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ORIGINAL RESEARCH ARTICLE

Use of Acitretin Among Girls and Women of Childbearing Age and Occurrence of Acitretin-Exposed Pregnancies in Germany

Jonas Reinold[1] · Bianca Kollhorst[2] · Hellen L. Temme[3,4] · Nadine Wentzell[1] · Ulrike Haug[1,5]

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Abstract

Background and Objective Acitretin has long-lasting teratogenic properties. Therefore, pregnancies must be avoided during and within 3 years after acitretin treatment. We aimed to describe (i) acitretin use in women of childbearing age in Germany, (ii) the occurrence of acitretin-exposed pregnancies, and (iii) malformations among children exposed in utero.

Methods Using 2004–2019 data from the German Pharmacoepidemiological Research Database (GePaRD—claims data from ~20% of the German population), we determined annual age-standardized prevalence of acitretin use among girls and women aged 13–49 years. In longitudinal analyses, we estimated the number of exposed pregnancies by assessing whether the exposure window assigned to the last dispensation before pregnancy (days covered by dispensation plus 3 years) overlapped the onset of pregnancy or whether there was a dispensation in the first eight weeks of pregnancy. Data of live-born children with in utero exposure to acitretin were reviewed to assess the presence of congenital malformations.

Results The age-standardized prevalence of acitretin use per 1000 girls and women was 0.04 in 2019. We identified 35 acitretin-exposed pregnancies; 94.3% of these pregnancies were classified as exposed because they occurred within 3 years after stopping acitretin treatment. Among 18 live-born children linked to their mother, four children (22.2%) had congenital malformations (three children with a major malformation).

Conclusions We observed 35 acitretin-exposed pregnancies mainly because treatment ended too late before pregnancy. Approximately one in five children born from these pregnancies had malformations, highlighting the importance of drawing more attention to the long-lasting teratogenicity of this drug.

Key Points

Between 2004 and 2019, a relevant number of pregnancies were identified that occurred too early after stopping treatment with acitretin.

One in five children born from acitretin-exposed pregnancies had malformations.

✉ Jonas Reinold
reinold@leibniz-bips.de

Bianca Kollhorst
kollhorst@leibniz-bips.de

Hellen L. Temme
hellen.temme@bnitm.de

Nadine Wentzell
wentzell@leibniz-bips.de

Ulrike Haug
haug@leibniz-bips.de

[1] Department of Clinical Epidemiology, Leibniz Institute for Prevention Research and Epidemiology–BIPS, Achterstraße 30, 28359 Bremen, Germany

[2] Department of Biometry and Data Management, Leibniz Institute for Prevention Research and Epidemiology–BIPS, Achterstraße 30, 28359 Bremen, Germany

[3] Health Communication, Department of Implementation Research, Bernhard Nocht Institute for Tropical Medicine–BNITM, Bernhard-Nocht-Straße 74, 20359 Hamburg, Germany

[4] Institute for Planetary Health Behaviour, University of Erfurt–IPB, Nordhäuser Straße 63, 99089 Erfurt, Germany

[5] Faculty of Human and Health Sciences, University of Bremen, Grazer Straße 2, 28359 Bremen, Germany

1 Introduction

The synthetic retinoid acitretin is used for the treatment of severe forms of keratinization disorders, mainly pustular and erythrodermic psoriasis but also palmoplantar keratodermas, ichthyosis, Darier's disease, keratosis pilaris and lichen planus [1]. As psoriasis incidence peaks around the age of 30–39 years [2], women of childbearing age are potentially exposed to acitretin. Similar to other retinoids, acitretin is highly teratogenic. Animal models showed craniofacial dysmorphogenesis resulting in cleft palate and interferences with limb bud development leading to long bone defects [3]. In two case reports, in utero exposure to acitretin was associated with craniofacial anomalies as well as anomalies of the ears, limbs and heart [4, 5]. Moreover, among 75 pregnancies occurring during or after acitretin treatment, reported to the marketing authorization holder of acitretin, malformations were observed in 12% of live-born children and in 5% of induced abortions [6]. A metabolite of acitretin, etretinate, has a long retention duration in adipose tissues and is also highly teratogenic [7]. Therefore, acitretin is not only absolutely contraindicated during pregnancy but there is also a vulnerable period after discontinuing acitretin [1].

