

**Analyses of spontaneous adverse drug reaction
reports focusing on specific patient groups and the
type of information included in reports from
physicians, pharmacists and consumers**

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List of abbreviations

ADR	Adverse Drug Reaction(s)
ADRED	Adverse Drug Reactions in Emergency Departments
ATC	Anatomical Therapeutic Chemical Classification
BfArM	Federal Institute for Drugs and Medical Devices
CI	Confidence Interval
DCGMA	Drug Commission of the German Medical Association
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
EV	EudraVigilance
HCP	Health Care Professionals
HLT	High Level Term
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
IMBIE	Institute for Medical Biometry, Informatics, and Epidemiology
IQR	Interquartile Range
MedDRA	Medical Dictionary for Regulatory Activities
NEC	Not elsewhere classified
Non-HCP	Non-Health Care Professionals

OR	Odds Ratio
OTC	Over-the-counter Drugs
PhiP	Pharmacist in Internship
PT	Preferred Terms
PTA	Pharmaceutical Technical Assistants
ROR	Reporting Odds Ratios
Sd	Standard Deviation
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TK	Techniker Krankenkasse
UMC	Uppsala Monitoring Centre
WHO	World Health Organization

1. Abstract

Drugs are used to prevent, alleviate and treat various diseases or to prevent their progression. Aside from its desired effects, every drug can cause noxious and unintended effects, so-called adverse drug reactions (ADR). ADR can range from mild symptoms to such requiring a hospitalisation or even causing the death of the patient. Beyond that, ADR have an impact on the healthcare system as well. According to a study published in 2011, around 434 million euros are spent annually for the treatment of ADR related hospitalisations only in Germany. Although any drug can theoretically cause an ADR, some patient specific factors increase the probability for it. These include for example the intake of multiple drugs and the presence of (co-)morbidities, which are particularly common in older people. Two other groups of patients, which tend to be affected by ADR as well are children and females.

In order to prevent ADR it is decisive to gain the best possible knowledge of specific factors contributing to a more frequent occurrence of ADR in certain groups of patients. An important data source for initial assessments of such correlations are spontaneous reports. These unsolicited reports on potential ADR arise from everyday life situations and can be submitted by anyone. However, the main reporting sources are physicians, pharmacists, and consumers. The latter mentioned group includes patients and their relatives. Although only few information must necessarily be included when submitting a report, those reports containing as comprehensive information as possible are usually more valuable. They provide deeper insights, for example with regard to an assessment of the causal relationship between a suspected drug and a reported reaction.

This thesis aims to analyse ADR in two selected demographic groups, children and females/males, in order to gain basic knowledge and to provide a basis for more in-depth analyses of age- and sex-specific ADR. Therefore, spontaneous reports from everyday life situations were compared to ADR reports systematically collected in two observational studies (KiDSafe, ADRED). Furthermore, spontaneous reports by the three most frequent reporting sources were analysed to determine the availability of certain information of specific interest for the assessment of potential ADR. These insights could help to identify reporter-specific, frequently missing information and serve as a basis for further studies aiming to define measures contributing to overall more complete reports.

2. Introduction and aims with references

Drugs are widely and successfully used in order to prevent, alleviate and treat diseases (German Medicinal Products Act). The progress of drug development and discovery within the last decades was enormous and nowadays, even severe diseases like AIDS and different types of tumours have become treatable (Banker and Rhodes, 2002; De Cock et al., 2021; Zhang and Zhang, 2020). Although the exact numerical impact is unclear, the considerable contribution of modern drugs on the overall increase of the life expectancy observed throughout the past fifty years is undoubted (Grootendorst et al., 2009). For these reasons, among others, it is hardly surprising that an extensive amount of people takes drugs on a regular basis (Knopf et al., 2017; Robert Koch-Institut, 2024; Techniker Krankenkasse (TK) et al., 2023). However, besides the desired and beneficial effects every drug can at the same time cause undesired effects, so called Adverse Drug Reactions (ADR) (Edwards and Aronson, 2000).

2.1 Adverse Drug Reactions

By definition, ADR are unintended and noxious reactions to a drug occurring at regular doses used for prophylaxis, diagnosis or treatment (Directive 2001/83/EC; World Health Organization (WHO), 1972). ADR can manifest in a variety of different reactions with severity ranging from mild to serious symptoms (Edwards and Aronson, 2000). All ADR leading to deadly or life-threatening outcomes, result in disability, incapacity, or a birth defect and those leading to a hospitalisation or a prolongation thereof are defined as serious ADR by the European Medicines Agency (EMA) (EMA, 2017a; Directive 2001/83/EC). According to various studies from all over the world comprised in different systematic reviews, the estimated share of hospitalisations potentially caused by an ADR varies from 0.03% to 30.0% (Bouvy et al., 2015; Haerdtlein et al., 2023; Silva et al., 2022). Regarding inpatients, mean rates for the occurrence of an ADR during hospitalisation were described with 17.0% and 21.6% (Bouvy et al., 2015; Laatikainen et al., 2017). A German prospective case cohort study carried out in four hospitals stated that 6.5% of all emergency department admissions of adults were ADR-related (Schurig et al., 2018). The estimated share of deaths potentially caused by ADR was among others quantified with up to 3.5% for the general public and 8.8% for inpatients (Patel and Patel, 2018; Silva et al., 2022; Wester et al., 2008). A large German analysis of spontaneous reports showed

that 3.4% of all reports including patients aged between 19 and 65 years were describing the seriousness criterion of death, while the number was noticeably higher with 9.1% for patients aged 65 years or older (Dubrall et al., 2020). Considering the demographic change resulting in an increasingly older population, it can be assumed that this problem will occur more often in the future (Dubrall et al., 2020; Oscanoa et al., 2017). Besides these severe consequences for the patients themselves, ADR have a huge economic impact. Rottenkolber et al. (2011) calculated that the average treatment of an ADR in Germany costs 2,250€, which results in a total of 434 million euros per year.

Though ADR can be associated with any drug and any person taking a drug can potentially be affected, few factors often described in literature, increase the overall probability of ADR. At least a substantial proportion of these can be related to certain patient groups.

2.1.1 General risk factors for Adverse Drug Reactions

Firstly, a key aspect is that the more drugs are taken by a patient, the higher is the likelihood to develop an ADR (Davies and O'Mahony, 2015; Evans et al., 2005; Osanlou et al., 2022; Schurig et al., 2018; Zhang et al., 2009). Along with the increased incidence of ADR, polypharmacy, which is often defined as an intake of five or more drugs, additionally increases the probability of interactions between the drugs taken (Masnoon et al., 2017). These interactions in turn can potentially result in (additional) ADR (Knopf and Grams, 2013; Rodrigues and Oliveira, 2016).

Secondly, patients with a higher number of (co-)morbidities are more often affected by ADR than those without any (Davies and O'Mahony, 2015; Evans et al., 2005; Osanlou et al., 2022). In particular, impaired function of the organs involved in the metabolism and elimination process of drugs, namely the liver or kidney, can pose a problem. As changes of the function of these organs can lead to altered pharmacokinetics and pharmacodynamics of specific drugs, it can for instance lead to an undesired dose accumulation. (Evans et al., 2005; Helldén et al., 2009; Osanlou et al., 2022; Turnheim, 2003; Won et al., 2022).

2.1.2 Adverse Drug Reactions in specific patient populations

The occurrence of the aforementioned conditions increases with age and is frequently observed for older patients (Davies and O'Mahony, 2015; Zazzara et al., 2021). As two or

more medical and psychiatric conditions, also referred to as multimorbidity, are very common among older people it does not astonish that consequently they often take one drug as a minimum (Davies and O'Mahony, 2015; Dubrall et al., 2020). In Germany more than every second adult takes at least one prescribed drug on a regular basis (Knopf et al., 2017; TK et al., 2023). People aged between 70 and 79 years surpassed these rates considerably. According to a German investigation about 95% of all people in this age group took at least one and almost every second person five or more drugs within the last seven days before the survey (Knopf and Grams, 2013). Considering the aforementioned reasons, advanced age is often described as an individual risk factor for ADR (Davies and O'Mahony, 2015; Dubrall et al., 2020; Osanlou et al., 2022; Turnheim, 2003; Wolfe et al., 2018).

However, not only people of advanced age are prone to ADR, so are the youngest members of our society, although the absolute numbers of occurrences seem to be lower in this population (Eberl et al., 2024). Children and adolescents are often treated with drugs, while there are considerable deviations regarding the total numbers of prescribed drugs, depending on the age(-group) and drug(-group)s observed. As an impressive example, almost every infant (younger than 12 months) covered by a large German health insurer received at least one prescribed painkiller and/or antipyretic drug within each observed year (TK et al., 2022).

Evidence-based data from clinical trials are often lacking and are frequently limited to adults only. Consequently, numerous drugs are prescribed to children beyond the scope of the existing marketing authorisation as so-called off-label use and the information obtained from adults is therefore extrapolated to paediatric patients (Joseph et al., 2015; Neiningner et al., 2022; Wimmer et al., 2015). The latter causes difficulties, as children have substantially differing pharmacokinetic and pharmacodynamic profiles compared to adults (Matalová et al., 2016). Furthermore, aspects such as the clearance, enzymatic activities and dermal absorption, among others, differ considerably even amongst the various subgroups of children (e.g. newborns, toddlers, adolescents). Carefully selected (calculation) models have to be utilised for dose finding and adaptation purposes as a result. (Elzagallaai et al., 2017; Wimmer et al., 2015). These factors, among others, lead to the fact that on average about one percent of all German children experience an ADR

at all (Knopf and Du, 2010), up to 6.9% are hospitalised due to it (Eberl et al., 2024; Haffner et al., 2005) and 9.2% to 14.1% suffer from it while being hospitalised (Haffner et al., 2005; Rashed et al., 2012).

However, age is not the only demographic factor influencing the occurrence and type of ADR. For a long time now, sex differences with regard to ADR have been described (Smith, 1966). In the meantime, several studies have been published revealing sex-specific differences concerning the drugs involved and resulting reactions. Nevertheless, differences can also be seen in the overall frequency, as certain studies attribute a 1.6 times higher risk to females for developing ADR compared to males (Banovac et al., 2017; Madla et al., 2021; Martin et al., 1998; Zopf et al., 2008). Again, in this context the inclusion in clinical trials plays a distinct role, as females were underrepresented in these for a long time and sex-stratified analysis became more common only recently (Dumanski and Ahmed, 2020; Geller et al., 2011; Madla et al., 2021; Reza et al., 2022). Just as children cannot be regarded as small adults, it is not possible to conclude the effect of drugs on females based on the findings of clinical studies carried out with male subjects. Factors contributing here include the aspect that males and females often differ, among others, in body fat distribution, hormonal factors and differences in the activity of various enzymes involved in the metabolism of drugs (Farkouh et al., 2020; Madla et al., 2021; Soldin and Mattison, 2009). Beyond these, the impact of an overall higher use of drugs and more frequent consultations of physicians by females in this regard remains unclear so far (Knopf et al., 2017; Thiessard et al., 2005).

2.1.3 Preventability of Adverse Drug Reactions

ADR are not always unexpected and unpredictable incidents. Indeed, different meta-analyses and reviews on ADR related hospitalisations and admissions to the emergency department indicated that on average each third to every second ADR was assessed as preventable. This share even increases up to 71% for patients aged 65 years or older (Hakkarainen et al., 2012; Laatikainen et al., 2017; Patel et al., 2017). In another study on children a preventability rate of 17% was found (Rashed et al., 2012). Especially ADR caused by medication errors, defined as all errors occurring in the medication process, are largely considered as preventable (Oyebode et al., 2024; Wittich et al., 2014). Avoiding a part of those preventable ADR could be a promising opportunity to improve the impact

on patients' health and the economic impact mentioned in chapter 2.1 (Aronson, 2009; Patel et al., 2023; Rinke et al., 2014).

A fundamental cornerstone for the prevention of ADR in general is to obtain as comprehensive knowledge as possible about the potential ADR. Thereby, among other factors, specific patient groups under risk can be identified. Based on these disclosures, measures such as contraindications can be defined and may eventually lead to a decrease of the ADR (Coleman and Pontefract, 2016; Schumock and Thornton, 1992).

2.2 Detection of Adverse Drug Reactions

Prior to marketing authorisation of any drug, clinical trials are conducted not only to prove a drug's efficacy, but to identify, assess and document associated ADR. As trials merely involve a limited number of patients, partially from carefully selected patient cohorts, it is impossible to determine a complete picture of all ADR related to this drug. Especially rare ADR are barely detectable under these circumstances (Coloma et al., 2013; Regulation EU 536/2014). Thus, pharmacovigilance, which is defined as all activities related to the detection, assessment, understanding and prevention of ADR is a crucial ongoing process after the authorisation of a drug (Fornasier et al., 2018; WHO, 1972, 2002). In this context, diverse data sources such as spontaneous reports, scientific literature and electronic health records are used to continuously monitor the prevalence of known ADR in everyday use. Moreover, they are used to identify potential new ADR, investigate them in greater depth and, if necessary, enforce regulatory consequences such as the withdrawal of the marketing authorisation (EMA, 2023; Moore et al., 2019).

2.2.1 Spontaneous reports

In the context of pharmacovigilance spontaneous reports, which are defined as unsolicited reports of suspected ADR arising from the everyday use of drugs, are by far the most frequently used data source (EMA, 2017b, 2023; Moore et al., 2019). Anyone is encouraged to report such suspected ADR. German physicians and pharmacists are obliged to do so by their professional codes of conduct (Apothekerkammer Nordrhein, 2020; Bundesärztekammer, 2011). Patients and their relatives, also referred to as consumers, are explicitly advised accordingly in the package leaflets (Directive 2001/83/EC). All spontaneous ADR reports arising in the European Economic Area (EEA)

are stored in the EudraVigilance database, which is operated by the EMA (EMA, 2024). Each individual report stored therein must include at least 1) an identifiable reporter 2) an identifiable patient 3) one suspected substance/medicinal product and 4) one suspected adverse reaction (EMA, 2017b). But these mandatory information are often not sufficient to permit more in-depth evaluation of the potential ADR on the basis of the respective spontaneous report, for example in terms of assessing a causal relationship between the drug and the observed reaction (Edwards et al., 1990; Plessis et al., 2017; Uppsala Monitoring Centre (UMC) and WHO, 2013). Consequently, it is desirable, especially for the better understanding of ADR, to ensure that as many spontaneous reports are as comprehensive as possible. Accordingly, obstacles and pitfalls leading to incomplete reports have to be investigated, addressed and hence a better quality of the data is ensured in the future (Bergvall et al., 2014; Durrieu et al., 2016).

2.3 Aims

This thesis should therefore contribute to gain further knowledge on two aspects related to ADR. First, analyses of ADR in the context of a hospitalisation were conducted for certain demographic groups, namely children (chapter 3.2) as well as adult males and females (chapter 3.1). For this purpose, two different data sources were used in each case. These included unsolicited spontaneous reports and reports collected in an observational study according to a defined study protocol. These two analyses should enable a better understanding of ADR in these populations and may provide a suitable basis for future studies aiming to prevent them. Since spontaneous reports are of great importance for pharmacovigilance, but in some regards only those reports with particularly comprehensive information are helpful, we conducted a further study. To this end, we analysed a quarter of a million spontaneous reports from the three main reporting sources (physicians, pharmacists and consumers) regarding the information included (chapter 3.3). Based on these analyses, frequently missing information can be identified for each reporting source. Thus, our study aims to provide the basis for further studies investigating the underlying causes and initiating improvement measures.

2.4 References

Apothekerkammer Nordrhein, 2020: Berufsordnung für Apothekerinnen und Apotheker der Apothekerkammer Nordrhein vom 13. Juni 2007 (MBI.NRW.2007 S. 619), zuletzt geändert am 17. Juni 2020 (MBI.NRW.2020 S. 455). https://www.aknr.de/files/downloads/infocenter/textsammlungen/text_berufsordnung.pdf (date accessed: 08.08.2024)

Aronson JK. Medication errors: what they are, how they happen, and how to avoid them. QJM 2009; 102: 513–521

Banker GS. Drug Products: Their Role in the Treatment of Disease, Their Quality, and Their Status and Future as Drug-Delivery Systems. In: Banker GS, Rhodes CT, eds. Modern Pharmaceutics, Fourth Edition Revised and Expanded. New York – Basel: Marcel Dekker Inc, 2002: 1-12

Banovac M, Candore G, Slattery J, Houyez F, Haerry D, Genov G, Arlett P. Patient Reporting in the EU: Analysis of EudraVigilance Data. Drug Saf 2017; 40: 629–645

Bergvall T, Norén GN, Lindquist M. vigiGrade: A Tool to Identify Well-Documented Individual Case Reports and Highlight Systematic Data Quality Issues. Drug Saf 2014; 37: 65–77

Bouvy JC, De Bruin ML, Koopmanschap MA. Epidemiology of Adverse Drug Reactions in Europe: A Review of Recent Observational Studies. Drug Saf 2015; 38: 437–453

Bundesärztekammer, 2011: (Muster-)Berufsordnung für die in Deutschland tätigen Ärztinnen und Ärzte - MBO-Ä 1997 - in der Fassung der Beschlüsse des 114. Deutschen Ärztetages 2011 in Kiel. https://www.bundesaerztekammer.de/fileadmin/user_upload/_old-files/downloads/MBO_08_20112.pdf (date accessed: 08.08.2024)

Coleman JJ, Pontefract SK. Adverse drug reactions. Clin Med (Lond) 2016; 16: 481–485

Coloma PM, Trifirò G, Patadia V, Sturkenboom M. Postmarketing Safety Surveillance: Where does Signal Detection Using Electronic Healthcare Records Fit into the Big Picture? Drug Saf 2013; 36: 183–197

Davies EA, O'Mahony MS. Adverse drug reactions in special populations – the elderly. *Br J Clin Pharmacol* 2015; 80: 796–807

De Cock KM, Jaffe HW, Curran JW. Reflections on 40 Years of AIDS. *Emerg Infect Dis* 2021; 27: 1553–1560

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. <https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:311:0067:0128:en:PDF> (date accessed: 08.08.2024)

Dubrall D, Just KS, Schmid M, Stingl JC, Sachs B. Adverse drug reactions in older adults: a retrospective comparative analysis of spontaneous reports to the German Federal Institute for Drugs and Medical Devices. *BMC Pharmacol Toxicol* 2020; 21: 25

Dumanski SM, Ahmed SB. Sex, Drugs, and Adverse Drug Reactions: Sex Differences in Laboratory Monitoring Outcomes After Initiation of Renin-Angiotensin-Aldosterone-System Inhibition Therapy. *Circ Cardiovasc Qual Outcomes* 2020; 13: e007045

Durrieu G, Jacquot J, Mège M, Bondon-Guitton E, Rousseau V, Montastruc F, Montastruc JL. Completeness of Spontaneous Adverse Drug Reaction Reports Sent by General Practitioners to a Regional Pharmacovigilance Centre: A Descriptive Study. *Drug Saf* 2016; 39: 1189–1195

Eberl S, Heus P, Toni I, Bachmat I, Neubert A. The epidemiology of drug-related hospital admissions in paediatrics – a systematic review. *Arch Public Health* 2024; 82: 81

Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet* 2000; 356: 1255–1259

Edwards IR, Lindquist M, Wiholm BE, Napke E. Quality criteria for early signals of possible adverse drug reactions. *Lancet* 1990; 336: 156–158

Elzagallaai AA, Greff MJE, Rieder MJ. Adverse Drug Reactions in Children: The Double-Edged Sword of Therapeutics. *Clin Pharmacol Ther* 2017; 101: 725–735

European Medicines Agency, 2017a: Guideline on good pharmacovigilance practices (GVP) Annex I - Definitions (Rev 4). https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-annex-i-definitions-rev-4-superseded_en.pdf (date accessed: 08.08.2024)

European Medicines Agency, 2017b: Guideline on good pharmacovigilance practices (GVP) module VI: collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2). https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-and-submission-reports-suspected-adverse-reactions-medicinal-products-rev-2_en.pdf (date accessed: 08.08.2024)

European Medicines Agency, 2023: 2022 Annual Report on EudraVigilance for the European Parliament, the Council and the Commission Reporting period: 1 January to 31 December 2022. https://www.ema.europa.eu/en/documents/report/2022-annual-report-eudravigilance-european-parliament-council-and-commission_en.pdf (date accessed: 08.08.2024)

European Medicines Agency, 2024: EudraVigilance. <https://www.ema.europa.eu/en/human-regulatory-overview/research-development/pharmacovigilance-research-development/eudravigilance> (date accessed: 08.08.2024)

Evans RS, Lloyd JF, Stoddard GJ, Nebeker JR, Samore MH. Risk Factors for Adverse Drug Events: A 10-Year Analysis. *Ann Pharmacother* 2005; 39: 1161–1168

Farkouh A, Riedl T, Gottardi R, Czejka M, Kautzky-Willer A. Sex-Related Differences in Pharmacokinetics and Pharmacodynamics of Frequently Prescribed Drugs: A Review of the Literature. *Adv Ther* 2020; 37: 644–655

Fornasier G, Francescon S, Leone R, Baldo P. An historical overview over Pharmacovigilance. *Int J Clin Pharm* 2018; 40: 744–747

Geller SE, Koch A, Pellettieri B, Carnes M. Inclusion, Analysis, and Reporting of Sex and Race/Ethnicity in Clinical Trials: Have We Made Progress? *J Womens Health (Larchmt)* 2011; 20: 315–320

German Medicinal Products Act - Arzneimittelgesetz: Gesetz über den Verkehr mit Arzneimitteln (Arzneimittelgesetz - AMG). Arzneimittelgesetz in der Fassung der Bekanntmachung vom 12. Dezember 2005 (BGBl. I S. 3394), das zuletzt durch Artikel 7 des Gesetzes vom 27. März 2024 (BGBl. 2024 I Nr. 109) geändert worden ist. https://www.gesetze-im-internet.de/amg_1976/ (date accessed: 08.08.2024)

Grootendorst P, Piérard E, Shim M. Life-expectancy gains from pharmaceutical drugs: a critical appraisal of the literature. *Expert Rev Pharmacoecon Outcomes Res* 2009; 9: 353–364

Haerdtlein A, Debold E, Rottenkolber M, Boehmer AM, Pudritz YM, Shahid F, Gensichen J, Dreischulte T. Which Adverse Events and Which Drugs Are Implicated in Drug-Related Hospital Admissions? A Systematic Review and Meta-Analysis. *J Clin Med* 2023; 12: 1320

Haffner S, Von Laue N, Wirth S, Thürmann PA. Detecting Adverse Drug Reactions on Paediatric Wards: Intensified Surveillance Versus Computerised Screening of Laboratory Values. *Drug Saf* 2005; 28: 453–464

Hakkarainen KM, Hedna K, Petzold M, Hägg S. Percentage of Patients with Preventable Adverse Drug Reactions and Preventability of Adverse Drug Reactions – A Meta-Analysis. *PLoS One* 2012; 7: e33236

Helldén A, Bergman U, Von Euler M, Hentschke M, Odar-Cederlöf I, Öhlén G. Adverse Drug Reactions and Impaired Renal Function in Elderly Patients Admitted to the Emergency Department: A Retrospective Study. *Drugs Aging* 2009; 26: 595–606

Joseph PD, Craig JC, Caldwell PHY. Clinical trials in children. *Br J Clin Pharmacol* 2015; 79: 357–369

Knopf H, Grams D. Arzneimittelanwendung von Erwachsenen in Deutschland: Ergebnisse der Studie zur Gesundheit Erwachsener in Deutschland (DEGS1). *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2013; 56: 868–877

Knopf H, Du Y. Perceived adverse drug reactions among non-institutionalized children and adolescents in Germany. *Br J Clin Pharmacol* 2010; 70: 409–417

Knopf H, Prütz F, Du Y. Use of medicines by adults in Germany. *J Health Monit* 2017; 2:103-109

Laatikainen O, Miettunen J, Sneek S, Lehtiniemi H, Tenhunen O, Turpeinen M. The prevalence of medication-related adverse events in inpatients—a systematic review and meta-analysis. *Eur J Clin Pharmacol* 2017; 73: 1539–1549

Madla CM, Gavins FKH, Merchant HA, Orlu M, Murdan S, Basit AW. Let's talk about sex: Differences in drug therapy in males and females. *Adv Drug Deliv Rev* 2021;175: 113804

Martin RM, Biswas PN, Freemantle SN, Pearce GL, Mann RD. Age and sex distribution of suspected adverse drug reactions to newly marketed drugs in general practice in England: analysis of 48 cohort studies. *Br J Clin Pharmacol* 1998; 46: 505–511

Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. *BMC Geriatr* 2017; 17: 230

Matalová P, Urbánek K, Anzenbacher P. Specific features of pharmacokinetics in children. *Drug Metab Rev* 2016; 48: 70–79

Moore N, Berdaï D, Blin P, Droz C. Pharmacovigilance – The next chapter. *Therapie* 2019; 74: 557–567

Neininger MP, Jeschke S, Kiesel LM, Bertsche T, Bertsche A. Physicians' perspectives on adverse drug reactions in pediatric routine care: a survey. *World J Pediatr* 2022; 18: 50–58

Osanlou R, Walker L, Hughes DA, Burnside G, Pirmohamed M. Adverse drug reactions, multimorbidity and polypharmacy: a prospective analysis of 1 month of medical admissions. *BMJ Open* 2022; 12: e055551

Oscanoa TJ, Lizaraso F, Carvajal A. Hospital admissions due to adverse drug reactions in the elderly. A meta-analysis. *Eur J Clin Pharmacol* 2017; 73: 759–770

Oyebode F. Clinical errors and medical negligence. *Med Princ Pract* 2013; 22: 323-333

Patel NS, Patel TK, Patel PB, Naik VN, Tripathi C. Hospitalizations due to preventable adverse reactions—a systematic review. *Eur J Clin Pharmacol* 2017; 73: 385–398

Patel TK, Patel PB. Mortality among patients due to adverse drug reactions that lead to hospitalization: a meta-analysis. *Eur J Clin Pharmacol* 2018; 74: 819–832

Patel TK, Patel PB, Bhalla HL, Dwivedi P, Bajpai V, Kishore S. Impact of suspected adverse drug reactions on mortality and length of hospital stay in the hospitalised patients: a meta-analysis. *Eur J Clin Pharmacol* 2023; 79: 99–116

Plessis L, Gómez A, García N, Cereza G, Figueras A. Lack of essential information in spontaneous reports of adverse drug reactions in Catalonia—a restraint to the potentiality for signal detection. *Eur J Clin Pharmacol* 2017; 73: 751–758

Rashed AN, Wong ICK, Cranswick N, Hefele B, Tomlin S, Jackman J, Lee K, Hon KLE, Ong J, Ghaleb M, Chua SS, Hui TM, Rascher W, Neubert A. Adverse Drug Reactions in Children – International Surveillance and Evaluation (ADVISE): A Multicentre Cohort Study. *Drug Saf* 2012; 35: 481–494

Regulation (EU) 536/2014 of the European Parliament and of the Council of 16 april 2014 on clinical trials on medicinal products for human use, and repealing directive 2001/20/EC (2014). <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32014R0536> (date accessed: 08.08.2024)

Reza N, Gruen J, Bozkurt B. Representation of women in heart failure clinical trials: Barriers to enrollment and strategies to close the gap. *Am Heart J Plus* 2022; 13: 100093

Rinke ML, Bundy DG, Velasquez CA, Rao S, Zerhouni Y, Lobner K, Blanck JF, Miller MR. Interventions to Reduce Pediatric Medication Errors: A Systematic Review. *Pediatrics* 2014; 134: 338–360

Robert Koch-Institut, 2024: Gesundheit in Deutschland aktuell - GEDA 2019/2020-EHIS https://public.tableau.com/app/profile/robert.koch.institut/viz/Gesundheit_in_Deutschland_aktuell/GEDA_20192020-EHIS (date accessed: 08.08.2024)

Rodrigues MCS, Oliveira CD. Drug-drug interactions and adverse drug reactions in polypharmacy among older adults: an integrative review. *Rev Lat Am Enfermagem* 2016; 24: e2800

Rottenkolber D, Schmiedl S, Rottenkolber M, Farker K, Saljé K, Mueller S, Hippus M, Thuermann PA, Hasford J. Adverse drug reactions in Germany: direct costs of internal medicine hospitalizations. *Pharmacoepidemiol Drug Saf* 2011; 20: 626–634

Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. *Hosp Pharm* 1992; 27: 538

Schurig AM, Böhme M, Just KS, Scholl C, Dormann H, Plank-Kiegele B, Seufferlein T, Gräff I, Schwab M, Stingl JC. Adverse Drug Reactions (ADR) and Emergencies. *Dtsch Arztebl Int* 2018; 115: 251-258

Silva LT, Modesto ACF, Amaral RG, Lopes FM. Hospitalizations and deaths related to adverse drug events worldwide: Systematic review of studies with national coverage. *Eur J Clin Pharmacol* 2022; 78: 435–466

Smith JW. Studies on the Epidemiology of Adverse Drug Reactions: V. Clinical Factors Influencing Susceptibility. *Ann Intern Med* 1966; 65: 629-640

Soldin OP, Mattison DR. Sex Differences in Pharmacokinetics and Pharmacodynamics. *Clin Pharmacokinet* 2009; 48: 143–157

Techniker Krankenkasse (TK), Egert-Schmidt AM, Holtz S, Kaufmann-Kolle P, Neubert A, Straßner C, Steinkat N, Wunsch A, 2022: Verordnungsreport 2022 - Kinder und Arzneimittel.

