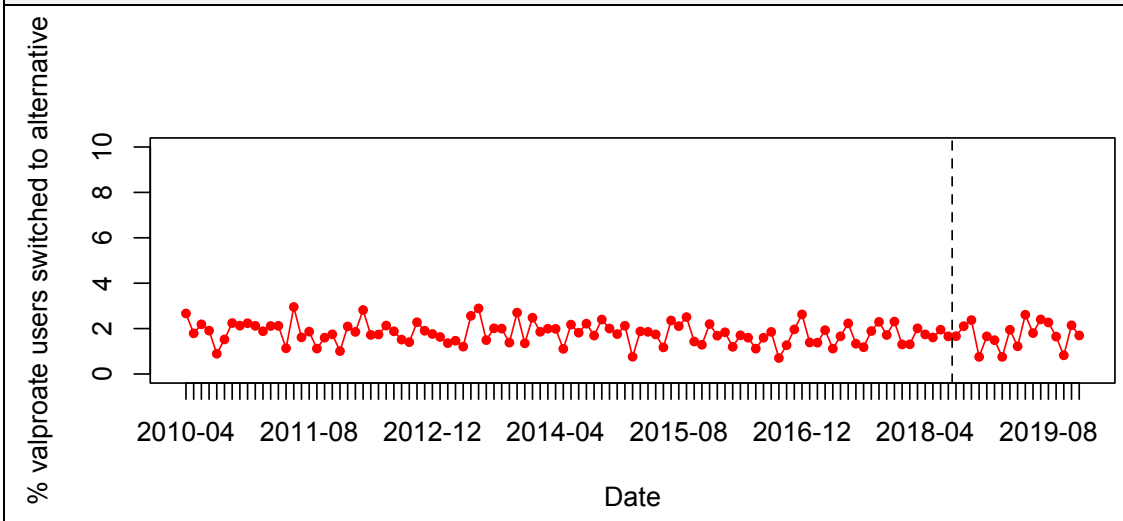
"Sensitivity analysis for the period 01.01.2015 until 29.02.2020"



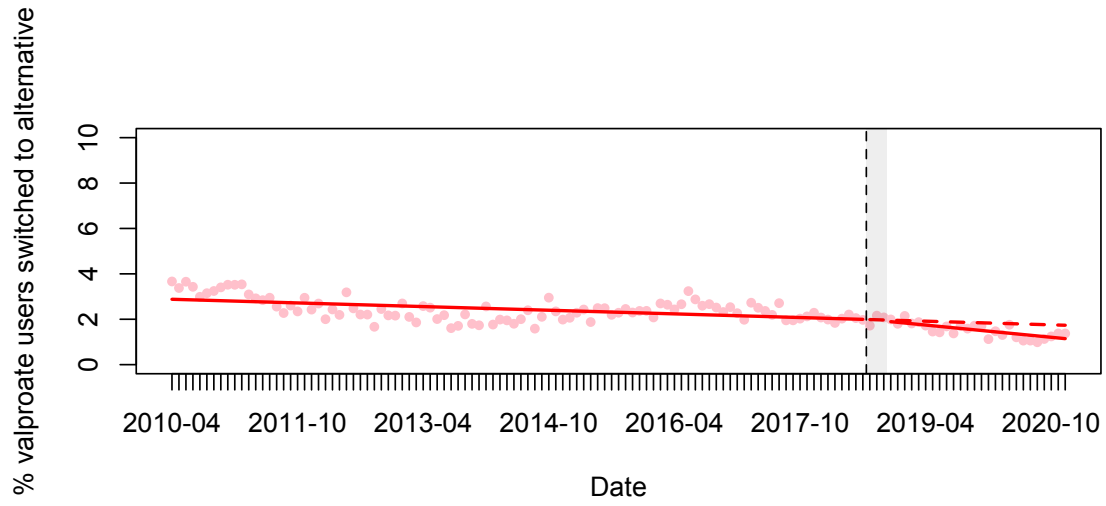
Level change: -0.267 switchers to alternative medications/100 valproate users, p=0.295