Given the high proportion of unintended pregnancies [8], EU [9] and German guidelines [10, 11] recommend that acitretin is only prescribed to girls and women of childbearing age if alternative therapies were not sufficiently effective. Furthermore, patients must use contraception in the month before the start and until 3 years after the end of treatment. Additionally, pregnancy tests must be performed before the first prescription, monthly during treatment and at intervals of 1–3 months during the 3 years after the end of treatment.

Due to the teratogenic properties of acitretin, it is important to monitor its use in girls and women of childbearing age as well as the occurrence of pregnancies exposed to this drug. However, there is a lack of population-based drug utilization studies on this topic. The most recent information was provided by a French study published in 2015, reporting 27 pregnancies per 1000 person-years among acitretin-exposed girls and women aged 15–49 years. The study also reported generally poor compliance with the recommendations of the pregnancy prevention program [12]. To the best of our knowledge, there is no study from Germany investigating utilization of acitretin in women of childbearing age or during pregnancy.

We therefore aimed to (i) describe the utilization of acitretin in girls and women of childbearing age in Germany between 2004 and 2019, (ii) describe the occurrence of pregnancies in women using acitretin, also considering the 3 years before pregnancy, and (iii) describe congenital malformations among children exposed to acitretin in early pregnancy (not to be mistaken with estimating causal effects).

2 Methods

2.1 Data Source

This study used the German Pharmacoepidemiological Research Database (GePaRD). GePaRD is based on claims data from four German statutory health insurance providers and currently includes information on approximately 25 million individuals who have been insured with one of the participating providers since 2004 or later. In GePaRD, information on drug dispensations, outpatient (i.e., from general practitioners and specialists) as well as inpatient services and diagnoses and demographic information are included. For each data year, there is information on approximately 20% of the general population and all geographical regions of Germany are represented [13].

In studies based on GePaRD, the Anatomical Therapeutic Chemical (ATC) code is used to identify drug dispensations in the outpatient setting. Exposure to acitretin was identified based on the ATC code D05BB02. Diagnoses in GePaRD are coded according to the International Classification of Diseases 10th revision, German modification (ICD-10-GM). Algorithms have been developed in GePaRD to identify and classify pregnancy outcomes [14, 15] and to estimate the beginning of pregnancy [16]. In addition, we used an algorithm to link mothers with their newborns, which enabled us to follow up the health status of live born children. This linkage leverages the fact that in Germany, children are usually co-insured with one of their parents and that there is a family ID that can be used to link family members insured via the main insurant [17].

2.2 Study Design and Study Population

2.2.1 Prevalence of Use Among Girls and Women of Childbearing Age

To assess the prevalence of use of acitretin over time, we conducted annual cross-sectional analyses from 2004 to 2019. Per calendar year, all girls and women were included in the numerator if they fulfilled the following criteria in the respective year: (i) at least one dispensation of acitretin, (ii) aged between 13 and 49 years, and (iii) actively insured on June 30 of that year. The denominator for each respective year included all girls and women aged between 13 and 49 years and who were actively insured on June 30 of that year.

2.2.2 Identification of Exposed Pregnancies

Using the algorithm for pregnancy outcomes, pregnancies ending between 2004 and 2019 and occurring among girls and women aged 13–49 years were identified at pregnancy

onset. A pregnancy was considered to be exposed to acitretin (i) if the exposure window of the last acitretin dispensation before pregnancy overlapped with the first day of pregnancy or (ii) if there was an acitretin dispensation during the first eight weeks of pregnancy. The exposure window was defined as the acitretin dispensation date plus the number of defined daily doses (DDDs) in the package plus an additional extension period of 3 years to account for the long-lasting teratogenic properties of acitretin [10]. For exposure assessment, mothers had to be continuously insured for at least the number of days covered by the largest available package of acitretin plus the additional extension period before pregnancy onset. In claims data, pregnancies for which no outcome is recorded (e.g., spontaneous abortions not requiring medical treatment, induced abortions without medical indication), would remain undetected, if only the outcome algorithm was applied. Therefore, we searched for these types of incomplete pregnancies. To be eligible for this category, there had to be at least one code indicating an expected delivery date as well as an indicator of pregnancy (e.g., a pregnancy-related examination) within a plausible time interval after the onset of pregnancy. We assessed the acitretin-exposure status of these pregnancies as described above. Pregnancies that were still ongoing at the end of observation were included in the analysis regarding the number of exposed pregnancies but not in the analysis on the distribution of pregnancy outcomes as the information on their outcomes was not available at that time.