<https://www.tk.de/resource/blob/2122734/b388426d5b7367626882cd9c020bcada/tk-report-kinder-und-arzneimittel-data.pdf> (date accessed: 08.08.2024)

Techniker Krankenkasse (TK), Meyer B, Grobe TG, Bessel S, 2023: Gesundheitsreport 2023 – Wie geht's Deutschlands Studierenden?
<https://www.tk.de/resource/blob/2149886/e5bb2564c786aedb3979588fe64a8f39/2023-tk-gesundheitsreport-data.pdf> (date accessed: 08.08.2024)

Thiessard F, Roux E, Miremont-Salamé G, Fourrier-Réglat A, Haramburu F, Tubert-Bitter P, Bégaud B. Trends in Spontaneous Adverse Drug Reaction Reports to the French Pharmacovigilance System (1986-2001). *Drug Saf* 2005; 28: 731–74

Turnheim K. When drug therapy gets old: pharmacokinetics and pharmacodynamics in the elderly. *Exp Gerontol* 2003; 38: 843–853

Uppsala Monitoring Centre (UMC), World Health Organization (WHO), 2013: The use of the WHO-UMC system for standardised case causality assessment. <https://www.who.int/publications/m/item/WHO-causality-assessment> (date accessed: 08.08.2024)

Wester K, Jönsson AK, Spigset O, Druid H, Hägg S. Incidence of fatal adverse drug reactions: a population based study. *Br J Clin Pharmacol* 2008; 65: 573–579

Wimmer S, Neubert A, Rascher W. The Safety of Drug Therapy in Children. *Dtsch Arztebl Int* 2015; 112: 781-787

Wittich CM, Burkle CM, Lanier WL. Medication Errors: An Overview for Clinicians. *Mayo Clin Proc* 2014; 89: 1116–1125

Wolfe D, Yazdi F, Kanji S, Burry L, Beck A, Butler C, Esmaeilisaraji L, Hamel C, Hersi M, Skidmore B, Moher D, Hutton B. Incidence, causes, and consequences of preventable adverse drug reactions occurring in inpatients: A systematic review of systematic reviews. *PLoS One* 2018; 13: e0205426

Won SH, Suh SY, Yim E, Ahn HY. Risk Factors Related to Serious Adverse Drug Reactions Reported through Electronic Submission during Hospitalization in Elderly Patients. *Korean J Fam Med* 2022; 43: 125–131

World Health Organization (WHO), 1972: International drug monitoring: the role of national centres. Report of a WHO meeting. <https://iris.who.int/handle/10665/40968> (date accessed: 08.08.2024)

World Health Organization (WHO), 2002: The importance of pharmacovigilance: safety monitoring of medicinal products. <https://www.who.int/publications/i/item/10665-42493> (date accessed: 08.08.2024)

Zazzara MB, Palmer K, Vetrano DL, Carfi A, Onder G. Adverse drug reactions in older adults: a narrative review of the literature. *Eur Geriatr Med* 2021; 12: 463–473

Zhang M, Holman CDJ, Price SD, Sanfilippo FM, Preen DB, Bulsara MK. Comorbidity and repeat admission to hospital for adverse drug reactions in older adults: retrospective cohort study. *BMJ* 2009; 338: a2752

Zhang Y, Zhang Z. The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications. *Cell Mol Immunol* 2020; 17: 807–821

Zopf Y, Rabe C, Neubert A, Gaßmann KG, Rascher W, Hahn EG, Brune K, Dormann H. Women encounter ADRs more often than do men. *Eur J Clin Pharmacol* 2008; 64: 999–1004

3. Publications

3.1 Identification and comparison of sex-specific serious adverse drug reactions in spontaneous reports and systematically collected reports (ADRED)

Christ P, Dubrall D, Just KS, Lewke B, Below M, Stingl JC, Schmid M, Sachs B. Identification and comparison of sex-specific serious adverse drug reactions in spontaneous reports and systematically collected reports (ADRED). Br J Clin Pharmacol 2024; 90: 776-792

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ORIGINAL ARTICLE

Identification and comparison of sex-specific serious adverse drug reactions in spontaneous reports and systematically collected reports (ADRED)

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Aims: Adverse drug reactions (ADRs) are known to show sex-specific differences in occurrence and phenotype. The aim of this study was to analyse sex-specific differences in ADR-drug combinations that required hospitalization based on two different datasets.

Methods: We performed a complementary analysis of (i) spontaneously reported ($n = 12\,564$, female = 51.7%) and (ii) systematically collected ADR reports from a prospective multicentre observational study (ADRED, $n = 2355$, female = 48.2%) from Germany in the ADR database EudraVigilance (EV). Both datasets were analysed separately concerning the suspected drugs, ADRs and ADR-drug combinations more frequently reported for females or males by calculating reporting odds ratios (ROR) with 95% confidence intervals. ADR-drug combinations more frequently reported for either females or males in EV reports were related to prescription data. Finally, the results from both datasets were discussed with regard to their (dis-)concordance.

Results: In both datasets, some antineoplastic agents and nervous system drugs were found to be reported more often for females than males (RORs ranging from 1.5 [1.1–2.1] for quetiapine in spontaneous reports to 41.3 [13.1–130.0] for trastuzumab in spontaneous reports). ADRs of the respiratory system, and haemorrhages were described predominantly for males in both datasets. In spontaneous reports the ADR-drug combination *self-injurious behaviour*–quetiapine was more often reported for females without and with consideration of drug prescriptions (ROR: 3.8 [1.3–11.0]). Quetiapine and psychiatric disorders (superordinate level) was exclusively reported for females in ADRED reports.

Conclusions: Our results can contribute to raise awareness and further knowledge regarding sex-specific ADRs. The findings require further in-depth investigation.

KEYWORDS

ADRED, adverse drug reactions, sex differences, spontaneous reports

Patrick Christ and Diana Dubrall contributed equally.

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1 | INTRODUCTION

In literature, sex differences with regard to the development of adverse drug reactions (ADRs) have been observed and described for at least more than 50 years.¹ For example, a study from 1998 already showed that females carry a 1.6-fold higher relative risk of experiencing an ADR compared to males.² Meanwhile, numerous studies have been published highlighting various sex-specific differences influencing the occurrence of ADRs and with a special focus on specific drug groups respectively ADRs.

Differences in body weight, height, body fat distribution and organ size as well as hormonal states vary between sexes. Drug metabolism and elimination of most drugs is e.g. influenced by sex dependent differences in the activity of cytochrome P450 enzymes, the most important drug metabolizing enzymes.³ These factors, along with others, may lead to differences in pharmacokinetic and pharmacodynamic characteristics of the same drug between females and males, which in turn may favour the aforementioned sex-specific differences of ADRs. The inclusion of females and implementation of sex-stratified analyses in clinical trials increased in the past but may differ between the different phases of clinical trials and for specific diseases.^{4–6} Mainly due to size constraints, not all ADRs can be detected during clinical trials.⁷ However, ADRs are highly relevant as they can affect patients' quality of life, compliance of drug therapy and even increase mortality.⁸ Pharmacoepidemiological and pharmacovigilance studies may extend the knowledge of sex as a *risk factor* for certain ADRs, and thus improve drug safety.⁹

In this study we aimed to identify—in two different datasets—sex-related differences regarding the reported ADRs, suspected drugs and ADR-drug combinations. Additionally, we analysed if the identified ADR-drug combinations more frequently reported for either sex remained more frequently reported by considering drug prescription data for both sexes. We also discussed whether the results of our complementary analysis of two independent datasets support each other.

2 | METHODS

In our complementary analysis we analysed (i) spontaneous ADR reports and (ii) systematically collected ADR reports from the ADRED study contained in the ADR database EudraVigilance (EV).^{10,11} The datasets differ regarding their nature of collection.

2.1 | EV

Comprehensive information about EV and reporting obligations of ADRs along with the definition and classification of seriousness of ADRs are described elsewhere.^{12,13} All ADR reports from healthcare professionals from Germany are stored in EV. There, ADRs are coded in accordance with the Medicinal Dictionary for Regulatory Activities (MedDRA) and drugs with the EV medicinal product

What is already known about this subject?

1. Sex is known to be a determinant of certain adverse drug reactions (ADRs).
2. Previous studies have shown that females are at a higher risk of suffering an ADR than males.
3. Certain drugs (drug groups) elicit specific ADRs either in females or in males.

What this study adds?

1. In our complementary approach, nervous system disorders related to dabigatran were more frequently reported for males and psychiatric disorders related to quetiapine for females.
2. A higher number of serious ADR-drug combinations were identified for males compared with females.

dictionary.¹⁴ Further information regarding data and quality management of spontaneous reports can be found in regulatory guidance documents.¹⁵

2.2 | ADRED study

The ADRED study was a prospective multicentre observational study (trial registration: DRKS-ID DRKS00008979). Briefly, ADR cases among adults presenting to four German emergency departments were enrolled after causality assessment.¹⁶ Cases were identified by study personnel during an observational period between September 2015 and December 2018. The patients gave informed consent and the study was approved by the responsible ethical committee of the University of Bonn (202/15). A more detailed description of the study design, the enrolment of patients, data collection and processing in the ADRED study is published elsewhere.^{10,11}

2.3 | Identification of EV and ADRED reports

The ADR reports from both datasets were identified in EV since all cases from the ADRED study had also been submitted to EV. In EV reports, the reporter assigned the drugs reported as suspected/interacting or concomitant. In ADRED, this assignment was performed by the study team classifying all drugs with an at least possible causal relationship to the ADR(s) as suspected. For the identification of the spontaneous reports the same inclusion criteria as for the ADRED study were used.¹⁵

We identified all spontaneous ADR reports related to drugs (vaccines and hyposensitization solutions were not included) from healthcare professionals from Germany received between September 2015 and December 2018 for patients older than 17 years that were coded with 'hospitalization' resulting in $n = 16\,077$ reports (Figure 1).

The ADRED reports enrolled until 31 December 2018 and received in EV until 31 December 2019 were identified in EV by their study ID, which starts with 'DE-ADRED' ($n = 2571$). These reports were excluded from the dataset of the spontaneous reports. There was a delay in forwarding the ADRED reports to EV (see receive date above), thus, the date of enrolment in the ADRED study may differ from the receive date in EV. Hence, only those reports received until December 2018 could be excluded from the spontaneous reports. Additionally, we identified and removed duplicates in both datasets by report identifiers. Further on, we excluded ADR reports referring to sex-specific drugs (sex hormones and modulators of the genital system, α -adrenoreceptor antagonists, testosterone-5- α reductase inhibitors, drugs used in erectile dysfunction) and ADRs listed within the MedDRA list of sex-specific preferred terms (e.g. *abortion* or *prostatitis*).¹⁷ Finally, 2355 reports from the ADRED study and 12 564 spontaneous reports were considered for further analysis. In the following, ADR reports from the ADRED study are designated as *ADRED reports* and the spontaneous ADR reports as *EV reports*.

2.4 | Analyses of EV and ADRED datasets

In EV and ADRED reports, the most frequently reported medical histories, drugs, ADRs, ADR-drug combinations, the number of drugs, ADRs and ADR-drug combinations per report, and the patients' demographics were analysed descriptively. Sex and age-group stratified analyses were performed by calculations following the principles of reporting odds ratios (RORs) and 95% confidence intervals (CIs) in order to identify the drugs, ADRs and ADR-drug combinations more frequently reported for either females or males (Figure 2). These calculations and their results are subject to the limitations known for signals identified in pharmacovigilance studies in spontaneous reports, especially reporting biases.^{18,19} Detailed information on these can be found in the discussion section. The age-groups were set in order to proxy the different hormonal status through menopause in females.²⁰ Thus, sex-stratified analysis was additionally performed for patients younger than 52 years (*younger patients*) and older than 51 years (*older patients*).

For the analyses of reported medical histories and ADRs, the aggregated high-level term (HLT) of the MedDRA terminology was used, which is a rather superordinate level of describing symptoms, diagnosis or laboratory results. Due to the smaller sample size of the ADRED dataset, we considered the identified ADR-drug combinations more frequently reported for either females or males in these reports at the highest level of MedDRA terminology

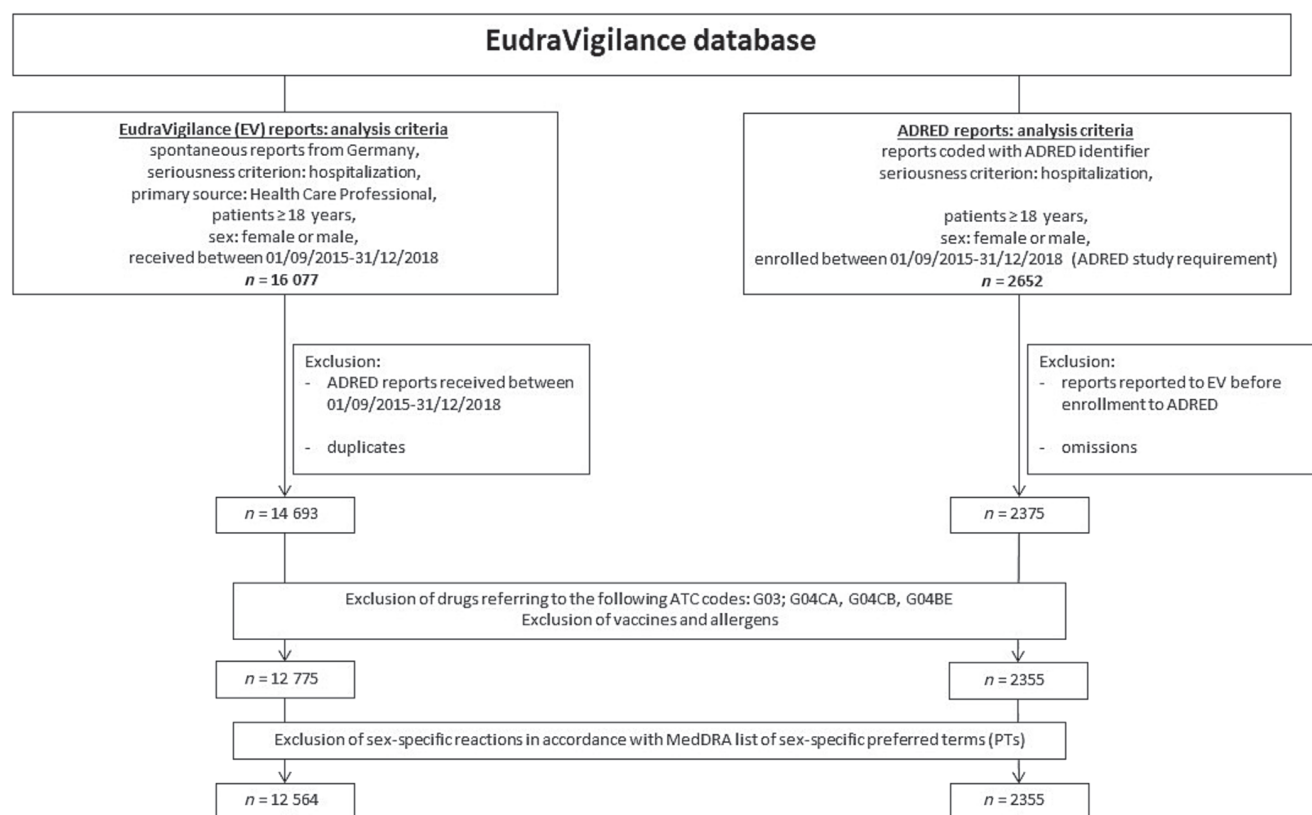


FIGURE 1 Identification of spontaneous reports and reports from the ADRED study in EudraVigilance (EV). ATC, anatomical therapeutic chemical classification; G03, sex hormones and modulators of the genital system; G04CA, α -adrenoreceptor antagonists; G04CB, testosterone-5- α reductase inhibitors; G04BE, drugs used in erectile dysfunction.

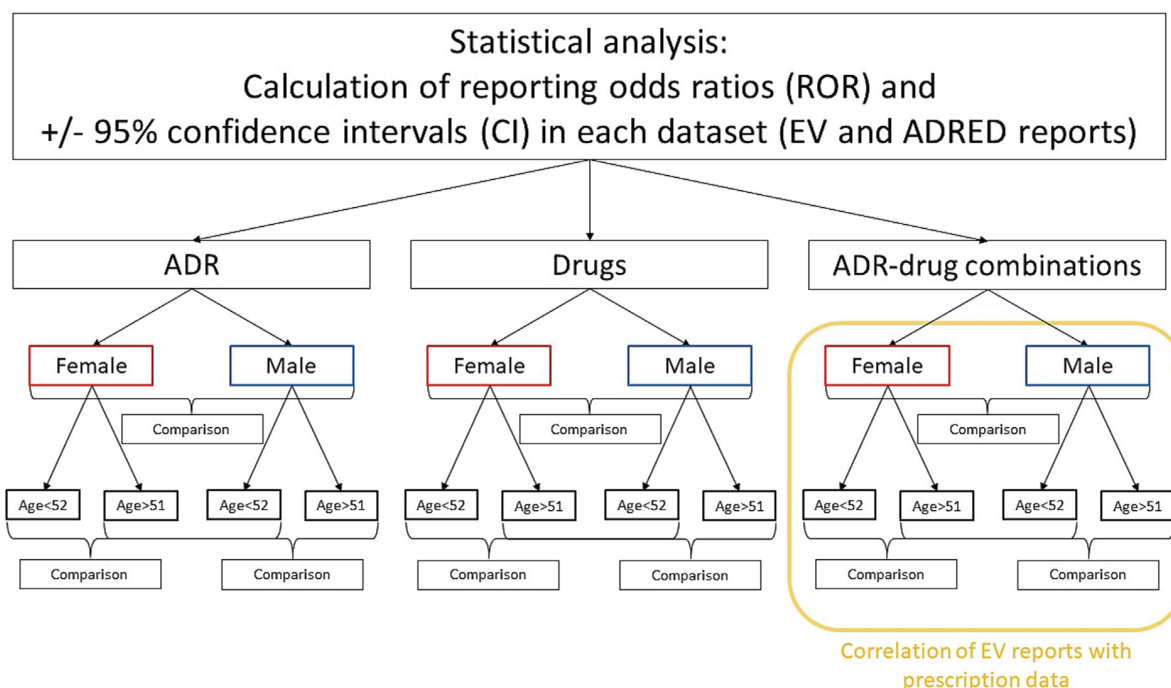


FIGURE 2 Overview of all sub-datasets formed and all statistical analyses carried out between the sub-datasets. ADR, adverse drug reaction; age-groups were built in order to proxy the different hormonal status through menopause in females; ADRED reports, reports from the ADRED study; EV reports, spontaneous reported ADRs.

the system organ class (SOC) and discussed them opposed to the EV reports. The SOC level describes the organ in which the ADR occurs. All MedDRA terms are italicized throughout the manuscript. Drug target nomenclature used in this manuscript conforms to the IUPHAR/BPS Guide to PHARMACOLOGY nomenclature classification.²¹

For the analyses of ADR-drug combinations, each suspected/interacting drug reported was combined with each ADR reported. Hence, for cases including more than one suspected/interacting drug and/or more than one ADR, more than one ADR-drug-combination was created per report. We did not perform an individual case assessment with regard to the causal relationship between the reported drugs and reported ADRs due to the large number of cases. We addressed this point by focussing on ADR-drug-combinations that were most frequently reported or were more frequently reported in accordance with the aims of our statistical analyses (see below), assuming that ADR-drug combinations not based on a causal association would largely be excluded by this approach.

2.5 | Statistical analyses

Means with standard deviations and medians with interquartile ranges were calculated for patients' age and the number of drugs, ADRs and ADR-drug combinations per report. Frequency distributions with percentages were calculated for all other criteria. For sex- and age-group analyses of the EV and ADRED reports, RORs with 95% CIs were

calculated. The calculation is based on a 2-by-2 table considering the number of reports for males/females in EV/ADRED reports, respectively those not containing the observed drug, ADR or ADR-drug combination as comparator (Figure 3). These results cannot be regarded as proven due to the given limitations, but should rather be interpreted like signals. CIs were not adjusted for multiple testing. The calculations were performed for both datasets separately. In our analysis we assumed that if the lower CI exceeded 1.0 the respective drug, ADR or ADR-drug combination was more frequently reported for females, respectively males depending on the sex under consideration. Due to the different sample sizes of the EV and ADRED reports, different cut-offs were set for further consideration of drugs, ADRs and ADR-drug combinations more frequently reported for females or males (EV > 10 reports, ADRED > 3 reports). Finally, the results of both datasets were discussed comparatively.

2.6 | Prescription data

Prescription data according to § 300 SGB V for the drugs of the ADR-drug combinations more frequently reported in either females or males in the EV reports were provided by the Central Research Institute for Ambulatory Health Care in Germany.^{22,23} These were supplied for all patients older than 17 years between September 2015 and December 2018. The number of drug prescriptions represents the total number of outpatient prescriptions for patients of the statutory health insurances (approximately 80–90% of the

		Female	Male
	Number of total cases in EV	6,494	6,070
A	Number of cases with ADR-drug combination in EV <i>Suicidal and self-injurious behavior - quetiapine</i>	22	4
	Number of prescriptions in observed period for quetiapine	4,592,160	3,153,215
B	Number of cases without ADR-drug combination in EV <i>Suicidal and self-injurious behavior - quetiapine</i>	6,472 =6,494–22	6,066 =6,070–4
C	Number of prescriptions without a report of ADR-drug combination <i>Suicidal and self-injurious behavior - quetiapine</i>	4,592,138 =4,592,160–22	3,153,211 =3,153,215–4

ROR = $\frac{A \cdot n_{\text{Cases female}}}{B \cdot n_{\text{Cases female}}} \cdot \frac{A \cdot n_{\text{Cases male}}}{B \cdot n_{\text{Cases male}}} = 5.2 = \frac{22}{6,472} \cdot \frac{4}{6,066}$

ROR (related to prescriptions) = $\frac{A \cdot n_{\text{Cases female}}}{C \cdot n_{\text{Quetiapine prescriptions female}}} \cdot \frac{A \cdot n_{\text{Cases male}}}{C \cdot n_{\text{Quetiapine prescriptions male}}} = 3.8 = \frac{22}{4,592,138} \cdot \frac{4}{3,153,211}$

$= 5.2 = \frac{22}{6,472} \cdot \frac{4}{6,066}$

$= 3.8 = \frac{22}{4,592,138} \cdot \frac{4}{3,153,211}$

FIGURE 3 Calculation of reporting odds ratios (RORs) and RORs in relation to prescription data on the example of *suicidal and self-injurious behaviour*–quetiapine in EudraVigilance. ADR, adverse drug reaction; EV, spontaneous reports from EudraVigilance; n, number of; ROR, reporting odds ratio. The figure shows all formulas and numbers used for the calculation of reporting odds ratios and reporting odds ratios in relation to the prescription data. All relevant data are included for the ADR–drug combination *suicidal and self-injurious behaviour*–quetiapine and the calculation of the reporting odds ratio and the reporting odds ratio in relation to the prescription data is presented here to illustrate how they are calculated in general.

German population) dispensed in German pharmacies. Inpatient prescriptions (e.g. partially antineoplastics) and over-the-counter drugs (e.g. doxylamine) are not covered. Moreover reimbursable but prescription-free drugs as described in pharmaceutical guideline annex I (permitted exceptions to the statutory prescription exclusion according to § 34 Abs. 1 Satz 2 SGB V; e.g. low-dose acetylsalicylic acid) are only covered to an unknown extent.

2.6.1 | Statistical analyses of prescription data for EV reports

Adjusted RORs based on prescription data were calculated for all identified ADR–drug combinations more frequently reported for females or males in the EV reports by using a 2-by-2 table including the number of drug prescriptions subtracted by the number of ADR reports for the respective ADR–drug combination as comparator (Figure 3).

2.7 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22.²⁴

3 | RESULTS

3.1 | Descriptive analyses of EV and ADRED reports

In the descriptive analyses of EV and ADRED reports differences between the two datasets were observed (Table 1). In summary, patients in EV reports were roughly 10 years younger (median: 64 years [49–76]) than patients in ADRED reports (median: 74 years [61–81]), and slightly more females (51.7%, $n = 6494$; males: 48.3%, $n = 6070$) were included in EV than in ADRED reports (51.8%, $n = 1221$; females: 48.2%, $n = 1134$).

In 78.0% of EV reports and 54.5% of ADRED reports, only one drug was reported as suspected/interacting. In both datasets, three of the five most frequently reported drugs were antithrombotics. The antithrombotics most frequently suspected differed between EV (apixaban, rivaroxaban, dabigatran) and ADRED (acetylsalicylic acid, phenprocoumon and clopidogrel).

In median, 2 [1–4] respectively 3 [2–4] ADRs were reported in EV and ADRED reports. The most frequently reported ADRs in EV reports referred to the HLT *central nervous system haemorrhages and cerebrovascular accidents* (9.4%, $n = 1181$).²⁵ In contrast, ADRs related to the HLT *general signs and symptoms not elsewhere classified* (NEC) were most frequently reported in ADRED reports (17.7%, $n = 416$).

TABLE 1 Descriptive analyses of EudraVigilance (EV) and ADRED reports.

	EV reports (n = 12 564)	ADRED reports (n = 2355)
Patient demographics		
Mean (SD) age	61.5 (± 18.1)	69.8 (± 16.0)
Median (IQR) age	64 (49–76)	74 (61–81)
Female	51.7% (n = 6494)	48.2% (n = 1134)
Male	48.3% (n = 6070)	51.8% (n = 1221)
Younger adults (< 52 years)	27.9% (n = 3505)	14.3% (n = 336)
Female	57.3% (2007/3505)	53.9% (181/336)
Male	42.7% (1498/3505)	46.1% (155/336)
Older adults (≥ 52 years)	72.1% (n = 9059)	85.7% (n = 2019)
Female	49.5% (4487/9059)	47.2% (953/2019)
Male	50.5% (4572/9059)	52.8% (1066/2019)
The 5 most frequently reported patient histories		
Information provided ^a	80.6% (n = 10 122)	20.3% (n = 477)
1.	24.3% vascular hypertensive disorders (n = 3052)	9.9% vascular hypertensive disorders (n = 234)
2.	12.5% diabetes mellitus (incl. subtypes) (n = 1569)	5.1% diabetes mellitus (incl. subtypes) (n = 119)
3.	9.6% supraventricular arrhythmias (n = 1206)	4.8% supraventricular arrhythmias (n = 114)
4.	8.4% renal failure and impairment (n = 1056)	4.6% coronary artery disorders (n = 108)
5.	7.5% coronary artery disorders (n = 939)	4.2% renal failure and impairment (n = 100)
Number of drugs per report		
Mean (SD) drugs per report	1.4 (± 1.1)	1.8 (± 1.1)
Median (IQR) drugs per report	1 (1–1)	1 (1–2)
Total number of reports with >1 drug reported as suspected/interacting (percentual)	2761 (22.0%)	1072 (45.5%)
The 5 most frequently reported drugs classified as suspected/interacting ^b		
1.	6.5% apixaban (n = 812)	14.1% acetylsalicylic acid (n = 333)
2.	6.3% rivaroxaban (n = 797)	8.7% metoprolol (n = 205)
3.	2.8% nivolumab (n = 352)	6.9% phenprocoumon (n = 163)
4.	2.5% dabigatran (n = 312)	5.3% ibuprofen (n = 125)
5.	2.0% risperidone (n = 251)	5.1% clopidogrel (n = 121)
Number of reported ADRs (HLT-level) per report		
Mean (SD) ADR per report	3.3 (± 3.5)	2.8 (± 1.7)
Median (IQR) ADR per report	2 [1–4]	3 [2–4]
The 5 most frequently reported ADRs (HLT-level) ^c		
1.	9.4% central nervous system haemorrhages and cerebrovascular accidents (n = 1181)	17.7% general signs and symptoms (n = 416)
2.	6.6% general signs and symptoms (n = 824)	17.1% non-site-specific gastrointestinal haemorrhages (n = 403)
3.	6.2% nausea and vomiting symptoms (n = 785)	15.1% breathing abnormalities (n = 355)
4.	6.2% breathing abnormalities (n = 778)	14.9% nausea and vomiting symptoms (n = 350)
5.	4.8% renal failure and impairment (n = 607)	13.2% neurological signs and symptoms (n = 310)

(Continues)

TABLE 1 (Continued)

	EV reports (n = 12 564)	ADRED reports (n = 2355)
Number of ADR–drug combinations per report		
Mean (SD) ADR–drug combinations per report	4.9 (±12.7)	5.2 (±4.8)
Median (IQR) ADR–drug combinations per report	3 [1–5]	4 [2–6]
The 5 most frequently reported drug–ADR-combinations ^d		
1.	2.4% apixaban–central nervous system haemorrhages and cerebrovascular accidents (n = 297)	7.5% acetylsalicylic acid–non-site-specific gastrointestinal haemorrhages (n = 177)
2.	2.3% rivaroxaban–central nervous system haemorrhages and cerebrovascular accidents (n = 286)	3.5% acetylsalicylic acid–anaemias (n = 82)
3.	1.4% dabigatran–central nervous system haemorrhages and cerebrovascular accidents (n = 171)	2.9% clopidogrel–non-site-specific gastrointestinal haemorrhages (n = 69)
4.	0.9% rivaroxaban–non-site-specific gastrointestinal haemorrhages (n = 118)	2.9% phenprocoumon–non-site-specific gastrointestinal haemorrhages (n = 69)
5.	0.8% denosumab–bone disorders (n = 102)	2.5% metoprolol–breathing abnormalities (n = 58)

Note: Table 1 shows the descriptive analyses of all EudraVigilance and ADRED reports with regard to the demographical parameters of the patients, the five most frequently reported patient histories, ADRs, drugs and ADR–drug combinations.