Trend change: 0.018 switchers to alternative medications/100 valproate users, p=0.355

c. PHARMO, NL



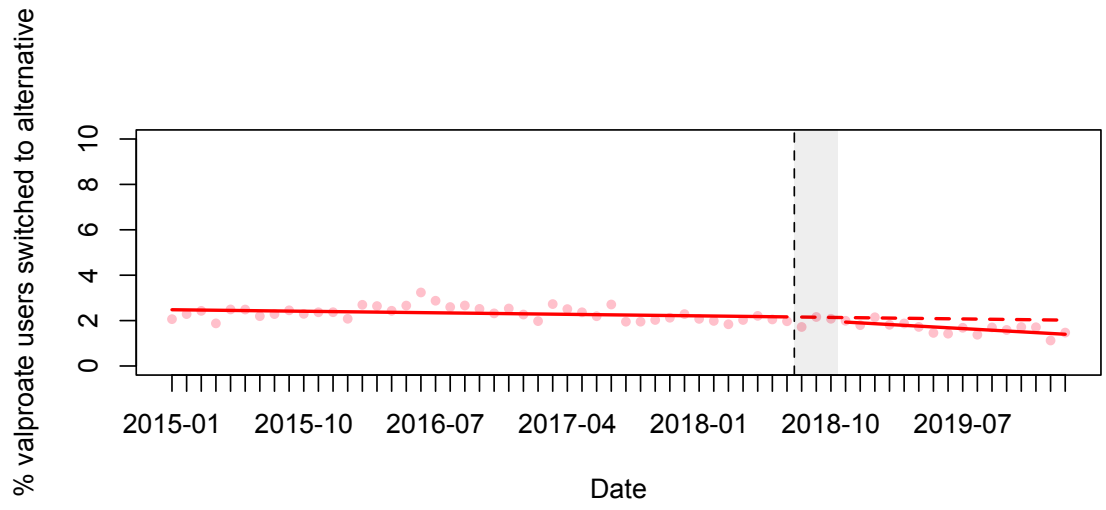
d. BIFAP, ES



Level change: 0.018 switchers to alternative medications/100 valproate users, p=0.957

Trend change: -0.021 switchers to alternative medications/100 valproate users, p=0.227

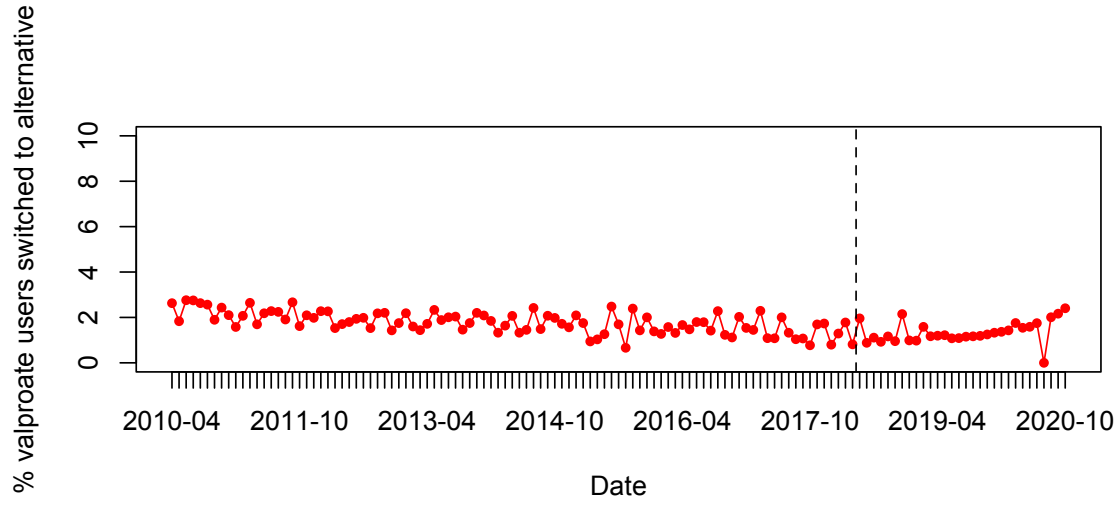
"Sensitivity analysis for the period 01.01.2015 until 29.02.2020"