2.2.3 Exploration of Potential Malformations Among Exposed Children

In order to explore the occurrence of potential congenital malformations among acitretin-exposed live born children, we applied the algorithm linking mothers with their children. Once the data on the mother and the child were linked, we followed up the child based on its claims data. Specifically, we identified linked children with any malformation code (ICD-10-GM Q00-Q99) recorded up to 1 year after birth. The presence of malformations in these children was verified in a patient profile review considering all information (codes for diagnoses, procedures and services, drug dispensation) available for them in GePaRD until the end of their observation period (end of insurance, death, or end of study period, i.e., December 31, 2020). Two independent reviewers conducted the patient profile review. Diagnoses of potential malformations were evaluated in the context of the patients' history (e.g., gestational age at birth or chromosomal abnormalities as potential alternative explanations for malformations) and considered information supporting or confirming the presence of malformations (e.g., whether or not it was coded in the inpatient setting, whether there were repeated diagnoses or specific treatments/surveillance examinations). In the case of disagreement between the reviewers one-third reviewer facilitated a consensus. The primary focus was on "major" malformations as categorized by the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT). However, malformations classified as "minor" according to EUROCAT were also included if treatment (e.g., surgical) or other information (e.g., physical impairment, malformation-related physician contacts) confirmed their presence.

2.3 Data Analysis

Age-specific and age-standardized prevalence for each year was determined for the cross-sectional analyses, using the German female population on December 31, 2019 as reference. In order to describe the prescribing physicians, all acitretin dispensations in the respective year among included girls and women were considered and the specialty of the prescribing physician was assigned based on the individual physician number [18].

We determined the number of pregnancies classified as exposed overall and described the pregnancy outcomes. Categorical variables were expressed as frequency counts (percentages). All statistical analyses were conducted using the software SAS version 9.4.

3 Results

3.1 Prevalence of Use Among Girls and Women of Childbearing Age

Overall, there were 1773 girls and women of childbearing age with at least one prescription of acitretin in GePaRD between 2004 and 2019. Across all years, 55%–75% of users were aged 41–49 years (Table S1). The age-standardized prevalence of acitretin use per 1000 girls and women was 0.06 in 2004 and 2006, 0.05 in most years between 2007 and 2017 and 0.04 in 2018 and 2019. The prevalence of acitretin use was highest in age group 41–49 years (≥ 0.1 per 1000 across years), followed by age group 31–40 years (0.03–0.06 per 1000 across years), while it was ≤ 0.03 per 1000 in age groups 21–30 years and 13–20 years. Between 2004 and 2019, the prevalences of acitretin use tended to decrease in the two older age groups and remained stable in the younger age groups (Fig. 1).

A total of 9117 prescriptions of acitretin were dispensed to girls and women of childbearing age during the study period. Most of these prescriptions were issued by dermatologists (74.9%), and 10.5% were prescribed by general practitioners (Table 1).

3.2 Characterization of Exposed Pregnancies

Overall, we identified 35 pregnancies classified as exposed to acitretin (see "Sect. 2"). In two of these pregnancies, there was a dispensation of acitretin during the first eight weeks of pregnancy. The remaining were classified as exposed due to the extension of the exposure window that considers the delayed elimination: six of these pregnancies occurred during the first year, 13 pregnancies during the second year and 14 pregnancies during the third year after treatment cessation.

The distribution of pregnancy outcomes is shown in Table 2, excluding two pregnancies that were ongoing at the end of the observation period (i.e. for these pregnancies the outcome was not yet available). Of the 33 pregnancies, 20 pregnancies (60.6%) ended in a live birth, six pregnancies (18.2%) ended in an induced abortion, and two pregnancies (6.1%) ended in a spontaneous abortion. For five pregnancies (15.2%), no outcome was recorded. The pregnancy outcomes of the two pregnancies with a dispensation of acitretin during the first eight weeks of pregnancy were "induced abortion" and "no pregnancy outcome was recorded".