Abbreviations: ADRED, reports from the ADRED study; EV, spontaneous reports from EudraVigilance; IQR, interquartile range; SD, standard deviation.

^apatients' history was analysed on the HLT level of MedDRA terminology. More than one medical history may be provided in each ADR report, thus one ADR report can be counted in several medical histories. The medical histories of the ADRED reports were not fully transferred to the structured format of the ADR reports in EudraVigilance. Information provided in the free text descriptions could not be analysed computer-based.

^bmore than one drug can be reported as suspected/interacting per ADR report, thus one ADR report can be counted for several drugs.

^cthe ADRs were analysed on the HLT level of MedDRA terminology. More than one ADR can be reported in each ADR report, thus one ADR report can be counted for several ADRs.

^dmore than one ADR–drug combination can be reported in each ADR report, thus one ADR report can be counted for several ADR–drug combinations.

3.2 | Analyses of drugs, ADRs and ADR–drug combinations more frequently reported for females or males in EV and ADRED reports

3.2.1 | Drugs

Females

For females, 47 drugs (younger 13, older 16) in EV, respectively seven drugs (younger 0, older 5) in ADRED, were identified as being reported more often compared to males (Table A1). Three antineoplastic drugs (trastuzumab, methotrexate, paclitaxel) and two psychotropic drugs (mirtazapine, quetiapine) were more often reported for females in EV and ADRED reports (Table 2).

Males

The number of drugs reported more often for males was marginally lower compared to females in EV (altogether 32, younger 1, older 12) while identical to the number observed for females in ADRED (altogether 7, younger 0, older 5; Table A1). Four antineoplastic drugs (irinotecan, etoposide, rituximab, fluorouracil) and acetylsalicylic acid were identified to be reported more often for males in EV and ADRED reports (Table 2).

3.2.2 | ADRs

Females

Thirty (younger 18, older 14) and 10 (younger 1, older 6) ADRs occurred more often in females compared to males in EV and ADRED reports, respectively (Table A2). *Paraesthesias and dysaesthesias, headaches NEC, sodium imbalance and nausea and vomiting symptoms* were identified in both datasets. The other identified ADRs were similar, however, more skin and allergy related ADRs and more detailed localisations of fractures and dislocations were reported in EV (e.g. *spinal fractures and dislocations* and *limb fractures and dislocations*) compared to ADRED reports (e.g. *fractures and dislocations NEC*).

Males

For males, 29 (younger 9, older 24) and six (younger 0, older 11) ADRs were identified in EV and ADRED, respectively. In both datasets, multiple ADRs describing respiratory system related symptoms as well as haemorrhagic ADRs (*gastric and oesophageal haemorrhages* and *central nervous system haemorrhages* in EV vs. *non-site-specific gastrointestinal haemorrhages* in ADRED) were reported more often for males compared to females although the encodings were not identical.

TABLE 2 The drugs reported more often by one sex in EudraVigilance (EV) and ADRED reports.

Drugs more frequently reported for females	EV reports (n = 12 564)			ADRED reports (n = 2355)		
	Number of reports for females	Number of reports for males	ROR [95% CI] For drugs more frequently reported for females in EV reports	Number of reports for females	Number of reports for males	ROR [95% CI] For drugs more frequently reported for females in ADRED reports
Trastuzumab	118	3	41.3 [13.1–130.0]	8	1	8.7 [1.1–69.4]
Methotrexate	72	49	1.5 [1.1–2.2]	23	10	2.5 [1.2–5.3]
Paclitaxel	136	32	4.5 [3.0–6.6]	23	11	2.3 [1.1–4.7]
Mirtazapine	75	42	1.9 [1.3–2.7]	22	6	4.0 [1.6–9.9]
Quetiapine	104	71	1.5 [1.1–2.1]	20	7	3.1 [1.3–7.4]
Drugs more frequently reported for males	EV reports (n = 12 564)			ADRED reports (n = 2355)		
	Number of reports for males	Number of reports for females	ROR [95% CI] for drugs more frequently reported for males in EV reports	Number of reports for males	Number of reports for females	ROR [95% CI] for drugs more frequently reported for males in ADRED reports
Irinotecan	18	5	3.7 [1.4–10.0]	17	3	6.0 [1.8–20.6]
Etoposide	16	6	2.7 [1.1–7.0]	28	7	4.2 [1.8–9.7]
Rituximab	81	53	1.6 [1.1–2.2]	18	6	3.2 [1.3–8.1]
Fluorouracil	39	18	2.2 [1.3–3.9]	36	19	2.0 [1.1–3.5]
Acetylsalicylic acid	124	71	1.8 [1.3–2.4]	201	132	1.6 [1.2–2.0]

Note: Table 2 shows the drugs and their reporting odds ratios with their 95% confidence intervals reported more often for females or males in the EV and the ADRED reports.

Abbreviations: ADRED, reports from the ADRED study; CI, confidence interval; EV, spontaneous reports from EudraVigilance; ROR, reporting odds ratio.

Apart from those ADRs reported more frequently for males in both datasets, especially cardiovascular ADRs and ADRs affecting the blood vessels, precisely those in the central nervous system, were described more often for males compared to females in EV.

3.2.3 | ADR-drug combinations

Females

In total, 30 ADR-drug combinations in EV and two in ADRED were reported more frequently for females compared to males, but none of those were identical (Table A3). Regarding the combinations in EV, most drugs belonged to the superordinate drug classes antineoplastic agents, immunosuppressants and psycholeptics. Comparing all ADR-drug combinations in ADRED with RORs >1 whose CI intersected 1 to combinations found in EV, several combinations describing gastrointestinal symptoms (e.g. *nausea and vomiting*) along with different drugs were found (Figure 4).

Males

In total, 40 ADR-drug combinations in EV and 8 in ADRED were reported more frequently for males compared to females.

In both datasets, bleeding events were more frequently reported for males. However, the locations of these bleedings differed between

the datasets (central nervous system in EV vs. gastrointestinal in ADRED).

Furthermore, on the superordinate drug class level antineoplastic (17 EV/5 ADRED) and antithrombotic agents (10 EV/6 ADRED) occurred most frequently in ADR-drug combinations identified for males in both datasets (Table A3). However, the drugs were not identical to each other (nivolumab, dabigatran in EV vs. etoposide, acetylsalicylic acid in ADRED).

In EV the second most commonly reported drug in the ADR-drug combinations more frequently reported for males was sacubitril/valsartan (n = 5). Additionally, ADR-drug combinations related to infections and immunologic, inflammatory diseases of the lower respiratory tract associated with antineoplastic agents were found to be reported more often for males compared to females several times in EV.

Age stratified analyses of ADR-drug combinations more frequently reported for females or males

In both datasets more ADR-drug combinations were identified for older females (10 EV/2 ADRED) and males (30 EV/4 ADRED) compared to younger females (7 EV/0 ADRED) and males (4 EV/0 ADRED).

Among the ADR-drug combinations for younger males in EV only neuroleptic drugs were observed, whereas those of older males

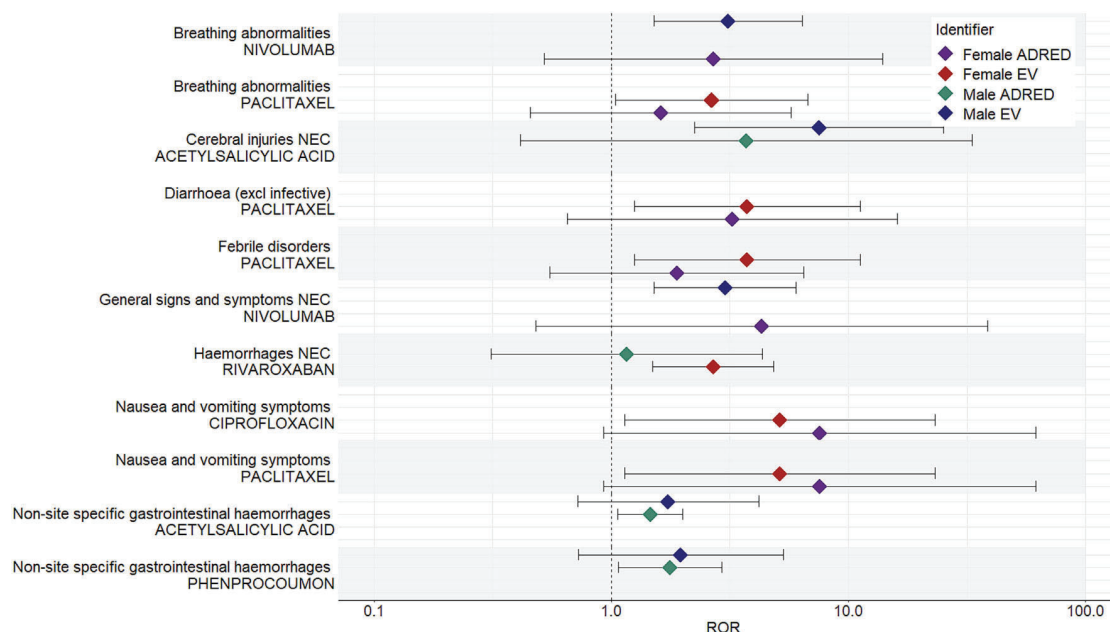


FIGURE 4 The adverse drug reaction (ADR)-drug (ADR on high-level term level) combinations reported more frequently for females or males in EV and ADRED reports. ADRED, reports from the ADRED study; CI, confidence interval; EV, spontaneous reports from EudraVigilance; NEC, not elsewhere classified; ROR, reporting odds ratio. The figure shows the ADR-drug combinations reported more frequently for males or females with a lower confidence interval (CI) > 1 in either EV or ADRED reports, which had at least a reporting odds ratio (ROR) > 1 in the respective other dataset. In the respective other dataset, the lower CI was allowed to intersect 1.

mainly contained nivolumab, sacubitril/valsartan and direct oral anti-coagulants associated with several reactions (e.g. breathing abnormalities, cerebral injuries).

Younger females in EV were more likely to report symptoms of multiple sclerosis related to immunosuppressants while various ADRs with different drugs were reported in the combinations for older females.

3.2.4 | ADR-drug combinations more frequently reported in females or males related to prescription data

Females EV

Only nine out of the previously identified 30 ADR-drug combinations more frequently reported for females remained more frequently reported with consideration of prescription data (Table 3 and Table A4). In these nine ADR-drug combinations, antineoplastic agents associated with gastrointestinal ADRs were predominantly reported (Table 3). The combinations *hepatocellular damage and hepatitis NEC-flupirtine*, *malabsorption syndromes-olmesartan*, *suicidal and self-injurious behaviour-quetiapine* and *sodium imbalance-hydrochlorothiazide* are mentioned here, as these represent rather severe ADRs.

Males EV

Among males, 16 out of the original 40 ADR-drug combinations continued to appear more commonly reported in males with

consideration of prescription data (Table 3 and Table A4). Antithrombotic, lipid-lowering and antidiabetic agents in association with *cerebral injuries NEC, nervous system disorders* together with *renal and urinary disorders* were mainly described in these reports (Table 3).

Two ADR-drug combinations originally more frequently reported for females compared to males, were more frequently reported for males than for females with consideration of prescription data (*diarrhoea [excl. infective]-trastuzumab*, *bone disorders NEC-denosumab*).

3.2.5 | Comparison of ADR-drug combinations in EV on HLT level to ADR-drug combinations in ADRED on SOC level

Females

The ADR-drug combination *psychiatric disorders (SOC level)-quetiapine*, which may reflect a superordinate level of the ADR-drug combination *suicidal and self-injurious behaviour (HLT level)-quetiapine* was only reported for females in the ADRED study. The same applies to the ADR-drug combinations *gastrointestinal disorders (SOC level)-trastuzumab* and *diarrhoea (excl. infective; HLT level)-trastuzumab* as well as *investigations (SOC level)-risperidone* and *pituitary analyses anterior (HLT level)-risperidone*. However, with consideration of prescription data the *diarrhoea (excl. infective; HLT level)-trastuzumab* combination was more often reported for males compared to females in the EV reports.

TABLE 3 ADR-drug combinations (ADR on HLT level) more frequently reported for females or males in EudraVigilance (EV) by considering prescription data.

EV reports (n = 12 564)					
ADR-drug combinations more frequently reported for females/males in EV reports	Number of reports for females	Number of reports for males	ROR [95% CI] for ADR-drug combinations more frequently reported for females/males without consideration of prescription data	ROR [95% CI] for ADR-drug combinations more frequently reported for females/males considering prescription data	
Reported more frequently for females without and with consideration of drug prescription data					
Hepatocellular damage and hepatitis-flupirtine	26	2	12.2 [2.9–51.4]	6.9 [1.6–29.1]	
Sodium imbalance–hydrochlorothiazide	21	2	9.8 [2.3–42.0]	7.9 [1.9–33.7]	
Suicidal and self-injurious behaviour–quetiapine	22	4	5.2 [1.8–15.0]	3.8 [1.3–11.0]	
Malabsorption syndrome–olmesartan	13	1	12.2 [1.6–93.1]	8.2 [1.1–62.4]	
Haemorrhages–rivaroxaban	43	15	2.7 [1.4–4.8]	2.5 [1.4–4.5]	
Nausea and vomiting symptoms–docetaxel	14	2	6.6 [1.5–28.9]	23.5 [5.3–103.9]	
Diarrhoea (excl. infective)–paclitaxel	16	4	3.7 [1.3–11.2]	3.9 [1.3–11.8]	
Febrile disorders–paclitaxel	16	4	3.7 [1.3–11.2]	3.9 [1.3–11.8]	
Nausea and vomiting symptoms–paclitaxel	11	1	5.1 [1.1–23.2]	5.4 [1.2–24.3]	
Reported more frequently for males without and with consideration of drug prescription data					
Cerebral injuries–acetylsalicylic acid	3	21	7.5 [2.2–25.2]	5.2 [1.5–17.3]	
Renal failure and impairment–empagliflozin	1	13	13.9 [1.8–106.6]	8.2 [1.1–63.0]	
Lower respiratory tract infections–azacitidine	2	14	7.5 [1.7–33.0]	4.9 [1.1–21.6]	
Gastrointestinal signs and symptoms–risperidone	1	12	12.9 [1.7–98.9]	15.6 [2.0–119.8]	
Cerebral injuries–rivaroxaban	10	26	2.8 [1.3–5.8]	3.0 [1.4–6.2]	
Paralysis and paresis (excl. cranial nerve)–dabigatran	10	26	2.8 [1.3–5.8]	2.7 [1.3–5.6]	
Urinary abnormalities–rivaroxaban	4	15	4.0 [1.3–12.1]	4.3 [1.4–13.0]	
Acute and chronic pancreatitis–dulaglutide	2	11	5.9 [1.3–26.6]	5.4 [1.2–24.4]	
Myopathies–simvastatin	13	29	2.4 [1.2–4.6]	2.1 [1.1–4.0]	
Blood and blood product treatment–apixaban	15	32	2.3 [1.2–4.2]	2.7 [1.5–5.1]	
Cerebral injuries–dabigatran	3	12	4.3 [1.2–15.2]	4.2 [1.2–14.7]	
Central nervous system haemorrhages and cerebrovascular accidents–dabigatran	69	102	1.6 [1.2–2.2]	1.5 [1.1–2.1]	
Central nervous system haemorrhages and cerebrovascular accidents–edoxaban	31	52	1.8 [1.2–2.8]	1.9 [1.2–3.0]	
Renal failure and impairment–simvastatin	4	13	3.5 [1.1–10.7]	4.2 [1.4–12.8]	
Haemorrhages–edoxaban	6	16	2.9 [1.1–7.3]	3.0 [1.2–7.7]	

(Continues)

TABLE 3 (Continued)

EV reports (n = 12 564)				
ADR-drug combinations more frequently reported for females/males in EV reports	Number of reports females	Number of reports for males	ROR [95% CI] for ADR-drug combinations more frequently reported for females/males without consideration of prescription data	ROR [95% CI] for ADR-drug combinations more frequently reported for females/males considering prescription data
<i>Speech and language abnormalities</i> — <i>dabigatran</i>	3	11	3.9 [1.1–14.1]	3.8 [1.1–13.6]
Reported more frequently for males by considering drug prescription data—reported more frequently for females without consideration of drug prescription data				
<i>Diarrhoea (excl. infective)</i> — <i>trastuzumab</i>	26	2	12.2 [2.9–51.4]	0.1 [0.0–0.4]
<i>Bone disorders</i> — <i>denosumab</i>	65	37	1.6 [1.1–2.5]	0.5 [0.3–0.7]

Note: Table 3 shows all adverse drug reaction (ADR)—drug combinations more frequently reported in EudraVigilance (EV) for females or males by considering prescription data. ADR-drug combinations, which remained reported more frequently by considering prescription data, are categorized as 'Still reported more frequently for females/males'. Combinations which were reported more frequently for females without consideration of prescription data, but changed to be reported more frequently for males when considering the prescription data were categorized as 'reported more frequently for males by considering prescription data'—reported more frequently for females without consideration of drug prescription data.

Abbreviations: CI, confidence interval; EV, spontaneous reports from EudraVigilance; ROR, reporting odds ratio.

Males

Three ADR-drug pairs describing *nervous system events* in combination with *dabigatran* which were reported more frequently in EV reports with and without consideration of drug prescriptions, were only reported on the superordinate level for males in the ADRED reports.

The combination of *lower respiratory tract and lung infections/infections and infestations*—*ibrutinib* was detected in both ADRED and EV, but when relating to prescription data, the lower CI of the observation in EV intersected 1.

4 | DISCUSSION

In both datasets we could identify drugs, ADRs, and ADR-drug combinations more frequently reported for one sex. Although these ADR-drug combinations were mostly not identical, similar tendencies in both datasets could be observed strengthening our results. Except for the younger patients, a higher number of serious ADR-drug combinations was detected to be more frequently reported for males compared to females.

4.1 | Descriptive analyses of EV and ADRED reports

Several differences between both datasets were observed, which may be due to differences in data collection. ADRED reports were systematically collected by trained professionals in a prospective multicentre observational study following a defined protocol. In contrast, spontaneous reports are reported spontaneously in an unstimulated way and outside a study setting. Thus, the lower total number of reports in ADRED is probably related to the fact that these originated from four emergency departments in Germany whereas EV reports were spontaneously submitted from all over Germany. In addition, older adults are more prone to visit an emergency department compared to younger adults, possibly leading to a higher enrollment of older adults in the ADRED study.²⁶

The drugs most frequently reported differed, which might reflect that physicians tend to spontaneously report ADRs related to newly market drugs (e.g. direct oral anticoagulants found in EV) more often compared to well-known drugs (e.g. acetylsalicylic acid, phenprocoumon found in ADRED).²⁷

4.2 | Drugs more frequently reported for females or males independent of drug prescriptions

Independent of drug prescriptions, *quetiapine*, *mirtazapine*, *trastuzumab* and *paclitaxel* were more frequently reported for females, and *irinotecan*, *etoposide*, *rituximab* and *fluorouracil* for males in both datasets. However, without considering drug prescriptions, no conclusions can be drawn whether females or males carry a higher risk to

TABLE 4 Comparison of adverse drug reaction (ADR)-drug combinations more frequently reported in EudraVigilance (EV) on HLT level to ADRED reports on SOC level.

ADR-drug combinations on HLT level in EV reports and superordinate ADR-drug combinations on SOC level in ADRED reports more frequently reported for females/males in EV reports	EV reports (n = 12 564)		ADRED (n = 2355)		
	Number of reports for females	Number of reports for males	ROR [95% CI] for ADR-drug combinations more frequently reported for females/males without consideration of prescription data	ROR (95% CI) for ADR-drug combinations more frequently reported for females/males by considering prescription data	Number of reports for females Number of reports for males
ADR-drug combinations on HLT level reported more frequently for females in EV reports with a match of the ADR-drug combinations on SOC level in ADRED reports					
Diarrhoea (excl. infective)/gastrointestinal disorders-trastuzumab	26	2	12.2 [2.9-51.4]	0.1 [0.0-0.4]	4 0
Diarrhoea (excl. infective)/gastrointestinal disorders-pertuzumab ^a	22	1	20.6 [2.8-153.1]	-	3 0
Suicidal and self-injurious behaviour/psychiatric disorders-quetiapine	22	4	5.2 [1.8-15.0]	3.8 [1.3-11.0]	8 0
Nausea and vomiting symptoms/gastrointestinal disorders-iron preparations	15	2	7.0 [1.6-30.7]	3.2 [0.7-13.9]	2 0
Pituitary analyses anterior/investigations-risperidone	11	2	5.1 [1.1-23.2]	4.2 [0.9-19.1]	1 0
ADR-drug combinations on HLT level reported more frequently for males in EV reports with a match of the ADR-drug combinations on SOC level in ADRED reports					
Paralysis and paresis (excl. cranial nerve)/nervous system disorders-dabigatran	10	26	2.8 [1.3-5.8]	2.7 [1.3-5.6]	0 3
Lower respiratory tract and lung infections/Infections and infestations-ibrutinib	2	11	5.9 [1.3-26.6]	3.0 [0.7-13.6]	0 1
Myopathies/musculoskeletal and connective tissue disorders-simvastatin	13	29	2.4 [1.2-4.6]	2.1 [1.1-4.0]	0 1
Central nervous system haemorrhages and cerebrovascular accidents/nervous system disorders-dabigatran	69	102	1.6 [1.2-2.2]	1.5 [1.1-2.1]	0 3

(Continues)

TABLE 4 (Continued)

ADR-drug combinations on HLT level in EV reports and superordinate ADR-drug combinations on SOC level in ADRED reports more frequently reported for females/males in EV reports	EV reports (n = 12 564)			ADRED (n = 2355)		
	Number of reports for females	Number of reports for males	ROR [95% CI] for ADR-drug combinations more frequently reported for females/males without consideration of prescription data	ROR (95% CI) for ADR-drug combinations more frequently reported for females/males by considering prescription data	Number of reports for females	Number of reports for males
<i>Speech and language abnormalities/nervous system disorders-dabigatran</i>	3	11	3.9 [1.1–14.1]	3.8 [1.1–13.6]	0	3

Note: Table 4 shows the adverse drug reaction (ADR)-drug combinations on HLT level more frequently reported for females or males in EV reports compared to ADR-drug combinations reported on superordinate SOC level in ADRED reports.

Abbreviations: ADRED, reports from the ADRED study; CI, confidence interval; EV, spontaneous reports from EudraVigilance; HLT, high-level term of MedDRA terminology; ROR, reporting odds ratio; SOC, system organ class level of MedDRA terminology.

^ano prescription data for pertuzumab for males were provided by the Central Research Institute for Ambulatory Health Care in Germany. Note that in-hospital prescriptions are not covered in the data provided. Thus, the identified report for pertuzumab for males may be related to an in-hospital prescription. However, also a coding error cannot be excluded.

develop ADRs related to these drugs. Sex-specific prevalence of diseases or indications of drugs may influence the number of drug-exposed females/males potentially at risk to develop an ADR and thus, effect the number of ADR reports. Concerning the above mentioned drugs, the prevalence of diagnosed depressions and the use of antidepressants is higher for females than for males in Germany.^{28,29} Trastuzumab and paclitaxel are commonly used for the treatment of breast cancer, which is more prevalent in females than in males. Etoposid is frequently used for the treatment of testicular carcinoma in males.

4.3 | ADR-drug combinations more frequently reported for females or males in relation to number of drug prescriptions

With consideration of prescription data, the number of ADR-drug combinations reported more often for females and males reduced drastically. Thus, the more frequent use of the respective drug by one sex probably led to the identification of some ADR-drug combinations to be more frequently reported for either females or males. In particular, this was apparent for combinations with immunosuppressants and antipsychotic drugs in females and combinations with antineoplastic agents besides sacubitril/valsartan in males.

Except for younger males, the number of ADR-drug combinations found to be more frequently reported for males was higher than the number of ADR-drug combinations for females, without and with consideration of prescription data. Likewise as in our study, a higher risk for males to develop more serious ADRs compared to females was observed in other studies.³⁰

Nine ADR-drug combinations remained more frequently reported for females compared to males with consideration of prescription data such as gastrointestinal symptoms related to antineoplastic agents (paclitaxel, docetaxel). Previous studies corroborate these associations as sex dependent ADRs for taxanes and related it to a lower drug clearance rate in females, consequently questioning the current dose-finding standards based on the patient's body surface area.³¹ Further on, antiemetics are commonly used as adjuvant therapy, however, the effectiveness of antiemetics seems to be lower in females. Further studies could suggest sex-specific dose and/or drug adjustments.³² Concerning the ADR-drug combination *hepatocellular damage and hepatitis NEC*-flupirtine, a predominance of female sex for flupirtine-associated hepatotoxicity was also described in a publication presenting the results of an analysis of spontaneous reports along with a case series from Germany.³³ Regarding hepatotoxicity, hepatic size and glutathione replenishment appear as relevant factors which seem to vary between sexes. Compared to males, females' liver weight in relation to their body mass index is lower. Additionally research in mice suggests lower glutathione levels in females.³⁴ Without further reference to sex-specific effects, a withdrawal of flupirtine due to serious liver problems was endorsed by the EMA in 2018.³⁵ Furthermore, the ADR-drug combinations *malabsorption syndromes*-olmesartan and *sodium imbalance*-hydrochlorothiazide are already reported in

literature to occur more frequently in females than in males.^{36,37} Hormonal influences of oestrogens further increasing the renal excretion of sodium may represent a decisive factor for this sex-specific ADR of diuretics.^{37,38}

The ADR–drug combination, *self-injurious behaviour*–quetiapine was also found on the superordinate level of the combination *psychiatric disorders*–quetiapine in the ADRED reports. An overall higher risk of self-injurious behaviour related to antipsychotics for females compared to males was also observed by others. However, it remains unclear whether the higher number of diagnosed nervous system disorders (e.g. depressions) for females compared to males may have impacted on these results.^{28,37,39} In general, a higher risk of self-injurious behaviour was reported for quetiapine compared to other antipsychotics.⁴⁰ Therefore, physicians should consider other known risk factors e.g. previous suicide attempts when prescribing quetiapine to females.⁴¹

With consideration of prescription data, remaining ADR–drug pairs for males ($n = 16$) largely contained antithrombotic (mainly related to *nervous system disorders* or *cerebral injuries*), lipid-lowering and antidiabetic agents.