Level change: -0.086 switchers to alternative medications/100 valproate users, *p*=0.740

Trend change: -0.028 switchers to alternative medications/100 valproate users, *p*=0.146

e. CPRD, UK



g) Other studied exposure or outcome measures: indications of valproate use, reasons for discontinuation, pregnancy testing and contraceptive coverage in 90-days before

Some more exposure and outcome measures were originally intended to be included in this study, in order to evaluate the implementation of the 2018 RMMs for valproate from various perspectives. However, it was found out later that these extra measures cannot be ascertained fully from our data sources, yielding to incomplete or unreliable results in these areas. Therefore, we only briefly mention them here, as the following:

- **Indications of valproate use** (i.e., epilepsy, bipolar disorder or migraine prophylaxis) were documented from ICD/Read/ICPC/SNOMED-coded diagnosis (3-months between diagnosis date and valproate treatment date) in the databases. In the absence of an indication in the 3-month prior window, earlier records were examined to identify the likely indication. If the likely indication could not be determined, the indication was labelled as 'unknown'. Subjects with more than one of the indications of interest were reported separately. We found that 'unknown' constituted the majority of indications for prevalent users in ARS Tuscany (monthly range of 70-94%), BIFAP (67-94%) and PHARMO (81-97%), while in CPRD epilepsy was the leading indication since 06.2011 onwards (monthly range of 25-56%).
- **Reasons for discontinuation** were categorised as pregnancy wish, pregnancy, adverse drug reaction (ADR), multiple or unknown during the 3 months preceding discontinuation. Pregnancy wish was coded if a female was prescribed folic acid during a treatment episode, which ends with discontinuation, or 90 days after. Pregnancy was assumed as the reason for discontinuation if a pregnancy start was observed during a treatment episode which ends with discontinuation. Nausea and tremor were considered as *very common* ADRs (>1/10) based on the SmPC for valproate, if there was a recorded event during an exposure period which ends with discontinuation. All discontinuations not meeting criteria specified above were classified as 'unknown'. The numbers of discontinuers of valproates were stratified by reasons for discontinuation. We found that 'unknown' was the leading reason for discontinuation across databases. We think, misclassification of some outcomes such as ADRs might have happened, as mild cases of nausea and tremor might not be recorded. Lack of free-text information available from the different sources was another pitfall, leaving us reliant on records of products and diagnoses. This has mainly limited our ability to determine the reasons for valproate discontinuation.
- **Pregnancy testing** was defined as any record of a pregnancy test, prescribed or witnessed. Pregnancy testing was defined as prior to initiation of treatment if a code for testing was recorded up to 90 days prior to a valproate record. Testing during valproate use was defined as a test code recorded within 90 days following a valproate record. The information on pregnancy testing was not available from most of our included databases (with some limited information available only in BIFAP). Only very few valproate prescriptions/dispensings were accompanied by a record of a pregnancy test in the 90 days before or 90 days after, with monthly counts always <5. Due to this limitation, modelling of any trend change in proportion of valproate prescriptions/dispensings with an adherent pregnancy test was not possible. Lack of data on over-the-counter pregnancy testing, which are not captured in any of the databases, might have resulted in an underestimation of the proportion of compliant valproate use with a pregnancy testing.
- **Contraceptive coverage in 90-days before** a valproate treatment episode was studied as another measure of compliance of prescribers with 2018 RMMs for valproates. This was analysed with the monthly proportion of valproate use with an episode of contraception in 90-days before, per each DAP. There was a monthly range of 11-17% (DNR), 8-22% (PHARMO), 0.2-6.0% (BIFAP), and 11-23% (CPRD) of valproate prescriptions/dispensings with a contraceptive prescription in the 90-days prior. We could retrieve limited information

on contraceptive use during (parts of) the study period from ARS Tuscany. Also as mentioned before, lack of data on over-the-counter contraceptives, not captured in any of the databases, might have resulted in an underestimation of the proportion of compliant valproate use with a contraceptive coverage in 90-days before.