The data of mother and baby could be linked for 18 of the 20 live births (90%). Of the 18 linked children, four (22.2%) had congenital malformations (Fig. 2). Three of these children had one malformation: Two had malformations of the circulatory system and one had a malformation of the urinary system. One child had malformations of the circulatory and the urinary system. The beginning of pregnancies of the four children with malformations were either in the second ($n = 1$) or third year ($n = 3$) after the end of acitretin exposure. Three of the children had a malformation classified as "major" according to EUROCAT. One child had an atrial septal defect but as the follow-up data beyond the first year of life did not show cardiology visits or other procedures indicating monitoring (i.e. such codes were only recorded in the first year of life), it was assumed to be the subtype of atrial septal defect classified as minor according to EUROCAT (ICD-10: Q21.11).

Table 1 Total number of prescriptions of acitretin dispensed to girls and women aged 13–49 years during the study period (2004–2019) and distribution according to the specialty of the prescribing physician

Specialty of the prescribing physician	Number of dispensations of acitretin ($N = 9117$)
Dermatologist, *n* (%)	6825 (74.9%)
General practitioner, *n* (%)	953 (10.5%)
Specialist for internal medicine, *n* (%)	154 (1.7%)
Other specialties, *n* (%)	579 (6.4%)
Assessment of specialty not possible, *n* (%)	606 (6.6%)

4 Discussion

In this population-based study covering 20% of the German population, we observed 35 pregnancies exposed to acitretin during the critical time window of pregnancy between 2004 to 2019. The majority of these pregnancies (94.3%) occurred within 3 years after discontinuing acitretin treatment, mostly during the second or third year after treatment cessation.

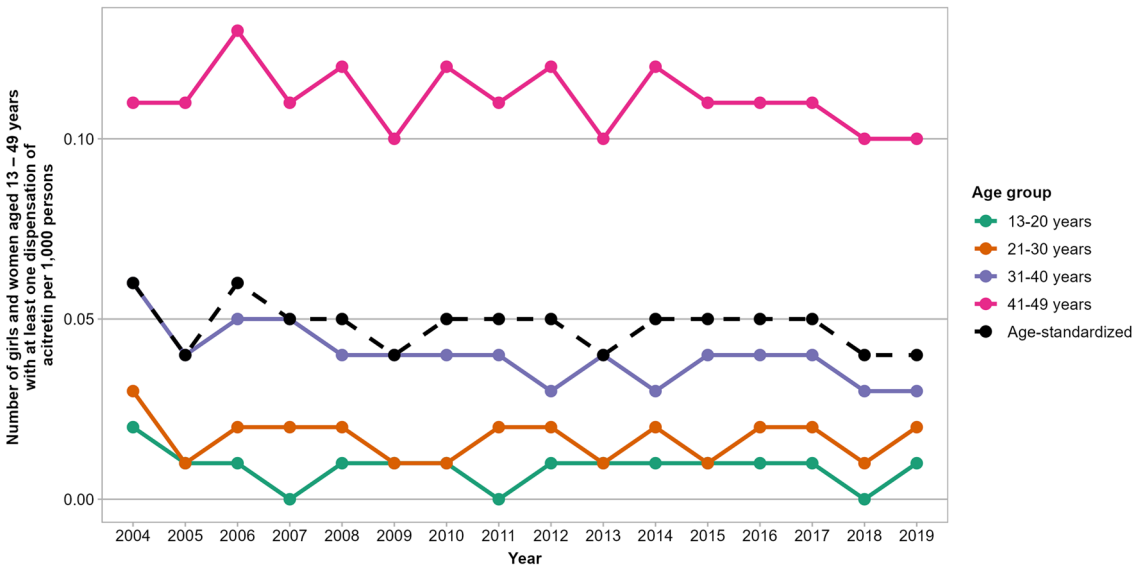

Fig. 1 Age-specific and age-standardized prevalence of acitretin use per 1000 girls and women aged 13–49 years in the years 2004–2019

Table 2 Distribution of pregnancy outcomes in pregnancies exposed to acitretin[a]

Outcomes of exposed pregnancies	Number of exposed pregnancies ($N=33$)[a]
Live birth, *n* (%)	20 (60.6%)
Thereof preterm birth, *n* (% of live births)	1 (5.0%)
Still birth, *n* (%)	0 (0.0%)
Induced abortion, *n* (%)	6 (18.2%)
Ectopic pregnancy or molar pregnancy, *n* (%)	0 (0.0%)
Spontaneous abortion, *n* (%)	2 (6.1%)
No pregnancy outcome was recorded[b], *n* (%)	5 (15.2%)

[a]Pregnancies that were still ongoing at the end of the observation period are not listed here as the outcome could not be determined yet (this applied to two pregnancies)