The combinations of *nervous system disorders* respectively *paralysis and paresis*, *central nervous system haemorrhages and cerebrovascular accidents* as well as *speech and language abnormalities* in combination with dabigatran were more frequently reported for males compared to females in both datasets. So far, literature is inconsistent with some studies reporting a higher prevalence of bleedings with DOACs in males while others observed higher risks of bleeding events for females or did not observe any sex differences regarding bleeding events at all.^{42–44} Sex-specific differences in the expression of enzymes affecting the metabolism and pharmacodynamics of dabigatran could contribute to these findings. Thus, further research on the underlying polymorphisms could investigate sex-specific genetic risk constellations requiring a dose adjustment of dabigatran.⁴⁵

In our analysis *myopathies* and *musculoskeletal and connective tissue disorders* in combination with simvastatin were more frequently reported for males compared to females in both datasets, also with consideration of prescription data. Literature is inconsistent whether these ADRs occur more frequently in males or females. Sex-related differences e.g. a higher *CYP3A4* activity in females result in different pharmacokinetics of statins that could contribute to sex differences in statin related myopathies, as they are presumed to be dose related. Dose adjustments may also be suggested.^{46–48}

4.4 | Strengths and limitations

The strengths of our analysis are the large database, the consideration of the number of reports in relation to drug prescriptions and the complementary study design. The consideration of ADR reports from two different study designs strengthens the relevance of our results.

Although the two datasets used are valuable sources of data, this study is subject to several limitations. For example, sometimes only

tendencies could be observed in both datasets potentially due to the lower number of ADRED reports, and differences in the used MedDRA terms to code these ADRs.

In accordance with the definition of the seriousness criteria, the EV reports can also be related to ADRs that occurred during a hospital stay and led to a prolongation thereof, while in ADRED only ADRs which led to an emergency department admission are captured. Further, in EV hospitalization was coded per report, thereby the ADR responsible for the hospitalization is not determinable. In both datasets, each suspected/interacting drug reported was combined with each reaction reported. Our analysis thus represents all possible ADR–drug combinations per report. Due to the huge number of reports, we could not assess the causal relationship between the drugs and ADRs reported, hence, it may be possible that some of the ADR–drug combinations are not causally related to each other. However, since we restricted the analyses to those ADR–drug combinations that were most frequently reported and with a lower bound of the 95% CI > 1 , we assume that ADR–drug combinations without a causal association would largely not be included in our analyses. Notably, sex differences in non-serious ADRs (not leading to hospitalisations) are not addressed in this study.

Another immanent limitation of the spontaneously reported ADRs in EV is the unknown amount of under-reporting, which may vary between specific ADRs (e.g. unexpected) and drugs (e.g. newly authorized drugs).^{27,49} Furthermore stimulated reporting for specific drugs and ADRs can occur, especially, after warnings were published (e.g. flupirtine).⁵⁰ Please note that this may also affect the ROR calculations. The limitations known for signal detection in pharmacovigilance studies apply here.^{18,19}

Finally, the prescription data used did not cover any inpatient prescriptions, prescriptions for privately insured patients and OTCs. Additionally, potentially reimbursable drugs (e.g. low-dose acetylsalicylic acid) are not fully covered. The amount of usage for these individual drugs cannot be quantified. Note that the ADRED reports could not be considered in relation to drug prescriptions.

4.5 | Conclusion

Our results can contribute to raise awareness and further knowledge regarding sex-specific differences in serious ADRs. Particular attention should be paid to males, since a higher number of serious ADR–drug combinations was found compared to females. Further research investigating possible explanations for the observed disparities are needed.

Healthcare professionals should be aware of sex-specific ADRs and record all ADRs in order to improve the safety of drug therapy for all sexes.

AUTHOR CONTRIBUTIONS

Diana Dubrall, Katja Susanne Just, Julia Carolin Stingl, Bernhardt Sachs and Patrick Christ contributed to the conception and design of the study. Julia Carolin Stingl and Katja Susanne Just contributed to

the design of the analysis of the ADRED study data. Diana Dubrall and Patrick Christ performed the analysis of EV and ADRED data. The evaluation and discussion of the EV and ADRED analysis results was performed by Diana Dubrall, Katja Susanne Just, Bernhardt Sachs, Patrick Christ and Julia Carolin Stingl. The first drafts of the manuscript were written by Patrick Christ, Diana Dubrall and Bernhardt Sachs. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTERESTS STATEMENT

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DATA AVAILABILITY STATEMENT

The pseudonymized ADR reports from EV are not publicly accessible due to data protection requirements. Distinct levels of access are provided for various stakeholders (<https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance/access-eudravigilance-data>). Being 1 of the competent authorities in Germany, the highest level of access is granted to the Federal Institute for Drugs and Medical Devices (BfArM). Nevertheless, even with lowest access level, researchers can perform the same analysis in EV with aggregated data (public access: www.adrreports.eu/en/index.html). For further information regarding the processing of personal data in the context of the operation of EV Human we refer to the European Medicines Agency's Data Protection Notice for EV Human.⁵¹

DISCLAIMER

The information and views set out in this manuscript are those of the authors and do not necessarily reflect the official opinion of the Federal Institute for Drugs and Medical Devices.

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REFERENCES

- Smith JW, Seidl LG. Studies on the epidemiology of adverse drug reactions: V. Clinical factors influencing susceptibility. *Ann Intern Med.* 1966;65(4):629. doi:10.7326/0003-4819-65-4-629
- Martin RM, Biswas PN, Freemantle SN, Pearce GL, Mann RD. Age and sex distribution of suspected adverse drug reactions to newly marketed drugs in general practice in England: analysis of 48 cohort studies. *Br J Clin Pharmacol.* 1998;46(5):505-511. doi:10.1046/j.1365-2125.1998.00817.x
- Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet.* 2009;48(3):143-157. doi:10.2165/00003088-200948030-00001
- Reza N, Gruen J, Bozkurt B. Representation of women in heart failure clinical trials: barriers to enrollment and strategies to close the gap. *Am Heart J Plus.* 2022;13:100093. doi:10.1016/j.ahjplus.2022.100093
- Dumanski SM, Ahmed SB. Sex, drugs, and adverse drug reactions: sex differences in laboratory monitoring outcomes after initiation of renin-angiotensin-aldosterone-system inhibition therapy. *Circ Cardiovasc Qual Outcomes.* 2020;13(9):e007045. doi:10.1161/CIRCOUTCOMES.120.007045
- Geller SE, Koch A, Pellettieri B, Carnes M. Inclusion, analysis, and reporting of sex and race/ethnicity in clinical trials: have we made progress? *J Womens Health (Larchmt).* 2011;20(3):315-320. doi:10.1089/jwh.2010.2469
- Martin K, Bégaud B, Latry P, Miremont-Salamé G, Fourier A, Moore N. Differences between clinical trials and postmarketing use. *Br J Clin Pharmacol.* 2004;57(1):86-92. doi:10.1046/j.1365-2125.2003.01953.x
- Sultana J, Cutroneo P, Trifirò G. Clinical and economic burden of adverse drug reactions. *J Pharmacol Pharmacother.* 2013;4(1_suppl):S73-S77. doi:10.4103/0976-500X.120957
- Lapeyre-Mestre M. Considering sex-specific adverse drug reactions should be a priority in pharmacovigilance and pharmacoepidemiological studies. *EClinicalMedicine.* 2019;17:100216. doi:10.1016/j.eclinm.2019.11.009
- Just KS, Dormann H, Böhme M, et al. Personalising drug safety results from the multi-Centre prospective observational study on adverse drug reactions in emergency departments (ADRED). *Eur J Clin Pharmacol.* 2020;76(3):439-448. doi:10.1007/s00228-019-02797-9
- Schurig AM, Böhme M, Just KS, et al. Adverse drug reactions (ADR) and emergencies. *Deutsches Ärzteblatt (Ausg a : Online)* Published Online April. 2018;115(15):251-258. doi:10.3238/arztebl.2018.0251
- Leitzen S, Dubrall D, Toni I, et al. Analysis of the reporting of adverse drug reactions in children and adolescents in Germany in the time period from 2000 to 2019. *PLoS ONE.* 2021;16(3):e0247446. doi:10.1371/journal.pone.0247446
- Dubrall D, Just KS, Schmid M, Stingl JC, Sachs B. Adverse drug reactions in older adults: a retrospective comparative analysis of spontaneous reports to the German Federal Institute for Drugs and Medical Devices. *BMC Pharmacol Toxicol.* 2020;21(1):25. doi:10.1186/s40360-020-0392-9
- European Medicines Agency. Public data from Article 57 database. Accessed February 7, 2023. <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/data-medicines-iso-idmp-standards/public-data-article-57-database>
- European Medicines Agency (EMA). Guideline on good pharmacovigilance practices (GVP) module VI—collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2). Published Online July 28, 2017. Accessed August 1, 2023. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf

16. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *The Lancet*. 2000;356(9237):1255-1259. doi:10.1016/S0140-6736(00)02799-9
17. MedDRA Gender Adverse Event Term Lists. Accessed July 5, 2023. <https://www.meddra.org/paediatric-and-gender-adverse-event-term-lists>
18. Montastruc JL, Sommet A, Bagheri H, Lapeyre-Mestre M. Benefits and strengths of the disproportionality analysis for identification of adverse drug reactions in a pharmacovigilance database: commentary. *Br J Clin Pharmacol*. 2011;72(6):905-908. doi:10.1111/j.1365-2125.2011.04037.x
19. Noguchi Y, Tachi T, Teramachi H. Detection algorithms and attentive points of safety signal using spontaneous reporting systems as a clinical data source. *Brief Bioinform*. 2021;22(6):bbab347. doi:10.1093/bib/bbab347
20. te Velde ER, Pearson PL. The variability of female reproductive ageing. *Hum Reprod Update*. 2002;8(2):141-154. doi:10.1093/humupd/8.2.141
21. Alexander SP, Kelly E, Marrion NV, et al. The concise guide to pharmacology 2017/18: overview. *Br J Pharmacol*. 2017;174(Suppl 1):S1-S16. doi:10.1111/bph.13882
22. § 300 Abrechnung der Apotheken und weiterer Stellen. Sozialgesetzbuch (SGB) Fünftes Buch (V) - Gesetzliche Krankenversicherung - (Artikel 1 des Gesetzes v. 20. Dezember 1988, BGBl. I S. 2477).
23. Central Research Institute of Ambulatory Health Care in Germany. Accessed February 23, 2023. <https://www.zi.de>
24. Alexander SPH, Cidlowski JA, Kelly E, et al. The concise guide to pharmacology 2021/22: enzymes. *Br J Pharmacol*. 2021;178(Suppl 1):S246-S263. doi:10.1111/bph.15540
25. Medical Dictionary for Regulatory Activities (MedDRA). Accessed February 8, 2023. <https://www.meddra.org>. <https://www.meddra.org>
26. Aminzadeh F, Dalziel WB. Older adults in the emergency department: a systematic review of patterns of use, adverse outcomes, and effectiveness of interventions. *Ann Emerg Med*. 2002;39(3):238-247. doi:10.1067/mem.2002.121523
27. Hasford J, Goettler M, Munter KH, Müller-Oerlinghausen B. Physicians' knowledge and attitudes regarding the spontaneous reporting system for adverse drug reactions. *J Clin Epidemiol*. 2002;55(9):945-950. doi:10.1016/S0895-4356(02)00450-X
28. Busch MA, Maske UE, Ryl L, Schlack R, Hapke U. Prävalenz von depressiver Symptomatik und diagnostizierter Depression bei Erwachsenen in Deutschland: Ergebnisse der Studie zur Gesundheit Erwachsener in Deutschland (DEGS1). *Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz*. 2013;56(5-6):733-739. doi:10.1007/s00103-013-1688-3
29. Schuler J, Dückelmann C, Beindl W, Prinz E, Michalski T, Pichler M. Polypharmacy and inappropriate prescribing in elderly internal-medicine patients in Austria. *Wien Klin Wochenschr*. 2008;120(23-24):733-741. doi:10.1007/s00508-008-1089-z
30. Brabete AC, Greaves L, Maximos M, Huber E, Li A, Lê ML. A sex- and gender-based analysis of adverse drug reactions: a scoping review of pharmacovigilance databases. *Pharmaceuticals*. 2022;15(3):298. doi:10.3390/ph15030298
31. Chmielewski NN, Limoli CL. Sex differences in taxane toxicities. *Cancer*. 2022;14(14):3325. doi:10.3390/cancers14143325
32. Schmetzer O, Flörcken A. Sex differences in the drug therapy for oncologic diseases. *Handb Exp Pharmacol*. 2013;411-442. doi:10.1007/978-3-642-30726-3_19
33. Douros A, Bronder E, Andersohn F, et al. Flupirtine-induced liver injury—seven cases from the Berlin case-control surveillance study and review of the German spontaneous adverse drug reaction reporting database. *Eur J Clin Pharmacol*. 2014;70(4):453-459. doi:10.1007/s00228-013-1631-4
34. Borlak J, van Bömmel F, Berg T. N-acetylcysteine and prednisolone treatment improved serum biochemistries in suspected flupirtine cases of severe idiosyncratic liver injury. *Liver Int*. 2018;38(2):365-376. doi:10.1111/liv.13538
35. Withdrawal of pain medicine flupirtine endorsed – EMA 23.03.2018. Accessed February 15, 2023. <https://www.ema.europa.eu/en/news/withdrawal-pain-medicine-flupirtine-endorsed>
36. Basson M, Mezzarobba M, Weill A, et al. Severe intestinal malabsorption associated with olmesartan: a French nationwide observational cohort study. *Gut*. 2016;65(10):1664-1669. doi:10.1136/gutjnl-2015-309690
37. Hendriksen LC, van der Linden PD, Lagro-Janssen ALM, et al. Sex differences associated with adverse drug reactions resulting in hospital admissions. *Biol Sex Differ*. 2021;12(1):34. doi:10.1186/s13293-021-00377-0
38. Stachenfeld NS, Splenser AE, Calzone WL, Taylor MP, Keefe DL. Selected contribution: sex differences in osmotic regulation of AVP and renal sodium handling. *J Appl Physiol*. 2001;91(4):1893-1901. doi:10.1152/jappl.2001.91.4.1893
39. Sørup FKH, Eriksson R, Westergaard D, Hallas J, Brunak S, Ejdrup AS. Sex differences in text-mined possible adverse drug events associated with drugs for psychosis. *J Psychopharmacol (Oxf)*. 2020;34(5):532-539. doi:10.1177/0269881120903466
40. Reutfors J, Brenner P, Brody B, Wray H, Andersen M, Brandt L. A post-authorization safety study of quetiapine as antidepressant treatment in Sweden: nested case-control analyses of select outcomes. *Drug Saf*. 2020;43(2):135-145. doi:10.1007/s40264-019-00889-0
41. Hawton K, Casañas I, Comabella C, Haw C, Saunders K. Risk factors for suicide in individuals with depression: a systematic review. *J Affect Disord*. 2013;147(1-3):17-28. doi:10.1016/j.jad.2013.01.004
42. Palareti G, Legnani C, Antonucci E, et al. Do women with venous thromboembolism bleed more than men during anticoagulation? Data from the real-life, prospective START-register. *Ther Adv Drug Saf*. 2021;12:20420986211062965. doi:10.1177/20420986211062965
43. Raccach BH, Perlman A, Zwas DR, et al. Gender differences in efficacy and safety of direct Oral anticoagulants in atrial fibrillation: systematic review and network meta-analysis. *Ann Pharmacother*. 2018;52(11):1135-1142. doi:10.1177/1060028018771264
44. Tsadok MA, Jackevicius C, Rahme E, Humphries K, Pilote L. Sex differences in dabigatran use, safety, and effectiveness in a population-based cohort of patients with atrial fibrillation. *J Am Coll Cardiol*. 2014;63(12):A438. doi:10.1016/S0735-1097(14)60438-1
45. Shi J, Wang X, Nguyen JH, et al. Dabigatran etexilate activation is affected by the CES1 genetic polymorphism G143E (rs71647871) and gender. *Biochem Pharmacol*. 2016;119:76-84. doi:10.1016/j.bcp.2016.09.003
46. Skilving I, Eriksson M, Rane A, Ovesjö ML. Statin-induced myopathy in a usual care setting—a prospective observational study of gender differences. *Eur J Clin Pharmacol*. 2016;72(10):1171-1176. doi:10.1007/s00228-016-2105-2
47. Abed W, Abujbara M, Batieha A, Ajlouni K. Statin induced myopathy among patients attending the National Center for diabetes, endocrinology, & genetics. *Ann Med Surg (Lond)*. 2022;74:103304. doi:10.1016/j.amsu.2022.103304
48. Farkouh A, Riedl T, Gottardi R, Czejka M, Kautzky-Willer A. Sex-related differences in pharmacokinetics and pharmacodynamics of frequently prescribed drugs: a review of the literature. *Adv Ther*. 2020;37(2):644-655. doi:10.1007/s12325-019-01201-3

49. Hazell L, Shakir SAW. Under-reporting of adverse drug reactions: a systematic review. *Drug Saf.* 2006;29(5):385-396. doi:[10.2165/00002018-200629050-00003](https://doi.org/10.2165/00002018-200629050-00003)
50. Ishiguro C, Hinomura Y, Uemura K, Matsuda T. Analysis of the factors influencing the spontaneous reporting frequency of drug safety issues addressed in the FDA's drug safety communications. *Pharmaceut Med.* 2014;28(1):7-19. doi:[10.1007/s40290-014-0043-9](https://doi.org/10.1007/s40290-014-0043-9)
51. European Medicines Agency (EMA). European Medicines Agency's Data Protection Notice for EudraVigilance Human (EV). Accessed February 7, 2023. https://www.ema.europa.eu/en/documents/other/european-medicines-agencys-data-protection-notice-eudravigilance-human-ev_en.pdf

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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3.1.1 Supplemental information: Identification and comparison of sex-specific serious adverse drug reactions in spontaneous reports and systematically collected reports (ADRED)

Table Appendix 1

Table Appendix 1: All drugs reported more often by one sex (in total/younger/older) in EV or/and ADRED reports

	EV reports (n=12,564)			ADRED reports (n=2,355)		
Drugs more frequently reported for females	Number of reports for females	Number of reports for males	ROR [lower-upper 95% CI] for drugs more frequently reported for females in EV reports	Number of reports for females	Number of reports for males	ROR [lower-upper 95% CI] for drugs more frequently reported for females in ADRED reports
Females in total						
Afatinib	16	6	2.8 [1.1 - 7.0]	-	-	-
Alemtuzumab	97	19	5.3 [3.3 - 8.7]	-	-	-
Amitriptyline	26	10	2.7 [1.3 - 5.6]	-	-	-
Bevacizumab	82	29	2.9 [1.9 - 4.5]	-	-	-
Botulinum toxin	10	1	10.3 [1.3 - 80.7]	-	-	-
Brivudine	18	4	4.7 [1.6 - 13.8]	-	-	-
Citalopram	40	19	2.2 [1.3 - 3.8]	-	-	-
Colecalciferol	11	2	5.7 [1.3 - 25.6]	-	-	-
Cyclophosphamide	58	22	2.7 [1.7 - 4.5]	-	-	-
Daclizumab	61	23	2.8 [1.7 - 4.5]	-	-	-
Denosumab	137	46	3.1 [2.2 - 4.4]	-	-	-
Dimethyl fumarate	78	42	1.9 [1.3 - 2.8]	-	-	-
Donepezil	12	3	4.1 [1.2 - 14.7]	-	-	-
Doxylamine	27	10	2.8 [1.4 - 5.8]	-	-	-
Duloxetine	36	15	2.5 [1.4 - 4.5]	-	-	-
Epirubicin	52	2	27.0 [6.6 - 111.0]	-	-	-
Fingolimod	59	22	2.8 [1.7 - 4.5]	-	-	-
Flupirtine	32	6	5.5 [2.3 - 13.2]	-	-	-
Gadobutrol	28	12	2.4 [1.2 - 4.8]	-	-	-
Gadoteric acid	36	19	2.0 [1.1 - 3.4]	-	-	-
Glatiramer	39	19	2.1 [1.2 - 3.7]	-	-	-
Hydrochlorothiazide	50	11	4.7 [2.5 - 9.1]	-	-	-
Iopromide	37	13	2.9 [1.6 - 5.6]	-	-	-
Iron preparations	45	17	2.7 [1.6 - 4.8]	-	-	-
Lamotrigine	29	12	2.5 [1.3 - 4.9]	-	-	-
Levothyroxine	-	-	-	11	3	4.0 [1.1 - 14.3]

Macitentan	16	6	2.8 [1.1 - 7.0]	-	-	-
Macrogol	11	3	3.8 [1.1 - 13.6]	-	-	-
Methotrexate	72	49	1.5 [1.1 - 2.2]	23	10	2.5 [1.2 - 5.3]
Metoclopramide	16	4	4.1 [1.4 - 12.4]	-	-	-
Metronidazole	12	3	4.1 [1.2 - 14.7]	-	-	-
Mirtazapine	75	42	1.9 [1.3 - 2.7]	22	6	4.0 [1.6 - 9.9]
Natalizumab	91	34	2.8 [1.9 - 4.1]	-	-	-
Olmesartan	15	1	15.5 [2.0 - 117.4]	-	-	-
Opipramol	-	-	-	9	2	4.9 [1.1 - 22.6]
Paclitaxel	136	32	4.5 [3.0 - 6.6]	23	11	2.3 [1.1 - 4.7]
Palbociclib	32	1	33.2 [4.5 - 242.8]	-	-	-
Pantoprazole	58	33	1.8 [1.2 - 2.8]	-	-	-
Pegfilgrastim	20	8	2.6 [1.1 - 5.9]	-	-	-
Peginterferon	18	6	3.1 [1.2 - 7.8]	-	-	-
Pertuzumab	82	2	42.8 [10.5 - 174.2]	-	-	-
Quetiapine	104	71	1.5 [1.1 - 2.1]	20	7	3.1 [1.3 - 7.4]
Sertraline	41	21	2.0 [1.2 - 3.4]	-	-	-
Tamoxifen	10	1	10.3 [1.3 - 80.7]	-	-	-
Teriflunomide	51	12	4.4 [2.4 - 8.3]	-	-	-
Tofacitinib	22	5	4.6 [1.7 - 12.0]	-	-	-
Trastuzumab	118	3	41.3 [13.1 - 130.0]	8	1	8.7 [1.1 - 69.4]
Treprostinil	14	3	4.8 [1.4 - 16.8]	-	-	-
Venlafaxine	64	34	2.0 [1.3 - 3.0]	-	-	-
Younger females (age=18-51 years)						
Alemtuzumab	87	17	3.9 [2.3 - 6.7]	-	-	-
Daclizumab	49	14	2.7 [1.5 - 4.8]	-	-	-
Dimethyl fumarate	53	22	1.8 [1.1 - 3.0]	-	-	-
Epirubicin	19	1	14.3 [1.9 - 107.0]	-	-	-
Fingolimod	45	15	2.3 [1.3 - 4.1]	-	-	-
Flupirtine	17	3	4.3 [1.2 - 14.6]	-	-	-
Iron preparations	34	5	5.1 [2.0 - 13.2]	-	-	-
Natalizumab	74	30	1.9 [1.2 - 2.9]	-	-	-
Paclitaxel	32	5	4.8 [1.9 - 12.4]	-	-	-
Pertuzumab	31	1	23.5 [3.2 - 172.2]	-	-	-
Sertraline	30	9	2.5 [1.2 - 5.3]	-	-	-
Teriflunomide	27	8	2.5 [1.2 - 5.6]	-	-	-

Trastuzumab	36	1	27.3 [3.7 - 199.7]	-	-	-
Older females (age>51 years)						
Bevacizumab	71	25	2.2 [1.4 - 3.4]	-	-	-
Brivudine	15	2	5.6 [1.3 - 24.7]	-	-	-
Citalopram	27	5	4.1 [1.6 - 10.6]	-	-	-
Denosumab	133	43	2.4 [1.7 - 3.4]	-	-	-
Duloxetine	21	3	5.3 [1.6 - 17.7]	-	-	-
Epirubicin	33	1	25.0 [3.4 - 183.2]	-	-	-
Flupirtine	15	3	3.8 [1.1 - 13.0]	-	-	-
Hydrochlorothiazide	46	11	3.2 [1.6 - 6.1]	-	-	-
Levothyroxine	-	-	-	9	2	4.9 [1.1 - 22.6]
Methotrexate	-	-	-	20	7	3.1 [1.3 - 7.4]
Mirtazapine	-	-	-	22	5	4.8 [1.8 - 12.7]
Natalizumab	17	4	3.2 [1.1 - 9.5]	-	-	-
Olmesartan	15	1	11.3 [1.5 - 85.4]	-	-	-
Opipramol	-	-	-	8	1	8.7 [1.1 - 69.4]
Paclitaxel	104	27	3.0 [1.9 - 4.6]	-	-	-
Palbociclib	31	1	23.5 [3.2 - 172.2]	-	-	-
Pertuzumab	51	1	39 [5.4 - 282.8]	-	-	-
Quetiapine	-	-	-	17	5	3.7 [1.4 - 10.1]
Teriflunomide	24	4	4.5 [1.6 - 13.1]	-	-	-
Tofacitinib	21	2	7.9 [1.9 - 33.8]	-	-	-
Trastuzumab	82	2	31.9 [7.8 - 129.8]	-	-	-
Drugs more frequently reported for males	Number of reports for males	Number of reports for females	ROR [lower-upper 95% CI] for drugs more frequently reported for males in EV reports	Number of reports for males	Number of reports for females	ROR [lower-upper 95% CI] for drugs more frequently reported for males in ADRED reports
Males in total						
Acetylsalicylic acid	124	71	1.8 [1.3 - 2.4]	201	132	1.6 [1.2 - 2.0]
Atezolizumab	13	1	13.4 [1.8 - 102.4]	-	-	-
Azacitidine	72	20	3.7 [2.2 - 6.1]	-	-	-

Bacillus calmette-guérin bacteria	39	2	20.0 [4.8 - 82.9]	-	-	-
Cetuximab	36	12	3.1 [1.6 - 5.9]	-	-	-
Cisplatin	48	12	4.1 [2.2 - 7.7]	-	-	-
Clopidogrel	-	-	-	75	46	1.7 [1.2 - 2.5]
Clozapine	76	42	1.9 [1.3 - 2.7]	-	-	-
Cytarabine	32	16	2.1 [1.1 - 3.8]	-	-	-
Dabigatran	181	131	1.4 [1.1 - 1.8]	-	-	-
Dapagliflozin	33	15	2.3 [1.2 - 4.2]	-	-	-
Dulaglutide	39	21	1.9 [1.1 - 3.3]	-	-	-
Emtricitabine/Tenofovir	12	1	12.4 [1.6 - 95.1]	-	-	-
Etoposide	16	6	2.7 [1.1 - 7.0]	28	7	4.2 [1.8 - 9.7]
Febuxostat	14	4	3.6 [1.2 - 11.0]	-	-	-
Fluorouracil	39	18	2.2 [1.3 - 3.9]	36	19	2.0 [1.1 - 3.5]
Folinic acid	-	-	-	16	6	2.8 [1.1 - 7.3]
Gadobenate dimeglumine	12	3	4.1 [1.2 - 14.6]	-	-	-
Heparin	23	8	3.0 [1.3 - 6.6]	-	-	-
Ibrutinib	68	28	2.5 [1.6 - 3.9]	-	-	-
Idelalisib	57	20	2.9 [1.8 - 4.9]	-	-	-
Ipilimumab	63	34	1.9 [1.3 - 2.9]	-	-	-
Irinotecan	18	5	3.7 [1.4 - 10.0]	17	3	6.0 [1.8 - 20.6]
Leuprorelin	11	2	5.7 [1.3 - 25.6]	-	-	-
Methylphenidate	11	2	5.7 [1.3 - 25.6]	-	-	-
Nintedanib	35	17	2.1 [1.2 - 3.8]	-	-	-
Nivolumab	231	120	2.0 [1.6 - 2.4]	-	-	-
Pembrolizumab	84	50	1.7 [1.2 - 2.5]	-	-	-
Rituximab	81	53	1.6 [1.1 - 2.2]	18	6	3.2 [1.3 - 8.1]
Sacubitril/Valsartan	119	42	2.9 [2.0 - 4.1]	-	-	-
Simvastatin	58	37	1.6 [1.1 - 2.4]	-	-	-
Sulfur hexafluoride	12	2	6.2 [1.4 - 27.6]	-	-	-
Temsirolimus	21	4	5.4 [1.9 - 15.7]	-	-	-
Ustekinumab	34	18	1.9 [1.1 - 3.4]	-	-	-
Younger Males (age=18-51 years)						
Clozapine	52	18	2.1 [1.2 - 3.6]			
Older Males (age>51 years)						
Acetylsalicylic acid	-	-	-	194	124	1.6 [1.2 - 2.0]
Atezolizumab	13	1	9.6 [1.3 - 73.6]	-	-	-
Azacitidine	69	20	2.5 [1.5 - 4.1]	-	-	-

Bacillus calmette-guérin bacteria	38	2	13.8 [3.3 - 57.4]	-	-	-
Cetuximab	35	10	2.6 [1.3 - 5.2]	-	-	-
Cisplatin	40	7	4.2 [1.9 - 9.3]	-	-	-
Clopidogrel	-	-	-	72	46	1.7 [1.1 - 2.4]
Etoposide	-	-	-	18	6	3.2 [1.3 - 8.1]
Fluorouracil	-	-	-	33	17	2.1 [1.1 - 3.7]
Heparin	22	6	2.7 [1.1 - 6.7]	-	-	-
Ibrutinib	66	27	1.8 [1.1 - 2.8]	-	-	-
Idelalisib	51	15	2.5 [1.4 - 4.4]	-	-	-
Irinotecan	-	-	-	15	3	5.3 [1.5 - 18.5]
Leuprorelin	11	1	8.2 [1.1 - 63.2]	-	-	-
Nivolumab	205	102	1.4 [1.1 - 1.7]	-	-	-
Sacubitril/Valsartan	118	42	2.0 [1.4 - 2.8]	-	-	-
Temsirolimus	16	3	3.9 [1.1 - 13.6]	-	-	-

4 EV= spontaneous reports from EudraVigilance; ADRED= reports from the ADRED study; ROR=
5 reporting odds ratio; CI= confidence interval

6 Legend Table Appendix 1: Table Appendix 1 shows all drugs and their reporting odds ratios with their
7 95% confidence intervals reported more often for females or males in the EV or/and the ADRED
8 reports

Table Appendix 2

Table Appendix 2: All ADR (on HLT-level) reported more often by one sex (in total/younger/older) in EV or/and ADRED reports

	EV reports (n=12,564)			ADRED reports (n=2,355)		
ADR (HLT-level) more frequently reported for females	Number of reports for females	Number of reports for males	ROR [lower-upper 95% CI] for ADRs more frequently reported for females in EV reports	Number of reports for females	Number of reports for males	ROR [lower-upper 95% CI] for ADRs more frequently reported for females in ADRED reports
Females in total						
<i>Allergic conditions NEC</i>	130	73	1.7 [1.3 - 2.2]	-	-	-
<i>Alopecias</i>	32	4	7.5 [2.7 - 21.2]	-	-	-
<i>Bone disorders NEC</i>	91	52	1.6 [1.2 - 2.3]	-	-	-
<i>Breast signs and symptoms</i>	11	1	10.3 [1.3 - 79.8]	-	-	-
<i>Candida infections</i>	35	16	2.1 [1.1 - 3.7]	-	-	-
<i>Cardiac signs and symptoms NEC</i>	59	28	2.0 [1.3 - 3.1]	-	-	-
<i>Dermatitis and eczema</i>	75	45	1.6 [1.1 - 2.3]	-	-	-
<i>Erythemas</i>	-	-	-	15	5	3.3 [1.2 - 9.0]
<i>Feelings and sensations NEC</i>	173	114	1.4 [1.1 - 1.8]	-	-	-
<i>Fractures and dislocations NEC</i>	-	-	-	18	7	2.8 [1.2 - 6.7]
<i>Gastrointestinal and abdominal pains (excl oral and throat)</i>	-	-	-	124	99	1.4 [1.1 - 1.8]
<i>Headaches NEC</i>	175	97	1.7 [1.3 - 2.2]	50	30	1.8 [1.2 - 2.9]
<i>Heart rate and pulse investigations</i>	44	20	2.1 [1.2 - 3.5]	-	-	-
<i>Herpes viral infections</i>	77	37	2.0 [1.3 - 2.9]	-	-	-
<i>Limb fractures and dislocations</i>	59	32	1.7 [1.1 - 2.7]	-	-	-
<i>Migraine headaches</i>	14	2	6.6 [1.5 - 28.9]	-	-	-
<i>Multiple sclerosis acute and progressive</i>	120	31	3.7 [2.5 - 5.5]	-	-	-

<i>Nausea and vomiting symptoms</i>	505	280	1.7 [1.5 - 2.0]	203	147	1.6 [1.3 - 2.0]
<i>Neurological signs and symptoms NEC</i>	268	189	1.3 [1.1 - 1.6]	-	-	-
<i>Non-site specific injuries NEC</i>	-	-	-	100	57	2.0 [1.4 - 2.8]
<i>Oral soft tissue swelling and oedema</i>	30	12	2.3 [1.2 - 4.6]	-	-	-
<i>Overdoses NEC</i>	184	131	1.3 [1.1 - 1.7]	-	-	-
<i>Pain and discomfort NEC</i>	203	134	1.4 [1.1 - 1.8]	-	-	-
<i>Paraesthesias and dysaesthesias</i>	120	70	1.6 [1.2 - 2.2]	19	8	2.6 [1.1 - 5.9]
<i>Polyomavirus infections</i>	49	22	2.1 [1.3 - 3.5]	-	-	-
<i>Product monitoring errors and issues</i>	-	-	-	56	34	1.8 [1.2 - 2.8]
<i>Pruritus NEC</i>	148	100	1.4 [1.1 - 1.8]	-	-	-
<i>Rashes, eruptions and exanthems NEC</i>	220	150	1.4 [1.1 - 1.7]	-	-	-
<i>Sodium imbalance</i>	109	47	2.2 [1.6 - 3.1]	16	5	3.5 [1.3 - 9.5]
<i>Spinal fractures and dislocations</i>	45	14	3.0 [1.7 - 5.5]	-	-	-
<i>Suicidal and self-injurious behaviour</i>	164	103	1.5 [1.2 - 1.9]	-	-	-
<i>Total fluid volume decreased</i>	-	-	-	40	23	1.9 [1.1 - 3.2]
<i>Tremor (excl congenital)</i>	98	45	2.1 [1.4 - 2.9]	-	-	-
<i>Urticarias</i>	76	41	1.7 [1.2 - 2.5]	-	-	-
<i>Vascular hypertensive disorders NEC</i>	117	69	1.6 [1.2 - 2.2]	-	-	-
<i>Visual impairment and blindness (excl colour blindness)</i>	80	50	1.5 [1.1 - 2.1]	-	-	-
Younger females (age=18-51years)						
<i>Alopecias</i>	14	1	10.5 [1.4 - 80.1]	-	-	-
<i>Angioedemas</i>	23	7	2.5 [1.1 - 5.8]	-	-	-
<i>Breathing abnormalities</i>	143	78	1.4 [1.1 - 1.9]	-	-	-
<i>Cardiac conduction disorders</i>	13	2	4.9 [1.1 - 21.6]	-	-	-
<i>Headaches NEC</i>	92	37	1.9 [1.3 - 2.8]	27	4	6.2 [2.3 -19.4]
<i>Herpes viral infections</i>	39	12	2.5 [1.3 - 4.7]	-	-	-

<i>Multiple sclerosis acute and progressive</i>	98	20	3.8 [2.3 - 6.2]	-	-	-
<i>Nausea and vomiting symptoms</i>	176	87	1.6 [1.2 - 2.0]	-	-	-
<i>Oral soft tissue swelling and oedema</i>	16	2	6.0 [1.4 - 26.2]	-	-	-
<i>Pain and discomfort NEC</i>	71	29	1.9 [1.2 - 2.9]	-	-	-
<i>Paraesthesias and dysaesthesias</i>	60	17	2.7 [1.6 - 4.6]	-	-	-
<i>Potassium imbalance</i>	20	5	3.0 [1.1 - 8.0]	-	-	-
<i>Red blood cell analyses</i>	20	5	3.0 [1.1 - 8.0]	-	-	-
<i>Skin structures and soft tissue infections</i>	21	6	2.6 [1.1 - 6.5]	-	-	-
<i>Tremor (excl congenital)</i>	52	19	2.1 [1.2 - 3.5]	-	-	-
<i>Urinary tract infections</i>	31	9	2.6 [1.2 - 5.5]	-	-	-
<i>Vascular tests NEC (incl blood pressure)</i>	42	14	2.3 [1.2 - 4.2]	-	-	-
<i>Visual impairment and blindness (excl colour blindness)</i>	32	7	3.5 [1.5 - 7.8]	-	-	-
Older females (age>51 years)						
<i>Allergic conditions NEC</i>	76	41	1.9 [1.3 - 2.8]	-	-	-
<i>Alopecias</i>	18	3	6.1 [1.8 - 20.8]	-	-	-
<i>Bone disorders NEC</i>	84	45	1.9 [1.3 - 2.8]	-	-	-
<i>Fractures and dislocations NEC</i>	-	-	-	18	6	3.4 [1.3 - 8.6]
<i>Heart rate and pulse investigations</i>	32	16	2.0 [1.1 - 3.7]	-	-	-
<i>Limb fractures and dislocations</i>	52	28	1.9 [1.2 - 3.0]	-	-	-
<i>Malabsorption syndromes</i>	16	5	3.3 [1.2 - 8.9]	-	-	-
<i>Nausea and vomiting symptoms</i>	329	193	1.8 [1.5 - 2.2]	162	118	1.6 [1.3 - 2.1]
<i>Non-site specific injuries NEC</i>	-	-	-	94	51	2.2 [1.5 - 3.1]

<i>Peritoneal and retroperitoneal disorders</i>	25	12	2.1 [1.1 - 4.2]	-	-	-
<i>Product monitoring errors and issues</i>	-	-	-	48	32	1.7 [1.1 - 2.7]
<i>Pruritus NEC</i>	96	68	1.4 [1.1 - 2.0]	-	-	-
<i>Rheumatoid arthropathies</i>	12	3	4.1 [1.2 - 14.5]	-	-	-
<i>Sodium imbalance</i>	99	39	2.6 [1.8 - 3.8]	15	5	3.4 [1.2 - 9.4]
<i>Spinal fractures and dislocations</i>	40	12	3.4 [1.8 - 6.5]	-	-	-
<i>Total fluid volume decreased</i>	-	-	-	39	23	1.9 [1.1 - 3.3]
<i>Tremor (excl congenital)</i>	46	26	1.8 [1.1 - 2.9]	-	-	-
<i>Vascular hypertensive disorders NEC</i>	87	47	1.9 [1.3 - 2.7]	-	-	-
ADR (HLT-level) more frequently reported for males	Number of reports for males	Number of reports for females	ROR [lower-upper 95% CI] for ADRs more frequently reported for males in EV reports	Number of reports for males	Number of reports for females	ROR [lower-upper 95% CI] for ADRs more frequently reported for males in ADRED reports
Males in total						
<i>Acute and chronic pancreatitis</i>	106	75	1.5 [1.1 - 2.0]	-	-	-
<i>Adrenal cortical hypofunctions</i>	13	4	3.5 [1.1 - 10.7]	-	-	-
<i>Aortic aneurysms and dissections</i>	12	1	12.9 [1.7 - 98.9]	-	-	-
<i>Apocrine and eccrine gland disorders</i>	-	-	-	34	12	3.0 [1.5 - 5.8]
<i>Behaviour and socialisation disturbances</i>	57	33	1.9 [1.2 - 2.9]	-	-	-
<i>Blood and blood product treatment</i>	41	19	2.3 [1.3 - 4.0]	-	-	-
<i>Cardiac therapeutic procedures NEC</i>	14	3	5.0 [1.4 - 17.4]	-	-	-
<i>Central nervous system haemorrhages and cerebrovascular accidents</i>	618	563	1.2 [1.1 - 1.3]	-	-	-

<i>Cerebral injuries NEC</i>	94	57	1.8 [1.3 - 2.5]	-	-	-
<i>Circulatory collapse and shock</i>	-	-	-	27	13	2.2 [1.1 - 4.3]
<i>Conditions associated with abnormal gas exchange</i>	32	18	1.9 [1.1 - 3.4]	-	-	-
<i>Coronary artery disorders NEC</i>	52	19	2.9 [1.7 - 5.0]	-	-	-
<i>Death and sudden death</i>	79	54	1.6 [1.1 - 2.2]	-	-	-
<i>Febrile disorders</i>	-	-	-	116	81	1.5 [1.1 - 2.0]
<i>Gastric and oesophageal haemorrhages</i>	33	18	2.0 [1.1 - 3.5]	-	-	-
<i>Glomerulonephritis and nephrotic syndrome</i>	20	8	2.7 [1.2 - 6.1]	-	-	-
<i>Heart failures NEC</i>	155	108	1.5 [1.2 - 2.0]	-	-	-
<i>Hypothalamic and pituitary disorders NEC</i>	20	3	7.2 [2.1 - 24.1]	-	-	-
<i>Ischaemic coronary artery disorders</i>	123	72	1.8 [1.4 - 2.5]	-	-	-
<i>Lower respiratory tract and lung infections</i>	276	180	1.7 [1.4 - 2.0]	-	-	-
<i>Lower respiratory tract inflammatory and immunologic conditions</i>	108	80	1.5 [1.1 - 1.9]	-	-	-
<i>Lower respiratory tract signs and symptoms</i>	20	9	2.4 [1.1 - 5.2]	-	-	-
<i>Muscle, tendon and ligament injuries</i>	20	9	2.4 [1.1 - 5.2]	-	-	-
<i>Myopathies</i>	98	53	2.0 [1.4 - 2.8]	-	-	-
<i>Nasal disorders NEC</i>	-	-	-	18	6	3.2 [1.3 - 8.1]
<i>Neoplasms malignant site unspecified NEC</i>	99	60	1.8 [1.3 - 2.5]	-	-	-
<i>Noninfectious myocarditis</i>	30	7	4.6 [2.0 - 10.5]	-	-	-
<i>Non-site specific gastrointestinal haemorrhages</i>	-	-	-	237	166	1.5 [1.2 - 1.8]

<i>Ocular bleeding and vascular disorders NEC</i>	12	3	4.3 [1.2 - 15.2]	-	-	-
<i>Renal failure and impairment</i>	352	255	1.5 [1.3 - 1.8]	-	-	-
<i>Respiratory tract disorders NEC</i>	-	-	-	17	4	4.5 [1.5 - 13.5]
<i>Total fluid volume decreased</i>	86	58	1.6 [1.1 - 2.2]	-	-	-
<i>Transplant rejections</i>	12	2	6.4 [1.4 - 28.7]	-	-	-
<i>Tuberculous infections</i>	35	12	3.1 [1.6 - 6.0]	-	-	-
<i>Urinary abnormalities</i>	82	47	1.9 [1.3 - 2.7]	-	-	-
Younger males (age=18-51years)						
<i>Acute and chronic pancreatitis</i>	37	28	1.8 [1.1 - 2.9]	-	-	-
<i>Behaviour and socialisation disturbances</i>	25	14	2.4 [1.3 - 4.7]	-	-	-
<i>Generalised tonic-clonic seizures</i>	23	14	2.2 [1.1 - 4.3]	-	-	-
<i>Ischaemic coronary artery disorders</i>	30	14	2.9 [1.5 - 5.5]	-	-	-
<i>Myopathies</i>	36	15	3.3 [1.8 - 6.0]	-	-	-
<i>Noninfectious myocarditis</i>	14	4	4.7 [1.6 - 14.4]	-	-	-
<i>Parenchymal lung disorders NEC</i>	15	6	3.4 [1.3 - 8.7]	-	-	-
<i>Skeletal and cardiac muscle analyses</i>	34	20	2.3 [1.3 - 4.0]	-	-	-
<i>Therapeutic procedures NEC</i>	31	21	2.0 [1.1 - 3.5]	-	-	-
Older males (age>51 years)						
<i>Apocrine and eccrine gland disorders</i>	-	-	-	24	10	2.7 [1.3 - 5.6]
<i>Asthenic conditions</i>	-	-	-	127	100	1.4 [1.1 - 1.8]
<i>Blood and blood product treatment</i>	41	18	2.3 [1.3 - 4.0]	-	-	-
<i>Breathing abnormalities</i>	-	-	-	181	142	1.4 [1.1 - 1.8]
<i>Cardiac therapeutic procedures NEC</i>	13	3	4.4 [1.3 - 15.5]	-	-	-
<i>Cerebral injuries NEC</i>	89	55	1.6 [1.2 - 2.3]	-	-	-

<i>Circulatory collapse and shock</i>	-	-	-	22	11	2.2 [1.1 - 4.6]
<i>Conditions associated with abnormal gas exchange</i>	28	11	2.6 [1.3 - 5.2]	-	-	-
<i>Coronary artery disorders NEC</i>	43	16	2.7 [1.5 - 4.8]	-	-	-
<i>Coughing and associated symptoms</i>	-	-	-	67	47	1.6 [1.1 - 2.3]
<i>Death and sudden death</i>	73	48	1.5 [1.1 - 2.2]	-	-	-
<i>Febrile disorders</i>	-	-	-	93	58	1.7 [1.2 - 2.4]
<i>General signs and symptoms NEC</i>	-	-	-	217	164	1.4 [1.1 - 1.8]
<i>Glomerulonephritis and nephrotic syndrome</i>	14	2	7.1 [1.6 - 31.3]	-	-	-
<i>Heart failures NEC</i>	141	90	1.6 [1.2 - 2.1]	-	-	-
<i>Hypothalamic and pituitary disorders NEC</i>	18	3	6.1 [1.8 - 20.7]	-	-	-
<i>Ischaemic coronary artery disorders</i>	93	58	1.6 [1.2 - 2.3]	-	-	-
<i>Lower respiratory tract and lung infections</i>	228	133	1.7 [1.4 - 2.1]	-	-	-
<i>Lower respiratory tract inflammatory and immunologic conditions</i>	97	63	1.6 [1.1 - 2.1]	-	-	-
<i>Lower respiratory tract signs and symptoms</i>	17	6	2.9 [1.1 - 7.3]	-	-	-
<i>Metabolic acidoses (excl diabetic acidoses)</i>	93	65	1.4 [1.1 - 2.0]	-	-	-
<i>Muscle infections and inflammations</i>	16	4	4.1 [1.4 - 12.2]	-	-	-
<i>Myopathies</i>	62	38	1.7 [1.1 - 2.5]	-	-	-
<i>Nasal disorders NEC</i>	-	-	-	16	6	3.0 [1.2 - 7.6]
<i>Neoplasms malignant site unspecified NEC</i>	83	49	1.7 [1.2 - 2.4]	-	-	-
<i>Neurological signs and symptoms NEC</i>	-	-	-	149	119	1.4 [1.1 - 1.8]
<i>Noninfectious myocarditis</i>	16	3	5.4 [1.6 - 18.6]	-	-	-

<i>Non-site specific gastrointestinal haemorrhages</i>	-	-	-	213	157	1.5 [1.2 - 1.8]
<i>Ocular bleeding and vascular disorders NEC</i>	12	3	4.1 [1.1 - 14.4]	-	-	-
<i>Renal failure and impairment</i>	310	205	1.5 [1.3 - 1.8]	-	-	-
<i>Respiratory tract disorders NEC</i>	-	-	-	16	3	5.9 [1.7 - 20.3]
<i>Sepsis, bacteraemia, viraemia and fungaemia NEC</i>	153	101	1.5 [1.2 - 2.0]	-	-	-
<i>Total fluid volume decreased</i>	78	49	1.6 [1.1 - 2.3]	-	-	-
<i>Tuberculous infections</i>	32	6	5.4 [2.3 - 12.9]	-	-	-
<i>Urinary abnormalities</i>	66	36	1.9 [1.2 - 2.8]	-	-	-

4 EV= spontaneous reports from EudraVigilance; ADRED= reports from the ADRED study; NEC= not
5 elsewhere classified; ROR= reporting odds ratio; CI= confidence interval

6 Legend Table Appendix 2: Table Appendix 2 shows all ADR and their reporting odds ratios with their
7 95% confidence intervals reported more often for females or males in the EV or/and the ADRED
8 reports

Table Appendix 3

Table Appendix 3: All ADR-drug combinations (ADR on HLT-Level) more frequently reported for females or males in EudraVigilance (EV) or/and ADRED

	EV reports (n=12,564)			ADRED reports (n=2,355)		
ADR-Drug combinations more frequently reported for females	Number of reports for females	Number of reports for males	ROR [lower-upper 95% CI] for ADR-drug combinations more frequently reported for females in EV reports	Number of reports for females	Number of reports for males	ROR [lower-upper 95% CI] for ADR-drug combinations more frequently reported for females in ADRED reports
Females in total						
<i>Bone disorders NEC - denosumab</i>	65	37	1.6 [1.1 - 2.5]	-	-	-
<i>Breathing abnormalities - gadoteric acid</i>	20	5	3.7 [1.4 - 10.0]	-	-	-
<i>Dental and gingival therapeutic procedures - denosumab</i>	28	12	2.2 [1.1 - 4.3]	-	-	-
<i>Diarrhoea (excl infective) - paclitaxel</i>	16	4	3.7 [1.3 - 11.2]	-	-	-
<i>Diarrhoea (excl infective) - pertuzumab</i>	22	1	20.6 [2.8 - 153.1]	-	-	-
<i>Diarrhoea (excl infective) - trastuzumab</i>	26	2	12.2 [2.9 - 51.4]	-	-	-
<i>Disturbances in consciousness NEC - doxylamine</i>	13	3	4.1 [1.2 - 14.2]	-	-	-
<i>Disturbances in consciousness NEC - pipamperone</i>	15	4	3.5 [1.2 - 10.6]	-	-	-
<i>Febrile disorders - alemtuzumab</i>	15	3	4.7 [1.4 - 16.2]	-	-	-
<i>Febrile disorders - paclitaxel</i>	16	4	3.7 [1.3 - 11.2]	-	-	-
<i>Haemorrhages NEC - rivaroxaban</i>	43	15	2.7 [1.5 - 4.8]	-	-	-
<i>Hepatocellular damage and hepatitis NEC - flupirtine</i>	26	2	12.2 [2.9 - 51.4]	-	-	-

<i>Herpes viral infections - dimethyl fumarate</i>	12	2	5.6 [1.3 - 25.1]	-	-	-
<i>Malabsorption syndromes - olmesartan</i>	13	1	12.2 [1.6 - 93.1]	-	-	-
<i>Multiple sclerosis acute and progressive - fingolimod</i>	18	3	5.6 [1.7 - 19.1]	-	-	-
<i>Multiple sclerosis acute and progressive - natalizumab</i>	25	4	5.9 [2.0 - 16.8]	-	-	-
<i>Nausea and vomiting symptoms - ciprofloxacin</i>	11	2	5.1 [1.1 - 23.2]	-	-	-
<i>Nausea and vomiting symptoms - docetaxel</i>	14	2	6.6 [1.5 - 28.9]	-	-	-
<i>Nausea and vomiting symptoms - iron preparations</i>	15	2	7.0 [1.6 - 30.7]	-	-	-
<i>Nausea and vomiting symptoms - metamizole</i>	-	-	-	8	1	8.7 [1.1 - 69.4]
<i>Nausea and vomiting symptoms - paclitaxel</i>	11	2	5.1 [1.1 - 23.2]	-	-	-
<i>Non-site specific injuries NEC - lorazepam</i>	-	-	-	10	1	10.9 [1.4 - 84.9]
<i>Overdoses NEC - doxylamine</i>	23	9	2.4 [1.1 - 5.2]	-	-	-
<i>Overdoses NEC - quetiapine</i>	19	5	3.6 [1.3 - 9.5]	-	-	-
<i>Peripheral embolism and thrombosis - apixaban</i>	13	3	4.1 [1.2 - 14.2]	-	-	-
<i>Pituitary analyses anterior - risperidone</i>	11	2	5.1 [1.1 - 23.2]	-	-	-
<i>Polyomavirus infections - natalizumab</i>	34	14	2.3 [1.2 - 4.2]	-	-	-
<i>Protein analyses NEC - alemtuzumab</i>	16	4	3.7 [1.3 - 11.2]	-	-	-
<i>Rashes, eruptions and exanthems NEC - alemtuzumab</i>	12	3	3.7 [1.1 - 13.3]	-	-	-
<i>Rate and rhythm disorders NEC - iron preparations</i>	13	2	6.1 [1.4 - 27.0]	-	-	-
<i>Sodium imbalance - hydrochlorothiazide</i>	21	2	9.8 [2.3 - 42.0]	-	-	-
<i>Suicidal and self-injurious behaviour - quetiapine</i>	22	4	5.2 [1.8 - 15.0]	-	-	-
Younger females (age=18-51years)						
<i>Hepatocellular damage and hepatitis NEC - flupirtine</i>	12	1	9.0 [1.2 - 69.3]	-	-	-
<i>Multiple sclerosis acute and progressive - daclizumab</i>	19	5	2.9 [1.1 - 7.7]	-	-	-

<i>Multiple sclerosis acute and progressive - fingolimod</i>	15	1	11.3 [1.5 - 85.4]	-	-	-
<i>Multiple sclerosis acute and progressive - natalizumab</i>	21	3	5.3 [1.6 - 17.7]	-	-	-
<i>Nausea and vomiting symptoms - iron preparations</i>	13	1	9.8 [1.3 - 74.7]	-	-	-
<i>Protein analyses NEC - alemtuzumab</i>	15	3	3.8 [1.1 - 13.0]	-	-	-
<i>Suicidal and self-injurious behaviour - quetiapine</i>	15	3	3.8 [1.1 - 13.0]	-	-	-
Older females (age>51 years)						
<i>Bone disorders NEC - denosumab</i>	63	36	1.8 [1.2 - 2.7]	-	-	-
<i>Dental and gingival therapeutic procedures - denosumab</i>	26	12	2.2 [1.1 - 4.4]	-	-	-
<i>Diarrhoea (excl infective) - trastuzumab</i>	19	1	19.4 [2.6 - 145.3]	-	-	-
<i>Disturbances in consciousness NEC - pipamperone</i>	11	2	5.6 [1.2 - 25.3]	-	-	-
<i>General signs and symptoms NEC - prednisolone</i>	14	3	4.8 [1.4 - 16.6]	-	-	-
<i>Haemorrhages NEC - rivaroxaban</i>	41	15	2.8 [1.5 - 5.1]	-	-	-
<i>Hepatocellular damage and hepatitis NEC - flupirtine</i>	14	1	14.3 [1.9 - 108.8]	-	-	-
<i>Malabsorption syndromes - olmesartan</i>	13	1	13.3 [1.7 - 101.6]	-	-	-
<i>Nausea and vomiting symptoms - docetaxel</i>	11	2	5.6 [1.2 - 25.3]	-	-	-
<i>Non-site specific injuries NEC - lorazepam</i>	-	-	-	9	1	10.2 [1.3 - 80.3]
<i>Rate and rhythm disorders NEC - digitoxin</i>	-	-	-	15	6	2.8 [1.1 - 7.3]
<i>Sodium imbalance - hydrochlorothiazide</i>	21	2	10.7 [2.5 - 45.9]	-	-	-
ADR-Drug combinations more frequently reported for males	Number of reports for males	Number of reports for females	ROR [lower-upper 95% CI] for ADR-drug combinations more frequently reported for	Number of reports for males	Number of reports for females	ROR [lower-upper 95% CI] for ADR-drug combinations more frequently reported for

			males in EV reports			reported for males in ADRED reports
Males in total						
<i>Acute and chronic pancreatitis - dulaglutide</i>	11	2	5.9 [1.3 - 26.6]	-	-	-
<i>Blood and blood product treatment - apixaban</i>	32	15	2.3 [1.2 - 4.2]	-	-	-
<i>Breathing abnormalities - nivolumab</i>	29	10	3.1 [1.5 - 6.4]	-	-	-
<i>Breathing abnormalities - prednisolone</i>	-	-	-	16	5	3 [1.1 - 8.2]
<i>Breathing abnormalities - sacubitril/valsartan</i>	14	3	5 [1.4 - 17.4]	-	-	-
<i>Central nervous system haemorrhages and cerebrovascular accidents - dabigatran</i>	102	69	1.6 [1.2 - 2.2]	-	-	-
<i>Central nervous system haemorrhages and cerebrovascular accidents - edoxaban</i>	52	31	1.8 [1.2 - 2.8]	-	-	-
<i>Cerebral injuries NEC - acetylsalicylic acid</i>	21	3	7.5 [2.2 - 25.2]	-	-	-
<i>Cerebral injuries NEC - dabigatran</i>	12	3	4.3 [1.2 - 15.2]	-	-	-
<i>Cerebral injuries NEC - rivaroxaban</i>	26	10	2.8 [1.3 - 5.8]	-	-	-
<i>Death and sudden death - nivolumab</i>	12	3	4.3 [1.2 - 15.2]	-	-	-
<i>Diarrhoea (excl infective) - idelalisib</i>	24	8	3.2 [1.4 - 7.2]	-	-	-
<i>Febrile disorders - bacillus calmette-guérin bacteria</i>	13	1	13.9 [1.8 - 106.6]	-	-	-
<i>Febrile disorders - etoposide</i>	-	-	-	17	4	4.0 [1.3 - 11.9]
<i>Gastrointestinal signs and symptoms NEC - risperidone</i>	12	1	12.9 [1.7 - 98.9]	-	-	-
<i>General signs and symptoms NEC - cisplatin</i>	-	-	-	16	5	3.0 [1.1 - 8.2]