[b]There were clear indicators of a pregnancy but no outcome was recorded. It can be assumed that these pregnancies ended in a spontaneous abortion not requiring medical care or an induced abortion not reimbursed by the health insurance provider

Even though acitretin is a rare exposure and we observed a decrease in its use in women aged 31–49 years between 2004 and 2019, the findings are relevant. One in five children born from acitretin-exposed pregnancies had a malformation and these pregnancies started 2 or 3 years after treatment cessation. This highlights the importance of drawing more attention to the long-lasting teratogenic properties of this drug. In addition, about one-third of exposed pregnancies did not end in a live birth (18.2% induced abortions, 6.1% spontaneous abortions, 15.2% without pregnancy outcome). This may indicate that the harmful effects were not limited to those observed in live-born children.

There is no study from Germany to which we can compare our findings and also the number of studies from other countries is very limited. The aforementioned study from France conducted among girls and women aged 15–49 years based on the Système National d'Informations Inter Régimes de l'Assurance Maladie (SNIIRAM) database (almost full population coverage) with data from 2006 to 2013 identified 470 pregnancies exposed to acitretin. In this study, pregnancy was classified as "exposed" if it started during acitretin treatment or within 2 years after the last prescription of acitretin. In our sample covering 20% of the German population, we identified 35 pregnancies classified as exposed to acitretin (considering 3 years after treatment cessation), i.e., it can be estimated that there were about 175 of such pregnancies in the whole of Germany between 2004 and 2019. This is by far less than the number reported for France. We cannot assess whether one reason for this difference could be a more frequent use of acitretin among girls and women of childbearing age in France compared to Germany given that the population-based prevalence of use was not reported for France. Regarding pregnancy outcomes, the French study reported 60% of acitretin-exposed pregnancies ending in live births and 37% in induced or spontaneous abortions [12], which is rather similar to the distribution of pregnancy outcomes in our study. A study from the USA using the National Ambulatory Medical Care Survey (NAMCS), a national sample of visits to physicians using data from the years 1990–2009, identified only one woman under the age of 50 years who received a prescription of acitretin [19].

Even though our study was not designed to assess causal effects and to quantify risks, the fact that 22% of the children born from acitretin-exposed pregnancies had malformations is striking. The malformations affected the circulatory and the urinary system. We did not observe craniofacial malformations among the children born from acitretin-exposed pregnancies. There were three children with cardiovascular malformations, specifically with codes related to atrial septal and ventricular septal defects. Similarly, the aforementioned case studies reported an atrial septal defect [4] and an atrioventricular septal defect [5].

To avoid exposure to acitretin or other drugs with teratogenic potential during pregnancy, risk minimization measures are in place in Germany, which consider pharmacokinetic properties of the drugs. For acitretin, a considerable number of exposed pregnancies, including those ending in live births with malformations, occurred after treatment cessation. Pregnancies starting too early after treatment cessation could also be observed for other teratogenic drugs in Germany [20–22]. This highlights the importance of drawing more attention to the vulnerable time period after treatment cessation among prescribing physicians and among girls and women using these drugs.

Some limitations should be considered in the interpretation of our study. First, in pharmacoepidemiological studies, there is, in general, uncertainty whether individuals are

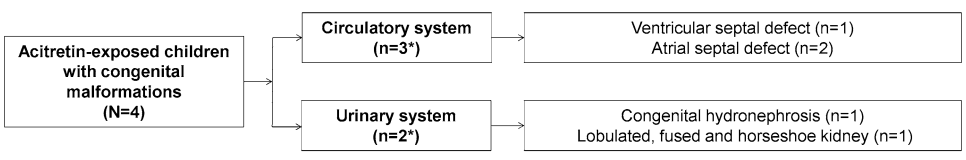

Fig. 2 Malformations observed in children exposed to acitretin during early pregnancy. *One child had a malformation of the circulatory system (atrial septal defect) and the urinary system (congenital hydronephrosis)