<i>General signs and symptoms NEC - etoposide</i>	-	-	-	12	3	3.7 [1.1 - 13.3]
<i>General signs and symptoms NEC - nivolumab</i>	31	11	3.0 [1.5 - 6.0]	-	-	-
<i>Haemorrhages NEC - edoxaban</i>	16	6	2.9 [1.1 - 7.3]	-	-	-
<i>Heart failures NEC - sacubitril/valsartan</i>	34	8	4.6 [2.1 - 9.9]	-	-	-
<i>Hepatocellular damage and hepatitis NEC - nivolumab</i>	24	11	2.3 [1.1 - 4.8]	-	-	-
<i>Liver function analyses - nivolumab</i>	16	4	4.3 [1.4 - 12.8]	-	-	-
<i>Lower respiratory tract and lung infections - azacitidine</i>	14	2	7.5 [1.7 - 33.0]	-	-	-
<i>Lower respiratory tract and lung infections - ibrutinib</i>	11	2	5.9 [1.3 - 26.6]	-	-	-
<i>Lower respiratory tract and lung infections - idelalisib</i>	14	2	7.5 [1.7 - 33.0]	-	-	-
<i>Lower respiratory tract and lung infections - nivolumab</i>	21	8	2.8 [1.2 - 6.4]	-	-	-
<i>Lower respiratory tract inflammatory and immunologic conditions - nivolumab</i>	32	13	2.6 [1.4 - 5.0]	-	-	-
<i>Metastases to specified sites - nivolumab</i>	18	8	2.4 [1.0 - 5.5]	-	-	-
<i>Myopathies - simvastatin</i>	29	13	2.4 [1.2 - 4.6]	-	-	-
<i>Neoplasms malignant site unspecified NEC - nivolumab</i>	56	33	1.8 [1.2 - 2.8]	-	-	-
<i>Neoplasms malignant site unspecified NEC - pembrolizumab</i>	14	5	3.0 [1.1 - 8.3]	-	-	-
<i>Neurological signs and symptoms NEC - acetylsalicylic acid</i>	-	-	-	31	13	2.2 [1.2 - 4.3]
<i>Neurological signs and symptoms NEC - clopidogrel</i>	-	-	-	15	3	4.7 [1.4 - 16.2]
<i>Neutropenias - azacitidine</i>	13	3	4.6 [1.3 - 16.3]	-	-	-
<i>Non-site specific gastrointestinal haemorrhages - acetylsalicylic acid</i>	-	-	-	107	70	1.5 [1.1 - 2.0]
<i>Non-site specific gastrointestinal</i>	-	-	-	45	24	1.8 [1.1 - 2.9]

<i>haemorrhages - phenprocoumon</i>						
<i>Paralysis and paresis (excl cranial nerve) - dabigatran</i>	26	10	2.8 [1.3 - 5.8]	-	-	-
<i>Physical examination procedures and organ system status - nivolumab</i>	12	3	4.3 [1.2 - 15.2]	-	-	-
<i>Renal failure and impairment - empagliflozin</i>	13	1	13.9 [1.8 - 106.6]	-	-	-
<i>Renal failure and impairment - sacubitril/valsartan</i>	40	13	3.3 [1.8 - 6.2]	-	-	-
<i>Renal failure and impairment - simvastatin</i>	13	4	3.5 [1.1 - 10.7]	-	-	-
<i>Renal function analyses - sacubitril/valsartan</i>	20	6	3.6 [1.4 - 8.9]	-	-	-
<i>Respiratory failures (excl neonatal) - nivolumab</i>	16	3	5.7 [1.7 - 19.6]	-	-	-
<i>Speech and language abnormalities - dabigatran</i>	11	3	3.9 [1.1 - 14.1]	-	-	-
<i>Therapeutic and nontherapeutic responses - paliperidone</i>	20	9	2.4 [1.1 - 5.2]	-	-	-
<i>Tuberculous infections - bacillus calmette-guérin bacteria</i>	25	1	26.9 [3.6 - 198.2]	-	-	-
<i>Urinary abnormalities - rivaroxaban</i>	15	4	4.0 [1.3 - 12.1]	-	-	-
<i>Vascular hypotensive disorders - sacubitril/valsartan</i>	18	8	2.4 [1.0 - 5.5]	-	-	-
Younger males (age=18-51years)						
<i>Disturbances in consciousness NEC - olanzapine</i>	11	4	3.7 [1.2 - 11.7]	-	-	-
<i>Dyskinesias and movement disorders NEC - haloperidol</i>	16	7	3.1 [1.3 - 7.5]	-	-	-
<i>Neutropenias - clozapine</i>	11	4	3.7 [1.2 - 11.7]	-	-	-
<i>Therapeutic and nontherapeutic responses - paliperidone</i>	14	7	2.7 [1.1 - 6.7]	-	-	-
Older males (age>51 years)						
<i>Blood and blood product treatment - apixaban</i>	32	15	2.1 [1.1 - 3.9]	-	-	-

<i>Breathing abnormalities - nivolumab</i>	28	10	2.8 [1.3 - 5.7]	-	-	-
<i>Breathing abnormalities - sacubitril/valsartan</i>	13	3	4.3 [1.2 - 15.0]	-	-	-
<i>Central nervous system haemorrhages and cerebrovascular accidents - dabigatran</i>	101	69	1.4 [1.1 - 2.0]	-	-	-
<i>Cerebral injuries NEC - acetylsalicylic acid</i>	20	3	6.6 [2.0 - 22.1]	-	-	-
<i>Cerebral injuries NEC - dabigatran</i>	12	3	3.9 [1.1 - 13.9]	-	-	-
<i>Cerebral injuries NEC - rivaroxaban</i>	26	10	2.6 [1.2 - 5.3]	-	-	-
<i>Death and sudden death - nivolumab</i>	12	3	3.9 [1.1 - 13.9]	-	-	-
<i>Diarrhoea (excl infective) - idelalisib</i>	23	6	3.8 [1.5 - 9.3]	-	-	-
<i>Febrile disorders - bacillus calmette-guérin bacteria</i>	13	1	12.8 [1.7 - 97.8]	-	-	-
<i>General signs and symptoms NEC - cisplatin</i>	-	-	-	16	5	2.9 [1.1 - 7.9]
<i>General signs and symptoms NEC - etoposide</i>	-	-	-	11	2	5.0 [1.1 - 22.4]
<i>General signs and symptoms NEC - nivolumab</i>	28	8	3.4 [1.6 - 7.6]	-	-	-
<i>Haemorrhages NEC - edoxaban</i>	16	5	3.1 [1.2 - 8.6]	-	-	-
<i>Heart failures NEC - sacubitril/valsartan</i>	34	8	4.2 [1.9 - 9.1]	-	-	-
<i>Hepatocellular damage and hepatitis NEC - nivolumab</i>	22	7	3.1 [1.3 - 7.3]	-	-	-
<i>Liver function analyses - nivolumab</i>	16	4	3.9 [1.3 - 11.8]	-	-	-
<i>Lower respiratory tract and lung infections - azacitidine</i>	12	2	5.9 [1.3 - 26.4]	-	-	-
<i>Lower respiratory tract and lung infections - idelalisib</i>	12	1	11.8 [1.5 - 90.8]	-	-	-
<i>Lower respiratory tract and lung infections - nivolumab</i>	18	7	2.5 [1.1 - 6.1]	-	-	-
<i>Lower respiratory tract inflammatory and immunologic conditions - nivolumab</i>	31	11	2.8 [1.4 - 5.5]	-	-	-
<i>Metastases to specified sites - nivolumab</i>	18	7	2.5 [1.1 - 6.1]	-	-	-

<i>Myopathies - simvastatin</i>	29	12	2.4 [1.2 - 4.7]	-	-	-
<i>Neoplasms malignant site unspecified NEC - nivolumab</i>	49	28	1.7 [1.1 - 2.7]	-	-	-
<i>Neurological signs and symptoms NEC - acetylsalicylic acid</i>	-	-	-	29	12	2.2 [1.1 - 4.3]
<i>Neurological signs and symptoms NEC - clopidogrel</i>	-	-	-	14	3	4.2 [1.2 - 14.7]
<i>Neutropenias - azacitidine</i>	12	3	3.9 [1.1 - 13.9]	-	-	-
<i>Paralysis and paresis (excl cranial nerve) - dabigatran</i>	25	10	2.5 [1.2 - 5.1]	-	-	-
<i>Renal failure and impairment - empagliflozin</i>	11	1	10.8 [1.4 - 83.8]	-	-	-
<i>Renal failure and impairment - sacubitril/valsartan</i>	40	13	3.0 [1.6 - 5.7]	-	-	-
<i>Renal function analyses - sacubitril/valsartan</i>	20	6	3.3 [1.3 - 8.2]	-	-	-
<i>Respiratory failures (excl neonatal) - nivolumab</i>	15	2	7.4 [1.7 - 32.3]	-	-	-
<i>Thrombocytopenias - heparin</i>	11	2	5.4 [1.2 - 24.4]	-	-	-
<i>Tuberculous infections - bacillus calmette-guérin bacteria</i>	25	1	24.7 [3.3 - 182.1]	-	-	-

4 EV= spontaneous reports from EudraVigilance; ADRED= reports from the ADRED study; NEC= not
5 elsewhere classified; ROR= reporting odds ratio; CI= confidence interval

6 Legend Table Appendix 3: Table Appendix 3 shows all ADR (on HLT-level)-drug combinations and
7 their reporting odds ratios with their 95% confidence intervals reported more often for females or
8 males in the EV or/and the ADRED reports

Table Appendix 4

- Table Appendix 4: All ADR-drug combinations (ADR on HLT-level) which did not remain more frequently reported for females or males with consideration of prescription data

EV reports (n=12,564)				
ADR-Drug combinations more frequently reported for females/males in EV reports	Number of reports for females	Number of reports for males	ROR [lower-upper 95% CI] of ADR-drug combinations more frequently reported for females/males without consideration of prescription data	ROR [lower-upper 95% CI] of ADR-drug combinations more frequently reported for females/males by considering prescription data
No longer reported more frequently for females by considering prescription data				
<i>Multiple sclerosis acute and progressive - natalizumab</i>	25	4	5.9 [2.0-16.8]	2.4 [0.8-6.8]
<i>Multiple sclerosis acute and progressive - fingolimod</i>	18	3	5.6 [1.7-19.1]	2.7 [0.8-9.1]
<i>Breathing abnormalities – gadoteric acid</i>	20	5	3.7 [1.4-10.0]	1.2 [0.4-3.1]
<i>Febrile disorder - alemtuzumab</i>	15	3	4.7 [1.4-16.2]	2.1 [0.6-7.1]
<i>Herpes viral infections – dimethyl fumarate</i>	12	2	5.6 [1.3-25.1]	2.5 [0.5-10.9]
<i>Protein analyses - alemtuzumab</i>	16	4	3.7 [1.3-11.2]	1.6 [0.5-4.9]
<i>Polyomavirus infections - natalizumab</i>	34	14	2.3 [1.2-4.2]	0.9 [0.5-1.7]
<i>Disturbances in consciousness - pipamperone</i>	15	4	3.5 [1.2-10.6]	2.5 [0.8-7.5]
<i>Nausea and vomiting symptoms - ciprofloxacin</i>	11	2	5.1 [1.1-23.2]	3.5 [0.8-16.0]
<i>Pituitary analyses anterior - risperidone</i>	11	2	5.1 [1.1-23.2]	4.2 [0.9-19.1]
<i>Dental and gingival therapeutic procedures - denosumab</i>	28	12	2.2 [1.1-4.3]	0.7 [0.3-1.3]
<i>Rashes, eruptions and exanthems - alemtuzumab</i>	12	3	3.7 [1.1-13.3]	1.6 [0.5-5.8]
<i>Overdoses - quetiapine</i>	19	5	3.6 [1.3-25.1]	2.6 [1.0-7.0]
<i>Peripheral embolism and thrombosis - apixaban</i>	13	3	4.1 [1.2-14.2]	3.4 [1.0-11.8]
<i>Nausea and vomiting symptoms - iron preparations</i>	15	2	7.0 [1.6-30.7]	3.2 [0.7-13.9]
<i>Rate and rhythm disorders - iron preparations</i>	13	2	6.1 [1.4-27.0]	2.8 [0.6-12.2]
Prescription data missing				
<i>Diarrhoea (excl. infective) - pertuzumab</i>	22	1	20.6 [2.8-153.1]	-
<i>Disturbances in consciousness - doxylamine</i>	13	3	4.1 [1.2-14.2]	-
<i>Overdoses - doxylamine</i>	23	9	2.4 [1.1-5.2]	-
No longer reported more frequently for males by considering prescription data				
<i>Tuberculosis infections - bacillus calmette-guérin bacteria</i>	1	25	26.9 [3.6-198.2]	6.2 [0.8-45.7]
<i>Heart failures – sacubitril/valsartan</i>	8	34	4.6 [2.1-9.9]	1.8 [0.8-3.9]

<i>Febrile disorders - bacillus calmette-guérin bacteria</i>	1	13	13.9 [1.8-106.6]	3.2 [0.4-24.6]
<i>Renal failure and impairment – sacubitril/valsartan</i>	13	40	3.3 [1.8-6.2]	1.3 [0.7-2.5]
<i>Respiratory failures (excl neonatal) - nivolumab</i>	3	16	5.7 [1.7-19.6]	2.3 [0.7-8.0]
<i>General signs and symptoms - nivolumab</i>	11	31	3.0 [1.5-6.0]	1.2 [0.6-2.4]
<i>Breathing abnormalities - nivolumab</i>	10	29	3.1 [1.5-6.4]	1.3 [0.6-2.6]
<i>Diarrhoea (excl infective) - idelalisib</i>	8	24	3.2 [1.4-7.2]	1.9 [0.9-4.3]
<i>Breathing abnormalities - sacubitril/valsartan</i>	3	14	5.0 [1.4-17.4]	2.0 [0.6-7.0]
<i>Renal function analyses – sacubitril/valsartan</i>	6	20	3.6 [1.4-8.9]	1.4 [0.6-3.6]
<i>Liver function analyses - nivolumab</i>	4	16	4.3 [1.4-12.8]	1.7 [0.6-5.2]
<i>Lower respiratory tract inflammatory and immunologic conditions - nivolumab</i>	13	32	2.6 [1.4-5.0]	1.1 [0.6-2.0]
<i>Neutropenias - azacitidine</i>	3	13	4.6 [1.3-16.3]	3.0 [0.9-10.7]
<i>Lower respiratory tract and lung infections - ibrutinib</i>	2	11	5.9 [1.3-26.6]	3.0 [0.7-13.6]
<i>Lower respiratory tract and lung infections - nivolumab</i>	8	21	2.8 [1.2-6.4]	1.1 [0.5-2.6]
<i>Death and sudden death - nivolumab</i>	3	12	4.3 [1.2-15.2]	1.7 [0.5-6.2]
<i>Physical examination procedures and organ system status - nivolumab</i>	3	12	4.3 [1.2-15.2]	1.7 [0.5-6.2]
<i>Neoplasms malignant site unspecified - nivolumab</i>	33	56	1.8 [1.2-2.8]	0.7 [0.5-1.1]
<i>Hepatocellular damage and hepatitis - nivolumab</i>	11	24	2.3 [1.1-4.8]	0.9 [0.5-1.9]
<i>Therapeutic and nontherapeutic responses - paliperidone</i>	9	20	2.4 [1.1-5.2]	1.4 [0.6-3.1]
<i>Neoplasms malignant and unspecified - pembrolizumab</i>	5	14	3.0 [1.1-8.3]	2.0 [0.7-5.5]
<i>Metastases to specified sites - nivolumab</i>	8	18	2.4 [1.1-5.5]	1.0 [0.4-2.3]
<i>Vascular hypotensive disorders – sacubitril/valsartan</i>	8	18	2.4 [1.1-5.5]	1.0 [0.4-2.2]
<i>Lower respiratory tract infections - idelalisib</i>	2	14	7.5 [1.7-33.0]	4.5 [1.0-19.8]

4 EV= spontaneous reports from EudraVigilance; ROR= reporting odds ratio; CI= confidence interval

5 Legend Table Appendix 4: Table Appendix 4 shows all ADR (on HLT level)-drug combinations and

6 their reporting odds ratios with their 95% confidence intervals in the EV reports which did not

7 remain more frequently reported for females or males by considering prescription data

3.2 Adverse Drug Reactions in Children: Comparison of Reports Collected in a Pharmacovigilance Project Versus Spontaneously Collected ADR Reports

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Adverse Drug Reactions in Children: Comparison of Reports Collected in a Pharmacovigilance Project Versus Spontaneously Collected ADR Reports

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Abstract

Background Adverse drug reactions (ADRs) and medication errors in children may result from a lack of appropriate drugs, dosages, and pharmaceutical forms. In addition, children may respond differently to drugs than adults. Reporting of ADRs in the pediatric population is therefore of importance in order to increase the amount of safety data. However, different methodological approaches are used to collect ADRs.

Objective The aim of the present study was to analyze whether there were differences in the ADRs collected in the KiDSafe project (845 ADR reports) compared with the spontaneous ADR reports sent to EudraVigilance (697 reports) in the same time period. The strengths and limitations of these two different approaches should be discussed.

Methods The same inclusion criteria were applied for the systematically collected ADRs in the KiDSafe project and the spontaneous reports from EudraVigilance, and only reports of ADRs coded with hospitalization were considered. In both datasets, the number of reports (related to number of hospitals), their documentation quality (VigiGrade), causal relationship (World Health Organization-Uppsala Monitoring Centre [WHO-UMC] criteria), most frequently reported drugs and ADRs, demographical parameters of the patients, reported medical histories, and the seriousness of ADR reports were analyzed descriptively. The results of the two analyses were compared.

Results There was considerable underreporting of ADRs via the spontaneous reports (0.4 reports per hospital; 697/1902) compared with 70.4 reports per hospital (845/12) in the systematically collected KiDSafe reports. Documentation quality assessment yielded similar results in both datasets. Among the 10 most frequently reported drugs, anticonvulsants such as levetiracetam (6.6%), valproic acid (5.6%), oxcarbazepine (3.6%), and lamotrigine (3.4%) were mainly reported in the KiDSafe reports, while in the EudraVigilance reports, mite allergen extract (4.4%) and allergens (3.6%) were preferentially reported. Seizures were the most frequently reported clinically specific ADRs in the KiDSafe reports, whereas anaphylactic reactions and urticaria were prominent in the spontaneous reports from EudraVigilance. Notably, the proportion of reports referring to medication errors and other medication safety related issues were more prominent in KiDSafe than in the spontaneous reports (27.8% vs. 12.6% and 46.0% vs. 29.0%, respectively).

Conclusion In general, reports from both data sources contributed to the identification of ADRs and dedicated issues related to drug therapy. However, these differed by nature and strength of the signal, likely due to the characteristics of the individual method. A combined approach could likely compensate for limitations inherent to the single approaches, but will most likely only be applied to dedicated pharmacovigilance topics or research objectives.

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Extended author information available on the last page of the article

Key Points

Differences in the most frequently reported drugs and adverse drug reactions (ADRs) were observed between the systematically collected ADRs in the KiDSafe project and the spontaneous reports from EudraVigilance, which may be related to the characteristics of each individual method.

The systematic collection of ADRs particularly identified medication errors and issues related to medication safety compared with the spontaneous collection of ADRs.

A combined approach may compensate for the limitations of each single approach.

1 Introduction

According to literature, 1.7% of children in Germany experienced adverse drug reactions (ADRs) under outpatient drug therapy [1] and 9.2–14.1% during a hospital stay [2, 3]. In addition, an estimated 3–5% of all hospital admissions of children are due to an ADR [4].

The reasons for this substantial risk of ADRs for children include, among others, the off-label administration of drugs, i.e. without dedicated data regarding safety and dosages in children [5]. Hence, postmarketing surveillance for drugs used in children is crucial.

Surveillance measures comprise, but are not limited to, the spontaneous reporting system, the analyses of electronic health records, registries, and systematic ADR collections as part of pharmacovigilance studies. Each of these instruments carries its inherent strengths and limitations [6].

The objective of the present study was to compare two different methodological approaches of pediatric postmarketing surveillance, i.e. solicited versus unsolicited reports [7]. Therefore, the results of a systematic collection of pediatric ADR reports as part of the KiDSafe project [8] (solicited) were compared with the results of analyses in a spontaneous reporting system (EudraVigilance reports; unsolicited). Based on this assessment, the strengths and limitations of these two different approaches were analyzed.

2 Material and Methods

2.1 Adverse Drug Reactions (ADRs)

An ADR is defined as a response to a medicinal product that is noxious and unintended [7]. In Germany, ADRs can be reported by health care professionals (HCP) and non-HCPs (e.g. patients), and these ADR reports are forwarded to the European ADR database (EudraVigilance) [9, 10].

Reporting obligations are reported elsewhere [10, 11]. The minimum criteria that should be provided in an ADR report include an identifiable patient, an identifiable reporter, one or more suspected drugs, and a suspected ADR [7].

ADR reports may either be unsolicited, i.e. they do not derive from a study or any organized data collection system, or they can be solicited, i.e. from organized data collection systems, including clinical trials, non-interventional studies, registries, etc. [7]. The two methodological approaches compared in the present study are representatives of unsolicited (EudraVigilance analysis) and solicited reports (KiDSafe project, see Sect. 2.2), respectively.

Within EudraVigilance, ADRs are coded in accordance with the terminology of the Medical Dictionary for Regulatory Activities (MedDRA) [12]. MedDRA terminology includes five hierarchical levels. The High Level Term (HLT) summarizes the Preferred Terms (PT) on a rather aggregated level of analysis, while the PT level describes the symptom, laboratory result, diagnosis or condition.

2.2 KiDSafe Project

The KiDSafe project was a large multicenter project aiming to improve pediatric drug safety.

One pillar of the project was the detection and reporting of ADRs leading to hospital admissions.

Study teams from 12 children's hospitals in Germany screened all non-elective patients aged 0–17 years admitted to their hospital between 1 July 2018 and 30 June 2020. Notably, oncological patients who were admitted as inpatients with a suspected ADR and had been in inpatient oncological treatment in the previous 4 weeks were excluded from the screening. The screening was performed by applying a standardized algorithm [13], identifying patients with a potential relationship between hospitalization and drug administration prior to admission. Cases with suspected ADRs detected by this algorithm were then reported to an independent expert group (Adverse Drug Event Expert Group) if consent for data processing was obtained. In cases where no consent could be obtained, reports with suspected ADRs with a reasonable time relationship to drug use were sent directly to the Drug Commission of the German Medical Association (DCGMA) [as obliged by the professional conduct code; see Sect. 2.1]. Both groups (Adverse Drug Event Expert Group and the DCGMA) assessed the causal relationship between the reported ADR and the suspected drugs (see below). The reports presented within this manuscript comprise only ADR reports sent directly to the DCGMA (without consent), which were then forwarded to the BfArM for inclusion in EudraVigilance. Since these reports were generated 'systematically' by the application of the algorithm, they are designated as 'systematically

collected ADR reports' from here on. Finally, these reports were identified in EudraVigilance based on their case identifier indicating a KiDSafe report.

2.3 Identification of ADR Reports in the EudraVigilance Database

Reports from EudraVigilance [10] sent spontaneously served as a comparison group. All spontaneous reports of ADRs referring to children and adolescents aged 0–17 years from Germany received between 1 July 2018 and 30 June 2020 were identified. Notably, the ADRs from the KiDSafe project *occurred* during the study period 1 July 2018–30 June 2020, whereas the EudraVigilance reports were *reported* within this study period. For technical reasons, the occurrence date of the ADRs in EudraVigilance reports could not be accessed computer-based for the complete dataset. However, all reports were designated as serious (referring to the ADR) and were thus subject to a reporting obligation of 15 days [7]. Only reports in which the ADR led to or prolonged hospitalization were included (see Sect. 2.5.2 and Fig. 1). Vaccines were excluded since vaccination is a medical process that is different from drug administration and is linked to specific age intervals, which would affect the age- and sex-stratified analyses.

Figure 1 shows the analyses criteria and number of ADR reports identified for both groups.

2.4 Documentation Quality and Causality Assessment of the Reports

Documentation quality was assessed by computer-based grading according to the VigiGrade score, a completeness score that measures the amount of information provided in structured formats [14]. Therefore, the VigiGrade score, which was developed for the VigiBase database [15], was slightly adapted to match the format and content of data in EudraVigilance. For assessment of the causal relationship, the World Health Organization–Uppsala Monitoring Centre (WHO-UMC) criteria [16] were used. The DCGMA conducted a causality assessment of 74.6% (630/845) of the KiDSafe reports as part of the KiDSafe project. A causality assessment was also available for 128 of the 697 spontaneous reports in the EudraVigilance final dataset (Table 1). With the exception of one report, this causality assessment was also performed by the DCGMA.

2.5 Strategy of Analyses

All ADR reports were analyzed with regard to the distribution of age and sex, seriousness criteria, reporting sources, medical histories, quality of documentation, causality, frequently reported suspected drugs, and ADRs. Means and

medians were calculated for the quality of documentation, and frequency distributions for all other variables.

Notably, not only were 'conventional' (substance-related) ADRs analyzed but also, according to a current ADR definition [7], medication safety-related [17] ADRs such as medication errors (e.g. product administration error), over- and underdoses (e.g. intentional overdose), and reports on abuses and misuses. As yet, there is no generally accepted definition for the term 'medication safety'. In the context of this publication, medication safety means all measures that contribute to the optimization of the drug treatment process with the aim of reducing medication errors/preventable harm from drug use (German definition of 'Arzneimitteltherapiesicherheit') [17]. Medication safety-related issues describe problems during the drug treatment process rather than 'conventional' (substance-specific) ADRs. According to guidance [7], all reports describing such scenarios retrieved in our analyses should be associated with an additional co-reported suspected ADR; however, we cannot fully exclude the presence of reports not being associated with an additional suspected ADR among the reports. In order to identify the number of reports describing medication errors in the KiDSafe and EudraVigilance reports, the standardized MedDRA query (SMQ) 'medication error (broad)' was used [12]. Furthermore, we identified the reported PTs that described a scenario relating to medication safety and determined the number of reports reporting such scenarios in both datasets.

Our analyses also retrieved reports that describe a lack of efficacy of drug therapy. Notably, per definition, lack of efficacy is not an ADR. However, in certain circumstances (e.g. drugs used for life-threatening diseases), reports on lack of therapeutic efficacy with no co-reported suspected ADR may need to be submitted to EudraVigilance [7].

2.5.1 Primary Reporting Source

Both datasets were limited to reports coded with hospitalization. Per default, all ADR reports in the KiDSafe project were reported by HCPs due to the study design, whereas the EudraVigilance reports, reported in the same study period, included the reports of HCPs and non-HCPs (e.g. patients).

2.5.2 Seriousness Criteria

The designation 'serious ADRs' corresponds to the legal definition of an ADR and not to its clinical severity [7]. Accordingly, all ADRs that led to death, were life-threatening, required or prolonged hospitalization, conferred lasting or significant disability or incapacity, led to congenital abnormalities/birth defects, or endangered the patient and required medical or surgical intervention/treatment ('other') were considered as serious. Multiple assignments could be

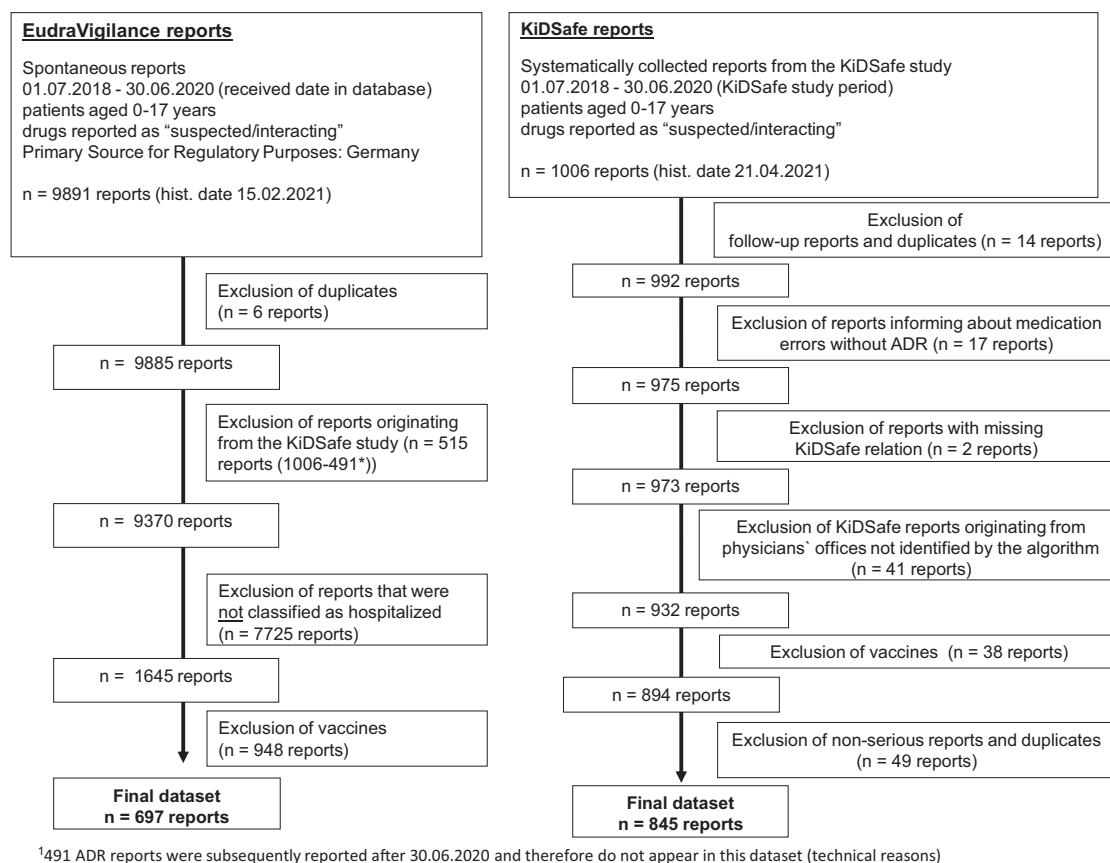


Fig. 1 Generation of the final datasets. *ADR* adverse drug reaction, *Hist. date* historical date

Table 1 Assessment of the causal relationship between the administration of the drug and the ADR in the systematically collected versus spontaneous ADR reports

Assessment of the causal association between the administration of the drug and the ADR (WHO-UMC criteria [16])	KiDSafe reports (systematically collected ADR reports) [n = 845] 74.6% (n = 630) with available assessment	EudraVigilance reports (spontaneous ADR reports) [n = 697] 18.4% (n = 128) with available assessment
Certain	0.6% (4/630)	0.8% (1/128)
Probable/likely	3.5% (22/630)	5.5% (7/128)
Possible	88.4% (557/630)	89.8% (115/128)
Unlikely	1.4% (9/630)	0% (0/128)
Conditional/unclassified	0.6% (4/630)	1.6% (2/128)
Unassessable/unclassifiable	5.4% (34/630)	2.3% (3/128)

ADR adverse drug reaction, *WHO-UMC* World Health Organization–Uppsala Monitoring Centre

Also covers medication error-related ADRs. Due to the extension of the ADR definition in 2012, conditions such as overdose, misuse, abuse, medication errors, and occupational exposure are now included in the ADR definition [7, 21]. Although, theoretically, all such reports retrieved in our analyses should be associated with a suspected co-reported ADR, we cannot exclude the presence of reports not being associated with a suspected co-reported ADR among the reports (see Sect. 2.5)

made in each ADR report. In order to differentiate whether the coding ‘hospitalization’ within the EudraVigilance reports was related to an outpatient-acquired ADR with subsequent hospitalization or an inpatient-acquired ADR that prolonged hospitalization, a random sample of 10% (68/697) of the EudraVigilance reports was analyzed in this regard.

2.5.3 Age and Sex Distribution

The age stratification of the National Association of Statutory Health Insurance Physicians [18] was modified according to the physiological development of children and adolescents (i.e. 0–1 month, 2 months–1 year, 2–3 years, 4–6 years, 7–12 years, and 13–17 years). Reports in the 0–1 month age group were additionally analyzed to determine whether the ADR was related to exposure to the drugs in utero or via breast milk. All age groups were also stratified with regard to sex.

2.5.4 Most Frequently Reported Drugs and Their Most Frequently Reported ADRs

The final datasets of the two groups were analyzed with regard to the 10 drugs most frequently reported as suspected. In addition, age-stratified analyses of the most frequently reported drugs were performed. Furthermore, the three most frequently reported ADRs were analyzed for each of the five most frequently suspected drugs.

2.5.5 Medical History

In order to provide a complete description of the ADR reports for both groups, the medical history, if reported, was also evaluated (PT level of the MedDRA terminology [12]).

2.6 Compliance with Ethical Standards and Ethics Approval

Due to data privacy requirements and the EudraVigilance access policy [19], the complete individual pseudonymized case reports were not available to the readership. Although different levels of access are granted for different stakeholders, even with the lowest level of access an analysis of aggregated data is possible. For further information regarding the processing of personal data in the context of the operation of EudraVigilance Human, we refer to the European Medicines Agency’s Data Protection Notice for EudraVigilance Human [20].

Approval for the protocol of the KiDSafe project was obtained from the Ethics Committee of the Friedrich-Alexander University Erlangen-Nürnberg under reference number 351_17 B, and approval for the analysis of the spontaneous reports from EudraVigilance was obtained from

the local Ethics Committee of the Medical Faculty of Bonn (009/17 and 100/21).

3 Results

3.1 Number of Reports

A total of 845 reports were reported via the 12 participating KiDSafe hospitals, and 697 reports were reported via the spontaneous reporting system in the same time period (Fig. 1).

3.2 Documentation Quality and Causal Relationship

Documentation quality based on calculation of the mean and median VigGrade score was comparable between the KiDSafe (mean 0.64 ± 0.25) and EudraVigilance (mean 0.63 ± 0.25) reports (median 0.61 vs. 0.61). However, the relative share of reports rated with a VigGrade score ≤ 0.3 , suggesting rather poorly documented reports, was smaller in the systematically collected reports compared with the spontaneous reports (1.3% vs. 6.0%) [electronic supplementary material (ESM) Table 1].

Assessment of the causal relationship [16] was available for 74.6% (630/845) of the systematically collected reports and 18.4% (128/697) of the spontaneous reports (see the Sect. 4 for further information). In these reports, an ‘at least possible’ causal relationship was noted in 92.5% (583/630) of the systematically collected reports and 96.1% (123/128) of the spontaneous reports (Table 1). No substantial differences between the two groups in relation to the different categories of causality could be observed.

3.3 Reporting Sources

Reflecting the study design, 100% (845/845) of the systematically collected reports were sent by HCPs compared with 87.4% (609/697) of the spontaneous reports; 12.6% (88/697) of spontaneous reports were from non-HCPs (see ESM Table 2).

3.4 Seriousness Criteria

Since hospitalization is one of the legally defined seriousness criteria, all of the systematically collected reports and spontaneous reports were classified as serious. A lower number of reports was classified as ‘life-threatening’ and ‘fatal’ in the systematically collected reports than in the spontaneous reports (life-threatening: 8.3% [70/845] vs. 13.7% [95/692]; fatal: 0.1% [1/845] vs. 2.3% [16/692]) [ESM Table 3]. None of the random sample reports from the EudraVigilance reports described a hospital-acquired ADR.

3.5 Age and Sex Distribution

The largest proportion for both systematically collected (47.6% [402/845]) and spontaneous reports (40.0% [279/697]) referred to the 13–17 years age group. The 0–1 month age group accounted for only 0.7% (6/845) of the systematically collected reports but 6.9% (48/697) of the spontaneous reports. Among the six systematically collected reports for this age group, only one (16.7%) referred to the mother taking the drug and the child experiencing the ADR, compared with 34/48 (70.8%) of the spontaneous reports.

In both datasets, a higher proportion of reports for the 13–17 years age group referred to females than males, with a similar ratio of approximately 2:1 (systematically collected: 70.4% [283/402] vs. 29.1% [117/402]; spontaneous reports: 62.0% [173/279] vs. 36.9% [103/279]). In the younger age groups (0–6 years) more reports referred to males than to females in both datasets (ESM Table 4).

3.6 Reported ADRs

Clinically, rather unspecific ADRs (vomiting, nausea, and dizziness) were among the 10 most commonly reported ADRs in both datasets (Table 2). It was striking that in the systematically collected reports, product administration errors ranked first and were clearly more often reported in KiDSafe reports than in EudraVigilance reports. In summary, 27.8% (235/845) of the KiDSafe reports included medication errors compared with 12.6% (88/697) of the EudraVigilance reports. Furthermore, the proportion of reports referring to scenarios relating to medication safety in the KiDSafe reports (46.0%, 389/845) was higher than in the EudraVigilance reports (29.0%, 202/697).

Seizure (8.8%) was the most frequently reported clinically specific ADR in the systematically collected reports, compared with allergic-like reactions in the spontaneous reports (anaphylactic reaction [6.0%] and urticaria [5.0%]). In summary, the ADR profile between the systematically collected reports and the spontaneous reports differed.

3.7 Most Frequently Suspected Drugs and Their Most Frequently Reported ADRs

3.7.1 Systematic ADR Collection

Overall, 7.5% (63/845) of the systematically collected reports referred to ibuprofen. In 46.0% (29/63) of these reports, the ADR *intentional overdose* was coded.

Two of the remaining top five drugs among the systematically collected reports were anticonvulsants (levetiracetam: 6.6% [$n=56$]; valproic acid: 5.6% [$n=47$]). In summary, 22% (182/845) of the systematically collected reports

referred to the drug class of anticonvulsants and 5.5% (10/182) of these were coded as life-threatening. Anticonvulsants were strongly represented in all age groups, except for the 13–17 years age group (ESM Table 6). An individual assessment of these 182 reports revealed that the respective ADR (e.g. seizure) occurred during outpatient treatment and resulted in an inpatient admission for readjustment to the anticonvulsant therapy (Table 3).

3.7.2 Spontaneous ADR Reports

Within the spontaneous reports, two of the top five drugs referred to allergens (mite allergen extract: 4.4% [$n=31$]; allergens: 3.6% [$n=25$]) [Table 3]. In summary, 11.5% (80/697) of the spontaneous reports related to allergens (Table 4). In these reports relating to allergens, mostly anaphylactic reactions and related symptoms were reported. Interestingly, if allergens were excluded from the spontaneous reports, anaphylactic reactions and related symptoms no longer appeared in the ranking of the 10 most frequently reported ADRs. The route of administration of these allergens was mostly subcutaneous (87.5% [70/80]) and rarely sublingual (12.5% [10/80]). 30.0% (24/80) of the EudraVigilance reports on these allergens were coded as life-threatening. Allergens were mainly reported for 7–12-year-olds (ESM Table 7).

Overall, 3.6% (25/697) of the spontaneous reports provided information about palivizumab. Individual case assessment revealed that the reported ADRs *respiratory syncytial virus infection* and *respiratory failure* were due to a lack of efficacy (for further explanation, see Sect. 2.5).

3.7.3 Drugs Occurring in Both Datasets

Insulin aspart and methylphenidate were among the five most frequently suspected drugs in both datasets. 5.7% (48/845) of the systematically collected reports related to insulin aspart. Here, *product administration errors* and *treatment non-compliance* were mainly reported (58.3%, $n=28$) [Table 3]. According to an individual assessment of these reports, inconsistent adherence to therapy, fear of self-injection, and fear of hypoglycemia were mentioned, among others. 33.3% (14/42) of the spontaneous reports on insulin aspart informed about product leakage as an ADR, following an individual review. In 85.7% (12/14) of these reports, damage to the cartridge caused insulin to leak into the cartridge compartment of the pump, and in only 14.3% (2/14) of the reports a wrong technique in the product-use process was reported (Table 3).

Methylphenidate was reported in 4.1% (35/845) of the systematically collected reports and 3.0% (21/697) of the spontaneous reports. Reported methylphenidate-related

Table 2 The 10 most frequently reported ADRs for both data sources (PT level)

KiDSafe reports (systematically collected reports) [<i>n</i> = 845]		EudraVigilance reports (spontaneous reports) [<i>n</i> = 697]	
Product administration error ^a	18.1 (153)	Vomiting ^c	10.0 (70)
Vomiting ^c	15.6 (132)	Anaphylactic reaction ^d	6.0 (42)
Intentional overdose ^b	13.0 (110)	Dyspnea ^c	5.9 (41)
Toxicity to various agents ^b	11.4 (96)	Pyrexia ^c	5.5 (38)
Treatment non-compliance ^b	9.9 (84)	Nausea ^c /urticaria ^d	5.0 (35)
Seizure ^d	8.8 (74)	Drug ineffective ^c /off-label use ^b	4.2 (29)
Nausea ^c	7.6 (64)	Dizziness ^c	3.7 (26)
Dizziness ^c	6.3 (53)	Fetal exposure during pregnancy/headache ^c /tachycardia ^d	3.6 (25)
Accidental exposure to the product by a child ^b	5.8 (49)	Abdominal pain ^c /product administration error ^{a,b}	3.4 (24)
Abdominal pain ^c	5.7 (48)	Rash ^d /somnolence ^c	3.2 (23)

Data are expressed as % (*n*)

ADRs adverse drug reactions, PT Preferred Term, SMQ standardized MedDRA query

^aConditions describing a medication error coded in the SMQ medication errors (broad) [12]. Although theoretically all such reports retrieved in our analyses should be associated with a co-suspected ADR [7], we cannot exclude the presence of reports not being associated with a co-suspected ADR among the reports (see Sect. 2.5)

^bConditions describing a scenario relating to medication safety. Although, theoretically, all such reports retrieved in our analyses should be associated with a co-suspected ADR [7], we cannot exclude the presence of reports not being associated with a co-suspected ADR among the reports (see Sect. 2.5)

^cClinically, rather unspecific ADRs that may occur as a symptom of many diseases compared with more specific ADRs that are suggestive of a specific disease. The classification of ‘unspecific’ versus ‘specific’ ADRs is arbitrarily based on the subjective medical and pharmaceutical expertise and judgment of the project team, since no respective guidance, applicable for this constellation, could be found

^dClinically specific ADRs. See explanation above referring to unspecific ADRs

^eDespite ‘drug ineffective/lack of efficacy’ not being considered an ADR per definition, in certain circumstances submission of these reports to EudraVigilance, even if not associated with an ADR, is required [7] (see Sect. 2.5). Hence, these reports are included in the present analyses and are depicted in the table

ADRs were gastrointestinal complaints such as *vomiting* and *nausea* as well as *headache* and *intentional overdoses* (systematically collected reports: 17.1% (6/35); spontaneous reports: *vomiting* 14.3% (3/21), *nausea* 19.0% (4/21), *headache* 14.3% (3/21), *intentional overdose* 19.0% (4/21) [Table 3].

An overview of the top 10 most frequently reported drugs for both datasets (KiDSafe and EudraVigilance reports) is presented in ESM Table 5. Table 3 shows the five most often suspected drugs and their three most often reported ADRs in both datasets.

3.8 Medical History

Epilepsy and type 1 diabetes ranked among the top two reported medical histories in both databases (PT level) [ESM Table 8]. In summary, half of the medical histories were among the top 10 in both datasets; however, they differed in ranking and their relative share, e.g. 18.4% (134/729) of the systematically collected reports with medical history reported epilepsy compared with 6.9% (36/519) of those in the spontaneous reports.

3.9 Summary Comparison of the Two Datasets

Both datasets pointed to product administration errors associated with insulin aspart. Related to the reported medical history and to the reported drugs among the systematically collected reports, epilepsy appeared to be a prominent issue compared with allergens in the spontaneous reports.

The following table describes the main results for the two different approaches with regard to selected criteria (Table 4).

4 Discussion

This descriptive analysis compared ADR reports referring to children from Germany collected systematically within a pharmacovigilance project (KiDSafe reports) with those being spontaneously reported (EudraVigilance reports).

4.1 Characteristics of the Reports

Although the systematically collected ADR reports originated from only 12 participating hospitals from different

Table 3 The five most often suspected drugs and their three most often reported ADRs (PT level)

KiDSafe reports (systematically collected reports) [n = 845]		% (n)	EudraVigilance reports (spontaneous reports) [n = 697]		% (n)
Ibuprofen [n = 63, 7.5%]	Intentional overdose ^{a,b}	46.0 (29)	Insulin aspart ^d [n = 42, 6.0%]	Blood glucose increased	38.1 (16)
	Toxicity to various agents ^{a,b}	34.9 (22)		Product leakage ^{a,b}	33.3 (14)
	Vomiting/dizziness	11.1 (7)		Diabetic ketoacidosis	31.0 (13)
Levetiracetam [n = 56, 6.6%]	Seizure	44.6 (25)	Mite allergen extract [n = 31, 4.4%]	Anaphylactic reaction	58.1 (18)
	Epilepsy/product administration error ^{a,b,c}	23.2 (13)		Dyspnea	25.8 (8)
Insulin aspart ^d [n = 48, 5.7%]	Treatment non-compliance ^{a,b}	17.9 (10)		Urticaria	16.1 (5)
	Product administration error ^{a,b,c} /treatment non-compliance ^{a,b}	58.3 (28)	Allergens [n = 25, 3.6%]	Anaphylactic reaction	44.0 (11)
	Blood glucose increased/ketoacidosis/vomiting	31.3 (15)		Dyspnea/urticaria	28.0 (7)
	Hyperglycemia	25.0 (12)		Anaphylactic shock/pruritus	12.0 (3)
Valproic acid [n = 47, 5.6%]	Seizure	38.3 (18)	Palivizumab [n = 25, 3.6%]	Respiratory syncytial virus infection ^e	60.0 (15)
	Epilepsy	17.0 (8)		Respiratory failure	16.0 (4)
	Status epilepticus/thrombocytopenia	12.8 (6)		Fluid intake reduced	12.0 (3)
Methylphenidate ^d [n = 35, 4.1%]	Headache/intentional overdose ^a /nausea/vomiting	17.1 (6)	Methylphenidate ^d [n = 21, 3.0%]	Intentional overdose ^a /nausea/vision blurred	19.0 (4)
	Abdominal pain/seizure/weight decreased	14.3 (5)		Headache/tachycardia/vomiting	14.3 (3)
	Dizziness/toxicity to various agents ^a	11.4 (4)		Agitation/decreased appetite/dizziness/electrocardiogram QT prolonged/feeling jittery/hallucination/mydriasis/personality change/suicide attempt ^a	9.5 (2)

ADRs adverse drug reactions, PT Preferred Term, SmPc Summary of Product Characteristics, SMQ standardized MedDRA query

^aConditions describing a scenario relating to the medication safety [17]. Although, theoretically, all such reports retrieved in our analyses should be associated with a co-suspected ADR [7], we cannot exclude the presence of reports not being associated with a co-suspected ADR among the reports (see Sect. 2.5)

^bReactions related to the administration process of medicinal products but not explicitly mentioned in the SmPC. Please note that manufacturers are required to compile their SmPCs in accordance with the regulatory guidance [22], which also describes which information should be included in which section of the SmPC. In addition, besides the SmPC, other pharmacovigilance documents, e.g., risk management plans safeguarding a medicinal product's safety, are required. Hence, certain reactions in the table above not mentioned in section 4.8 of the SmPC do not necessarily imply a safety concern.

^cConditions describing a medication error coded in SMQ medication errors (broad) [12]. Although, theoretically, all such reports retrieved in our analyses should be associated with a co-suspected ADR [7], we cannot exclude the presence of reports not being associated with a co-suspected ADR among the reports (see Sect. 2.5).

^dDrugs that are listed in the top five of both datasets

^eLack of efficacy (following individual case assessment) not mentioned in the SmPC. Despite 'drug ineffective/lack of efficacy' not being considered an ADR per definition, in certain circumstances submission of these reports to EudraVigilance, even if not associated with an ADR, is required [7] (see Sect. 2.5). Hence, these reports are included in the present analyses and are depicted in Table 3

geographic clusters of Germany, the number of reports ($n = 845$) exceeded the number of reports ($n = 697$) leading to hospitalization received via the spontaneous reporting system from all over Germany. Thus, the ADR rate *per participating hospital* was much higher for the systematically collected reports (70.4 reports [845/12]) than that of the spontaneous reports related to the number from any hospital in Germany (0.4 reports [697/1902 hospitals [23]]). Notably, this comparison is hampered, since, among others, the number of hospitals with a pediatric department in Germany was not available and the spontaneous reports could have been

sent by HCPs working in a hospital, HCPs not working in a hospital, or non-HCPs. Nevertheless, these findings suggest a considerable underreporting for pediatric ADRs leading to hospitalization in the spontaneous reporting system, which was also observed in another study from The Netherlands [24]. Common reasons for underreporting are, among others, lack of time and not reporting of well-known ADRs [24, 25], which may also apply to pediatric ADRs. Although, in principle, every ADR can be reported, certain ADRs are of special interest from a pharmacovigilance point of view (e.g.

Table 4 Comparison of the main characteristics of the analyses

Comparison criteria	KiDSafe reports (systematically collected reports)	EudraVigilance reports (spontaneous reports)
Number of ADR reports	845	697
Reporting rate per hospital	70.4 reports (845/12 ^a)	0.4 reports (697/1902 ^b)
Documentation quality (VigiGrade score) [14] [mean $\pm$ SD]	0.63 $\pm$ 0.26	0.63 $\pm$ 0.25
Causality assessment available (WHO-UMC criteria [16])	74.6% (630/845) 630 reports had been assessed by the DCGMA	18.4% (128/697) 127 reports had been assessed by the DCGMA and, additionally, one external evaluation was performed
Most frequent rating	Possible: 88.4% (557/630)	Possible: 89.8% (115/128)
Information about medical history	86.3% (729/845)	74.5% (519/697)
ADR reports on 0–1 month	0.7% (6/845)	6.9% (48/697)
Thereof, reports that are due to the mother's intake of the drug during breastfeeding/pregnancy	16.7% (1/6)	70.8% (34/48)
Highlighted drug classes in this dataset ^c	Anticonvulsants 21.5% (182/845)	Allergens 11.5% (80/697)
Number of reports describing medication errors ^d	27.8% (235/845)	12.6% (88/697)
Number of reports describing issues related to the safety of drug therapy	46.0% (389/845)	29.0% (202/697)

ADR adverse drug reaction, SD standard deviation, WHO-UMC World Health Organization-Uppsala Monitoring Centre, DCGMA Drug Commission of the German Medical Association, SMQ standardized MedDRA query

^aNumber of participating hospitals in the KiDSafe project

^bNumber of hospitals in Germany [23] minus the participating hospitals in the KiDSafe project

^cHighlighted drug classes may not correspond to the most frequently reported drug classes but is based on analysis of the 10 most frequently suspected drugs. No analyses referring to drug classes were performed for the complete dataset

^dNumber of reports that describe a condition coded in SMQ 'medication error (broad)' [12]

serious ADRs, unknown ADRs [not listed in the SmPC], and ADRs of new drugs [marketed for < 5 years]) [26].

Interestingly, there were only small differences with regard to the quality of documentation between the KiDSafe (0.64 $\pm$ 0.25) and EudraVigilance reports (0.63 $\pm$ 0.25). However, the relative share of reports with a VigiGrade score $\leq$ 0.3, indicating a rather poor documentation quality, was higher in EudraVigilance reports versus KiDSafe reports (6.0% vs. 1.3%). Notably, whereas all KiDSafe reports originated from HCPs, 12.6% of the EudraVigilance reports originated from non-HCPs. However, the quality of documentation was only slightly higher for HCPs (mean 0.64) compared with non-HCPs (mean 0.57) in the EudraVigilance reports. It has to be noted that the VigiGrade score was calculated by means of a computer-based algorithm not considering any additional information provided in the free-text descriptions of the reports that may have upgraded the quality of documentation. This limitation applies to both datasets. In the original publication by Bergvall et al., reports with a VigiGrade score > 0.8 were defined as being well-documented, and this was achieved in 13% of the studied reports (median score 0.41) [14]. In

our study, 30.4% of EudraVigilance reports and 31.3% of KiDSafe reports had a score > 0.8 (median score 0.61 in both groups). Thus, compared with the analysis by Bergvall et al., our data performed better. However, it has to be taken into account that the period of analyses differed and that our analysis only included reports from Germany, whereas Bergvall et al. included more than 100 countries. Bergvall et al. stated that there are countries with a higher proportion of well-documented reports, such as Germany [14].

The share of ADR reports with an 'at least possible' causal relationship was high and comparable in both datasets (systematic ADR collection: 88.4% [557/630]; spontaneous reports: 96.1% [123/128]). However, in only 18.4% (128/697) of the spontaneous reports, a causality assessment was available compared with 74.6% (630/845) of the systematically collected ADR reports. This difference reflects that the systematic ADR collection according to the protocol required a causality assessment by the DCGMA. Systematically collected reports without causality assessment (215/845; 25.4%) referred to reports informing about, for example, accidental intoxication or overdoses without clinically manifest ADR, which were thus not assessed

for causality. In contrast, only those (127/128) spontaneous reports that were forwarded to BfArM by the DCGMA contained a causality assessment, whereas reports not provided by the DCGMA usually do not contain a causality assessment. Due to the huge number of reports, no causality assessment is routinely performed by the competent authorities, and marketing authorization holders are not obliged to provide a causality assessment when submitting the report to EudraVigilance [9]. However, it should be considered that these reports without causality assessment still carry an ‘implied causal association’ since, as one minimum criterion (as required by EudraVigilance), there was suspicion of an ADR. The high proportion of reports with a possible causal relationship was also observed in other studies from our group [27, 28], as well as in other ADR database analyses [29]. This finding may be related to the fact that often not all information (e.g. comedications, histories) required to exclude that the reported ADR could also be related to other drugs or diseases is provided. The latter also applies to the KiDSafe reports explaining why the causality assessment performed worse compared with other studies of similar design. In addition, it has to be taken into account that in other studies, different methods for the assessment of the causality, i.e. not WHO-UMC [16], may have been applied, which could explain a higher proportion of ADRs assessed as probable in these studies compared with KiDSafe.

4.2 Reporting Sources and Seriousness Criteria

Because of the study design [13], all KiDSafe reports originated from HCPs compared with 87.4% (609/697) of the EudraVigilance reports. More spontaneous than systematically collected reports were designated as life-threatening (13.7% vs. 8.3%), fatal (2.3% vs. 0.1%) and disabling (1.3% vs. 0.1%) [ESM Table 3]. This may to some extent reflect a considerable underreporting of non-serious ADRs since physicians may tend to preferentially report serious ADRs [30]. In summary, the spontaneous ADR collection included consumer reports but inherently may carry a selection bias towards more serious ADRs.

4.3 Age and Sex Distribution

The high proportion of ADR reports for 7- to 12- and 13- to 17-year-olds in both datasets underlines the importance of intensive monitoring of drug administration in these age groups. It may however also reflect a higher drug exposure in these age groups, which we did not assess in the present study. According to a study from Germany, the latter was at least applicable for 14- to 17-year-olds [31]. In contrast, two other prospective studies performed at a university hospital in Germany also showed a higher ADR incidence for 11- to 18-year-olds compared with 0- to 10-year-olds [32].

4.4 Medical History

Interestingly, a much higher proportion of epilepsy was reported in the medical histories of the systematically collected reports than the spontaneous reports. In summary, depending on the inclusion and exclusion criteria, systematic ADR reporting may include different patients (e.g. with different medical histories) than spontaneous ADR reporting and may therefore be more focused on a specific group of patients, whereas spontaneous reporting may principally cover all patient groups.

4.5 Reported ADRs and Drugs

The analyses of the reported ADRs from both datasets showed similarities and differences. Whereas the spontaneous reports draw attention to anaphylactic ADRs related to allergens, the systematic ADR collection pointed to anti-convulsant-related ADRs. This might be due to the fact that patients with epilepsy are often readmitted to hospitals due to unsatisfactory seizure control, while at the same time, seizures may occur as ADRs of some anticonvulsants. Whereas this could deter physicians from reporting suspected ADRs via the spontaneous reporting system, the KiDSafe team members were explicitly asked to report any ADR to the DCGMA with an assumed, at least reasonable, time relationship to the administration of the drug. In contrast, allergens were prominent in the spontaneous reports, indicating that ADRs associated with allergens used for hyposensitizations, such as ADRs associated with ‘conventional’ drugs, are also reported. These spontaneous reports mostly described hyposensitizations that resulted in anaphylactic reactions and patients being hospitalized for treatment or monitoring. The latter finding may also reflect that patients who receive hyposensitization are intensively monitored and explicitly asked about the occurrence of ADRs before they are allowed to leave the doctor’s office. Hence, the physicians may be confronted with more ADRs for this particular drug class, which may increase the likelihood of allergen-related ADRs being reported by physicians. Notably, in our analysis, almost all of the spontaneous reports referring to allergens originated from physicians (97.5% [78/80]).