taking the drugs dispensed to them. However, for drugs such as acitretin that are used to treat chronic diseases, this uncertainty is considered to be relatively low. Second, information on the prescribed dose is not available in GePaRD. We therefore used the DDD to estimate the number of days covered by the last dispensation of acitretin before pregnancy. Although this is not optimal, we think it had little effect upon our results given that most pregnancies classified as exposed to acitretin occurred well after the end of treatment. Third, while our study was designed to describe prevalence of use and pregnancies exposed to acitretin, our database would not have been suitable to assess whether risk minimization measures were followed on an individual level. This would have required comprehensive information on contraceptive measures, which is limited in GePaRD as in most other claims databases given that for most women of childbearing age contraceptives are not reimbursable [23]. Fourth, with regard to pregnancy outcomes and malformations, our study was merely descriptive, so causal conclusions cannot be drawn. Estimating causal effects would have required a different design including an appropriate control group, the consideration of relevant confounders, potentially mediating effects related to the mother's disease as well as a larger sample of exposed children. Fifth, to assess the presence of malformations in children exposed during pregnancy, we conducted an in-depth patient profile review based on all diagnoses and procedure codes available in GePaRD but did not have additional data that would, for example, in some cases be relevant to classify malformations into "major" and "minor" according to EUROCAT. However, for three of the four children, there was no doubt that they had at least one major malformation. For one child with an atrial septal defect, the follow up data did not show cardiology visits or other procedures indicating monitoring of a heart defect beyond the first year of life, so we assumed that this is the subtype of atrial septal defect classified as minor by EUROCAT (ICD-10: Q21.11). Sixth, we did not systematically assess whether the mothers of the acitretin-exposed children were exposed to other teratogenic drugs before or during pregnancy. However, based on datasets from other studies of our working group, we could exclude in utero exposure to isotretinoin [22], methotrexate [21], fingolimod, teriflunomide, cladribine [20] and leflunomide in the children observed with malformations this study.

A main strength of our study is the large claims database shown to be representative of persons with statutory health insurance coverage in Germany in terms of drug dispensations [24]. The available data allowed us to assess trends in acitretin dispensations over a 15-year period. Due to the use of claims data, our analyses were not affected by recall or non-responder bias. Furthermore, the sophisticated methods developed for GePaRD (i) to identify pregnancy outcomes [15], which were further optimized to capture incomplete pregnancies, (ii) to link data of mothers and children and [25] (iii) to estimate the beginning of pregnancy—predominantly based on the estimated date of delivery—which is expected to minimize misclassification of gestational age [16], are strengths of our study.

5 Conclusion

We observed 35 pregnancies exposed to acitretin mainly because treatment ended too late before pregnancy. Approximately one in five children born from these pregnancies had malformations. This highlights the importance of drawing more attention to the long-lasting teratogenicity of this drug and the existing risk minimization measures including the use contraception in the month before the start and until 3 years after the end of treatment.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40261-023-01314-2.

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Declarations

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Conflict of interest Jonas Reinold, Nadine Wentzell, Bianca Kollhorst, and Ulrike Haug are working at an independent, non-profit research institute, the Leibniz Institute for Prevention Research and Epidemiology – BIPS. Unrelated to this study, BIPS occasionally conducts studies financed by the pharmaceutical industry. Almost exclusively, these are post-authorization safety studies (PASS) requested by health authorities. The design and conduct of these studies as well as the interpretation and publication are not influenced by the pharmaceutical industry. The study presented was not funded by the pharmaceutical industry and was performed in line with the ENCePP Code of Conduct. All authors have declared that no competing interests exist.

Ethics and approvals In Germany, the utilization of health insurance data for scientific research is regulated by the Code of Social Law. All involved health insurance providers as well as the German Federal Office for Social Security and the Senator for Health, Women and Consumer Protection in Bremen as their responsible authorities approved the use of GePaRD data for this study. Informed consent for studies based on claims data is required by law unless obtaining consent appears unacceptable and would bias results, which was the case in this study. According to the Ethics Committee of the University of Bremen studies based on GePaRD are exempt from institutional review board review.

Author contributions JR and UH: study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of manuscript. BK: data management and statistical analysis, critical revision of manuscript. HLT: critical revision of manuscript. NW: interpretation of data, critical revision of manuscript. The final version of the manuscript was approved by all authors.

Availability of data and materials As we are not the owners of the data we are not legally entitled to grant access to the data of the German Pharmacoepidemiological Research Database. In accordance with German data protection regulations, access to the data is granted only to BIPS employees on the BIPS premises and in the context of approved research projects. Third parties may only access the data in cooperation with BIPS and after signing an agreement for guest researchers at BIPS.

Consent to participate Not applicable.

Consent for publication Not applicable.

Code availability Not applicable.

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