In other studies, antibiotics were frequently reported as the drug class most often associated with ADRs in children and adolescents [32–35]. Please note that our analysis was performed at the drug ingredient level and not at an aggregated drug class level, which may have impacted on the order of the most frequently reported drugs or drug classes compared with other studies. Furthermore, the previous studies were performed before 2017 and antibiotic prescriptions in Germany decreased enormously between 2010 and 2019 [36], which may have also impacted on the number of ADR reports referring to antibiotics in our study. However, if

antiepileptics and allergens were excluded, antibiotics would rank sixth (amoxicillin) and tenth (cefuroxime), respectively, in the ranking of the most frequently reported drugs in the KiDSafe and EudraVigilance reports.

Notably, oncological patients were not considered in the KiDSafe project (see the Sect. 2). In consequence, respective drugs were not among the suspected drugs in the KiDSafe reports. With regard to the EudraVigilance reports, these were also reported as suspected drugs, in particular in the age-stratified analysis (see ESM Table 7); however, they did not rank among the first 10 suspected drugs in the overall analysis.

In summary, these are two different pharmacovigilance issues originating from the two different approaches; however, they both illustrate the necessity to closely monitor patients during drug therapy.

Reports on insulin aspart describing application problems during treatment were contained in both datasets. Children, adolescents, and their parents need to be well-educated on how to correctly use the medical device [37, 38], and both parents and HCPs should assist in this process until it can be applied unassisted. This education should also convey the importance of insulin therapy for the health of the patient.

Remarkably, more KiDSafe reports described medication errors and other medication safety related issues compared with EudraVigilance reports. In other words, the systematic ADR collection pointed to a pharmacovigilance issue that is crucial for drug safety and that has not been identified in comparable strength in the spontaneous reports. The reasons for its assumed underreporting in daily routine may relate to the limited time and personnel resources.

With regard to medication errors and other scenarios relating to medication safety, the fear of legal consequences may also play a role. In the literature, a considerable number of medication errors or scenarios relating to the safety of drug therapy were also reported for children and adolescents admitted to hospitals [33, 34, 39, 40].

5 Conclusion

In summary, both approaches carry inherent advantages and disadvantages from a pharmacovigilance point of view that should be considered when interpreting the results of the respective analyses. Systematic ADR collection may be helpful if there is a focus on a particular ADR, drug, or region, and may also point to dedicated safety issues not emerging from the spontaneous reports. It is thus applied both when a signal has already occurred, e.g. as part of the spontaneous reporting system requiring further investigation, and for signal generation.

Although possibly providing a broader spectrum of ADR reports, the spontaneous ADR collection will, conversely,

most likely deliver fewer spontaneous reports to a particular ADR or drug of interest compared with a targeted systematic ADR report collection. In fact, its main purpose is to deliver signals of rare, serious, and as yet unknown ADRs, typically based on disproportionality analysis [41].

Beyond these considerations, the spontaneous reporting system is more cost effective and available without a time delay, but limited by considerable underreporting and the unknown amount of drug-exposed individuals.

Systematic ADR collection is more cost expensive and personnel intensive and may be subject to biases depending on the protocol of the individual study. Additionally, investigating rare ADRs may require sufficiently large, and thus expensive and logistically complex, studies.

A combined approach could likely compensate for limitations inherent to the single approaches. However, in clinical practice, since the systematic ADR collection is more expensive and complex, such a combined approach will most likely only be applied to dedicated pharmacovigilance topics or research objectives.

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Conflict of interest Sarah Leitzen, Diana Dubrall, Irmgard Toni, Julia Stingl, Patrick Christ, Ursula Köberle, Matthias Schmid, Antje Neubert, and Bernhardt Sachs have no conflicts of interest to declare.

Ethics approval Approval for the protocol of the KiDSafe project was obtained from the Ethics Committee of the Friedrich-Alexander University Erlangen-Nürnberg under reference number 351_17 B, and approval for the analysis of the spontaneous reports from EudraVigilance was obtained from the local Ethics Committee of the Medical Faculty of Bonn (009/17 and 100/21).

Consent to participate Not applicable.

Consent to publication Not applicable.

Data availability Due to data protection requirements and the EudraVigilance access policy, the individual pseudonymized case reports are not accessible to the readership since different levels of access are granted for different stakeholders [16]. The Federal Institute for Drugs and Medical Devices (BfArM), as the competent authority in Germany, is granted the highest access level; however, even with the lowest level of access researchers can perform the same analyses in EudraVigilance with aggregated data (public access: <http://www.adrreports.eu/en/index.html>).

Code availability Not applicable.

Authors' contributions Sarah Leitzen, Diana Dubrall and Bernhardt Sachs contributed to the conception and design of the analysis. Irmgard Toni and Antje Neubert contributed to the design of the analysis of the KiDSafe data and provided input to the interpretation and discussion of the data. Patrick Christ and Diana Dubrall contributed to data evaluation. Ursula Köberle gave advice regarding ADR reporting and supervised the recording and assessing within the DCGMA. The first drafts of this manuscript were written by Sarah Leitzen and Bernhardt Sachs. All authors commented on previous versions of the manuscript, and read and approved the final version.

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References

- Knopf H, Du Y. Perceived adverse drug reactions among non-institutionalized children and adolescents in Germany. *Br J Clin Pharmacol*. 2010;70:409–17.
- Haffner S, von Laue N, Wirth S, Thürmann PA. Detecting adverse drug reactions on paediatric wards: intensified surveillance versus computerised screening of laboratory values. *Drug Saf*. 2005;28(5):453–64.
- Rashed AN, Wong IC, Cranswick N, Hefe B, Tomlin S, Jackman J, et al. Adverse Drug Reactions in Children-International Surveillance and Evaluation (ADVISE): a multicentre cohort study. *Drug Saf*. 2012;35(6):481–94.
- Smyth RL, Peak M, Turner MA, Nunn AJ, Williamson PR, Young B, et al. ADRIC: adverse drug reactions in children: a programme of research using mixed methods. *NIHR J Libr*. 2014. <https://doi.org/10.3310/pgfar02030>.
- Wimmer SN, Neubert A, Rascher W. Arzneimitteltherapiesicherheit bei Kindern. *Dtsch Arztebl Int*. 2015;112:781–7.
- Aurich B, Apele-Freimane D, Banaschewski T, Chouchana L, Day S, Kaguelidou F, et al. c4c: paediatric pharmacovigilance: methodological considerations in research and development of medicines for children: a c4c expert group white paper. *Br J Clin Pharmacol*. 2021. <https://doi.org/10.1111/bcp.15119>.
- European Medicines Agency. Module VI—Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2). https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf.
- Neubert A, Urschitz M, Schwab M, Rascher W. KiDSafe—Verbesserung der Arzneimitteltherapiesicherheit bei Kindern und Jugendlichen. *Kinder und Jugendarzt*. 2019;50(2/19):30–3.
- European Medicines Agency (EMA). EudraVigilance—European database of suspected adverse drug reaction reports. <https://www.adrreports.eu/>.
- Kommas E, Lex D, Huber M, Paeschke N. Verdachtsfälle melden—Warum am behördlichen Nebenwirkungsmelde-System kein Weg vorbeiführt. *Deutsche ApothekerZeitung*. 2019;37.
- Dubrall D, Schmid M, Alesik E, Paeschke N, Stingl J, Sachs B. Frequent adverse drug reactions, and medication groups under suspicion. *Dtsch Arztebl Int*. 2018;115(23):393–400.
- Medical Dictionary for Regulatory Activities. 2022 (08.02.2022). <https://www.meddra.org/>.
- Schulze C, Toni I, Moritz K, Eberl S, Rascher W, Neubert A. Development and adjustment of an algorithm for identifying drug-related hospital admissions in pediatrics. *J Patient Saf*. 2022;18(5):421–9.
- Bergvall T, Norén GN, Lindquist M. vigiGrade: a tool to identify well-documented individual case reports and highlight systematic data quality issues. *Drug Saf*. 2014;37(1):65–77.
- Uppsala Monitoring Center. VigiBase. <https://who-umc.org/vigibase/>.
- World Health Organization. The use of the WHO-UMC system for standardised case causality assessment. 2013 (08.02.2022). https://cdn.who.int/media/docs/default-source/medicines/pharmacovigilance/whocausality-assessment.pdf?sfvrsn=5d8130bb_2&download=true.
- Arzneimittelkommission der deutschen Ärzteschaft (Akdäe). Arzneimitteltherapiesicherheit. https://www.akdae.de/fileadmin/user_upload/akdae/Kommission/Presse/DAe/20141031.pdf.
- Kassenärztliche Bundesvereinigung. Altersgruppen 2022 (08.02.2022). https://www.kbv.de/tools/ebm/html/4.3.5_162395004446927562274884.html.
- European Medicines Agency. Access to EudraVigilance data 2022. <https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance/access-eudravigilance-data>.
- European Medicines Agency (EMA). European Medicines Agency's Data Protection Notice for EudraVigilance Human (EV). https://www.ema.europa.eu/en/documents/other/european-medicines-agencys-data-protection-notice-eudravigilance-human-ev_en.pdf.
- Kaumanns K, Kayser C, Paeschke N, von Mallek D, Stingl J, Köberle U, et al. Medikationsfehler im Fokus der Forschung und Pharmakovigilanz. *Bulletin zur Arzneimittelsicherheit*; 2015. https://www.bfarm.de/SharedDocs/Downloads/DE/Arzneimittel/Pharmakovigilanz/Bulletin/2015/2-2015.pdf?__blob=publicationFile.
- A guideline on summary of products characteristics. September 2009. https://ec.europa.eu/health/system/files/2016-11/smpc_guideline_rev2_en_0.pdf.
- Statista. Anzahl der Krankenhäuser in Deutschland in den Jahren 2000 bis 2019; 2022 (08.02.2022). <https://de.statista.com/statistik/daten/studie/2617/umfrage/anzahl-der-krankenhaeuser-in-deutschland-seit-2000/>.
- Dittrich ATM, Draaisma JMT, van Puijenbroek EP, et al. Analysis of reporting adverse drug reactions in paediatric patients in a university hospital in the Netherlands. *Pediatr Drugs*. 2020;22:425–32.

25. Gupta R, Malhotra A, Malhotra P. A study on determinants of underreporting of adverse drug reactions among resident doctors. *Int J Res Med Sci.* 2018;6(2).
26. Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ). Nebenwirkungen melden—Ein Leitfaden für Ärzte. 2019 (15.02.2022). https://www.akdae.de/Arzneimitteltherapie/LF/PDF/Nebenwirkungen_melden.pdf.
27. Dubrall D, Just KS, Schmid M, et al. Adverse drug reactions in older adults: a retrospective comparative analysis of spontaneous reports to the German Federal Institute for Drugs and Medical Devices. *BMC Pharmacol Toxicol.* 2020;21:25.
28. Dubrall D, Leitzen S, Toni I, et al. Descriptive analysis of adverse drug reaction reports in children and adolescents from Germany: frequently reported reactions and suspected drugs. *BMC Pharmacol Toxicol.* 2021;22:56.
29. Stammschulte T, Ludwig WD, Mühlbauer B, et al. Metamizole (dipyrone)-associated agranulocytosis. An analysis of German spontaneous reports 1990–2012. *Eur J Clin Pharmacol.* 2015;71:1129–38.
30. Schneeweiss S, Göttler M, Hasford J, Swoboda W, Hippus M, Hoffmann A, et al. First results from an intensified monitoring system to estimate drug related hospital admissions. *Br J Clin Pharmacol.* 2001;52(2):196–200.
31. Knopf H, Sarganas G, Grams D, et al. Application of medicines and nutritional supplements in childhood and adolescence in Germany. *Bundesgesundheitsblatt.* 2020;63:1287–96.
32. Oehme AK, Rashed AN, Hefe B, et al. Adverse drug reactions in hospitalised children in Germany are decreasing: results of a nine year cohort-based comparison. *PLoS One.* 2012;7(9): e44349.
33. Smyth RMD, Gargon E, Kirkham J, et al. Adverse drug reactions in children—a systematic review. *PLoS One.* 2012;7(3): e24061.
34. Zed PJ, Haughn C, Black KJL, et al. Medication-related emergency department visits and hospital admissions in pediatric patients: a qualitative systematic review. *J Pediatr.* 2013;163(2):477–83.
35. Vazquez-Alvarez AO, Brennan-Bourdon LM, Rincon-Sanchez AR, et al. Improved drug safety through intensive pharmacovigilance in hospitalized pediatric patients. *BMC Pharmacol Toxicol.* 2017;18:79.
36. Holstiege J, Bätzing J, Akmatov MK, et al. Rückgang der ambulanten Antibiotikaverordnungen bei Kindern und Jugendlichen in Deutschland 2010–2019. Regionale Entwicklung in den deutschen KV-Regionen. *Monatsschr Kinderheilkd.* 2022;170:392–402.
37. Baharvand P, Hormozi M. Can parents' educational level and occupation affect perceived parental support and metabolic control in adolescents with type 1 diabetes? *J Educ Health Promot.* 2019;8:11.
38. Zysberg L, Lang T. Supporting parents of children with type 1 diabetes mellitus: a literature review. *Patient Intell.* 2015;7:21–31.
39. Sutherland A, Phipps DL, Tomlin S, et al. Mapping the prevalence and nature of drug related problems among hospitalised children in the United Kingdom: a systematic review. *BMC Pediatr.* 2019;19:486.
40. Gallagher RM, Mason JR, Bird KA, et al. Adverse drug reactions causing admission to a paediatric hospital. *PLoS One.* 2012;7(12): e50127.
41. Raschi E, Moretti U, Salvo F, Pariente A, Antonazzo IC, De Ponti F, et al. Evolving roles of spontaneous reporting systems to assess and monitor drug safety. In: Kothari CS, Shah M, Patel RM, editors., et al., Pharmacovigilance. London: IntechOpen; 2018. <https://doi.org/10.5772/intechopen.79986>.

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3.2.1 Supplemental information: Adverse Drug Reactions in Children: Comparison of Reports Collected in a Pharmacovigilance Project Versus Spontaneously Collected ADR Reports

Electronic supplementary material [ESM])

Title: Adverse drug reactions in children: comparison of reports collected in a pharmacovigilance project versus spontaneously collected ADR reports

Journal: Pediatric drugs

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The analyzed ADRs cover also medication error related ADRs [7, 17]. Due to the extension of the ADR definition in 2012, conditions like overdose, misuse, abuse, medication errors and occupational exposure are now included in the ADR definition. Although, theoretically all such reports retrieved in our analyses should be associated with a suspected ADR, we cannot exclude the presence of reports not being associated with a co-suspected ADR among them (see section 2.5).

Table 1. Evaluation of documentation quality.

	KiDSafe reports (systematically collected reports) n = 845	EudraVigilance reports (spontaneous reports) n = 697
Mean	0.64	0.63
SD	0.25	0.25
IQR	0.45	0.48
Q0	0.22	0.17
Q25	0.45	0.42
Q50	0.61	0.61
Q75	0.90	0.9
Q100	1	1
Range	0.22-1	0.17-1

SD = standard deviation. IQR= interquartile range. Q0= lowest value. Q25=lowest quartile.

Q50=medium quartile. Q75= upper quartile. Q100= highest value. Range = from lowest to highest value

Table 2. Primary reporting source.

	KiDSafe reports (systematically collected reports) n = 845	EudraVigilance reports (spontaneous reports) n = 697
HCP	845 (100.0 %)	609 (87.4 %)
non-HCP	0 (0.0 %)	88 (12.6 %)

HCP = Healthcare Professionals; non-HCP = non- Healthcare Professionals

Table 3. Seriousness criteria. Multiple assignments were possible.

Seriousness Criterion	KiDSafe reports (systematically collected reports) n = 845	EudraVigilance reports (spontaneous reports) n = 692^a
Death	1 0.1 %	16 2.3 %
Life-threatening	70 8.3 %	95 13.7 %
Hospitalisation	845 100.0 %	692 100.0 %
Disabling	1 0.1 %	9 1.3 %
Congenital Anomaly	0 0.0 %	11 1.6 %
Other	149 17.6 %	211 30.5 %

^aThis in depth analysis was performed on a later date than the analyses depicted in the main manuscript. The main manuscript refers to 697 reports. However, 5 cases were subsequently deleted from EudraVigilance by the EMA and thus the analyses depicted above refers to n=692 reports.

Table 4. Age and sex distribution.

	KiDSafe reports (systematically collected reports) n = 843^a				EudraVigilance reports (spontaneous reports) n = 696^a			
Age group	SUM	Female (n= 479, 56.8%)	Male (n= 361, 42.8%)	Not specified (n= 4, 0.5%)	SUM	Female (n= 358, 51.4%)	Male (n= 325, 46.7%)	Not specified (n= 13, 1.9%)
0-1M	6 100.0%	3 50.0%	3 50.0%	0 0.0%	48 100%	12 25.0%	32 66.7%	4 8.3%
2M-1Y	100 100.0%	42 42.0%	58 58.0%	0 0.0%	81 99.9%	41 50.6%	36 44.4%	4 4.9%
2-3Y	95 100%	37 38.9%	57 60.0%	1 1.1%	57 100%	24 42.1%	33 57.9%	0 0.0%
4-6Y	83 100%	36 43.4%	47 56.6%	0 0.0%	56 100%	26 46.4%	29 51.8%	1 1.8%
7-12Y	157 99.9%	77 49.0%	79 50.3%	1 0.6%	175 100.1%	82 46.9%	92 52.6%	1 0.6%
13-17Y	402 100%	283 70.4%	117 29.1%	2 0.5%	279 100%	173 62.0%	103 36.9%	3 1.1%

^a Two reports from the KiDSafe group and one report from the EudraVigilance group were without age information.

Table 5. Top 10 drugs most frequently reported as suspected.

Top 10 suspected drugs KiDSafe reports (systematically collected reports) n = 845			Top 10 suspected drugs EudraVigilance reports (spontaneous reports) n = 697		
IBUPROFEN	7.5%	63	INSULIN ASPART	6.0%	42
LEVETIRACETAM	6.6%	56	MITE ALLERGEN EXTRACT	4.4%	31
INSULIN ASPART	5.7%	48	ALLERGENS	3.6%	25
VALPROIC ACID	5.6%	47	PALIVIZUMAB	3.6%	25
METHYLPHENIDATE	4.1%	35	METHYLPHENIDATE	3.0%	21
OXCARBAZEPINE	3.6%	30	IBUPROFEN	2.6%	18
LAMOTRIGINE	3.4%	29	VALPROIC ACID	2.4%	17
PARACETAMOL	3.3%	28	ADALIMUMAB	2.2%	15
AMOXICILLIN	2.7%	23	CORYLUS AVELLANA	2.2%	15
INSULIN GLARGINE	2.7%	23	PLANTAGO LANCEOLATA	2.2%	15

Table 6. Drugs most frequently reported as suspected per age group within the KiDSafe reports (systematically collected reports; n = 845).

0-1M			2M-1Y			2-3Y			4-6Y			7-12Y			13-17Y		
Active Substance (High Level)	in %	(n = 6)	Active Substance (High Level)	in %	(n = 100)	Active Substance (High Level)	in %	(n = 95)	Active Substance (High Level)	in %	(n = 83)	Active Substance (High Level)	in %	(n = 157)	Active Substance (High Level)	in %	(n = 402)
CAFFEINE. ERYTHROMYCIN. OPIPRAMOL. PERMETHRIN. THEOPHYLLIN. ZIDOVUDINE	16.7	1	LEVETIRACETAM	13	13	VALPROIC ACID	8.4	8	OXCARBAZEPINE	13.3	11	INSULIN ASPART	8.9	14	IBUPROFEN	11.4	46
			AMOXICILLIN	8	8	LEVETIRACETAM	6.3	6	LEVETIRACETAM/ VALPROIC ACID	10.8	9	VALPROIC ACID	8.3	13	INSULIN ASPART	8.2	33
			VALPROIC ACID/ CEFACLOR	6	6	CICLOSPORIN	5.3	5	SALBUTAMOL/ SULTIAME	4.8	4	OXCARBAZEPINE	7.6	12	PARACETAMOL	6.5	26
			CO-TRIMOXAZOLE	4	4	DIMENHYDRINATE/ IBUPROFEN	4.2	4	AMOXICILLIN/CLOB AZAM	3.6	3	METHYLPHENIDATE	7.0	11	METHYLPHENIDATE	5.7	23
			CEFIXIME.IBUPROFEN. LAMOTRIGINE. PHENO- BARBITAL. PREDNISOLONE. SALBUTAMOL. SULTAMI- CILLIN. TACROLIMUS. TOPIRAMATE	3	3	CEFACLOR. DIMETINDEN. LORAZEPAM. AMOXI-CILLIN	3.2	3	CEFACLOR. CEFUROXIME.DIAZEP AM.FLUTICA SONE.IBUPR OFEN.INSULI N			LEVETIRACETA M	6.4	10	FLUOXETINE	4.7	19
			CEFPODOXIME. CEFU- ROXIME CIPROFLOXACIN. CLOBAZAM. DIMEN- HYDRINATE. FLUTICA- SONE. LITHIUM. METHO- TREXATE. TRAMADOL. VIGABATRIN. XYLOMETAZOLINE	2	2	FERROUS GLYCINE. CEFUROXIME. ERYTHROMYC IN.ETHOSUXI MIDE.HALOPE RAIDOL.LAMO TRIGINE.MYC OPHENOLATE. PREDNISOLON E.TACROLIMU S.VIGABATRIN	2.1	2	HUMAN.LEV OTHYROXIN E.MIDAZOLA M.MYCOPHE NOLATE.PAR ACETAMOL. SULFAMETH OXAZOLE.VI GABATRIN.V ITAMIN D	2.4	2	IBUPROFEN	5.1	8	LAMOTRIGINE	4.2	17

Table 7. Drugs most frequently reported as suspected per age group within the EudraVigilance reports (spontaneous reports; n = 697).

0-1M			2M-1Y			2-3Y			4-6Y			7-12Y			13-17Y					
Active Substance (High Level)	in %	n = 48	Active Substance (High Level)	in %	n = 81	Active Substance (High Level)	in %	n = 57	Active Substance (High Level)	in %	n = 56	Active Substance (High Level)	in %	n = 175	Active Substance (High Level)	in %	n = 279			
MISOPROSTOL	12.5	6	PALIVIZUMAB	29.6	24	NUSINERSEN	12.3	7	VALPROIC ACID	8.9	5	MITE ALLERGEN EXTRACT	13.7	24	INSULIN ASPART	7.5	21			
PAROXETINE	4.2	2	DIMENHYDRINATE	4.9	4	AMOXICILLIN	5.3	3	INSULIN ASPART	7.1	4	ALLERGENS	10.3	18	METHYLPHENIDATE	5.4	15			
PIVMECILLINAM	4.2	2	CYTARABINE	3.7	3	ASFOTASE ALFA. CANDESARTAN. CEFACLO. CEFUROXIME. ECULIZUMAB. IBUPROFEN. INFLIXIMAB. VALPROIC ACID	3.5	2	IBUPROFEN	5.4	3	INSULIN ASPART	8.0	14	METAMIZOLE	3.9	11			
55 further drugs and combinations ^a	2.1	1	PREDNISONE	3.7	3				MIDAZOLAM	5.4	3	CORYLUS AVELLANA	5.7	10	ADALIMUMAB	3.6	10			
			VINCRIStINE	3.7	3				OXCARBAZEPI NE	5.4	3	PLANTAGO LANCEOLATA	5.7	10	DIENOGEST. ETHINYLESTRADIOL	3.2	9			
			ADALIMUMAB. ALEMTUZUMAB. ALPROSTADIL. AMOXICILLIN. BLINATUMOMAB. CEFACLO. CEFIXIME. CEFUROXIME. CYCLOPHOSPHAMIDE. FLUDARABINE. INSULIN ASPART. PEGINTERFERON BETA-1A. PHENPROCOUMON. SULTAMICILLIN	2.5	2				SALBUTAMOL	5.4	3	SECALE CEREALE	5.7	10	IBUPROFEN	2.9	8			
									AZACITIDINE. EVEROLIMUS. FLUTICASONE. HUMAN NORMAL IMMUNOGLOBULI. LAMOTRIGIN. SULTIAME	3.6	2	ALNUS. ALUMINIUM HYDROXIDE. ARTEMISIA VULGARIS. BETULA. CORYLUS AVELLANA. PHLEUM PRATENSE. PLANTAGO LANCEOLATA. TRITICUM AESTIVUM and Combinations	5.1	9	MYCOPHENOLIC ACID	2.9	8			
															QUETIAPINE	2.9	8			
															ISOTRETINOIN. METOCLOPRAMIDE	2.5	7			

^aALEMTUZUMAB, AMISULPRIDE, AMITRIPTYLINE, AMPICILLIN, SULBACTAM, ARIPIRAZOLE, CAFFEINE, CANDESARTAN, CERTOLIZUMAB,

CLOZAPINE, COLECALCIFEROL, CYTARABINE, DAUNORUBICIN, DOXEPIN, DRONABINOL, ESKETAMINE, ETOPOSIDE, GLATIRAMER, INFLIXIMAB,

INSULIN ASPART, INSULIN HUMAN, INTERFERON BETA-1A, KETAMINE, KLEBSIELLA PNEUMONIAE (INACTIVATED), LAMOTRIGINE, LANOLIN, LIDOCAINE, PRILOCAINE, LISINOPRIL, METFORMIN HYDROCHLORIDE (& Combinations), METHYLDOPA, METYRAPONE, NATALIZUMAB, NIFEDIPINE, NITRIC OXIDE, NITROUS OXIDE & OXYGEN, OCTENIDINE DIHYDROCHLORIDE, OPIPRAMOL, OXYCODONE, OXYMETAZOLINE, PALIVIZUMAB, PARACETAMOL, PENTOOXYVERINE, PHENOBARBITAL, PHENYLEPHRINE, POTASSIUM (& Combinations), PREGABALIN, PRILOCAINE, PROPOFOL, RIVAROXABAN, SERTRALINE, SILDENAFIL, TRAMADOL, TROPICAMIDE

Table 8. Reported medical history.

Patient Medical History PT KiDSafe reports (systematically collected reports) n = 729 with medical history			Patient Medical History PT EudraVigilance reports (spontaneous reports) n = 519 with medical history		
Epilepsy ^a	18.4 %	n = 134	Type 1 diabetes mellitus	7.1 %	n = 37
Type 1 diabetes mellitus	10.3 %	n = 75	Epilepsy ^a	6.9 %	n = 36
Depression	7.8 %	n = 57	Asthma	6.2 %	n = 32
Attention deficit hyperactivity disorder	6.3 %	n = 46	Premature baby	6.2 %	n = 32
Pyrexia	5.8 %	n = 42	Non-tobacco user	5.4 %	n = 28
Partial seizures	4.9 %	n = 36	Depression	4.4 %	n = 23
Developmental delay	4.9 %	n = 36	Attention deficit hyperactivity disorder	4.2 %	n = 22
Upper respiratory tract infection	3.4 %	n = 25	Abstains from alcohol	4.0 %	n = 21
Asthma	3.3 %	n = 24	Seasonal allergy	4.0 %	n = 21
Obesity	3.2 %	n = 23	Hypersensitivity	3.5 %	n = 18

^a In addition, the number of reports related to epilepsy was analyzed on HLT-level in both datasets in order to prevent inconsistent epilepsy coding in the spontaneous reports which could have resulted in a lower number of these reports. At the HLT-level, the terms *absence seizures*, *generalized tonic-clonic seizures*, *partial complex seizures*, *partial simple seizures NEC*, and *seizures and seizure disorders NEC* were included. For the systematically collected reports, the share was 25.4% (185/729), and for the spontaneous reports 6.9% (59/519).

3.3 Comparative Analysis of Information Provided in German Adverse Drug Reaction Reports Sent by Physicians, Pharmacists and Consumers

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Comparative Analysis of Information Provided in German Adverse Drug Reaction Reports Sent by Physicians, Pharmacists and Consumers

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Abstract

Introduction Adverse drug reactions (ADRs) can be reported by Health Care Professionals (HCPs; e.g., physicians, pharmacists) and non-Health Care Professionals (non-HCPs; e.g., consumers). Previous studies investigating differences between reports from HCPs and non-HCPs rarely considered the completeness of information provided. In addition, they mostly did not distinguish between physicians and pharmacists or were performed years ago. The aim of our study was to analyse and compare the completeness of information provided in reports from physicians, pharmacists and consumers from Germany in a more recent dataset.

Materials and methods We analysed all spontaneous reports from Germany received between 2018 and 2021 in the ADR database EudraVigilance exclusively reported by physicians ($n = 69,976$), pharmacists ($n = 42,396$) or consumers ($n = 121,144$). Demographical parameters of the patients were analysed descriptively. Completeness of reports was evaluated applying an established score (vigiGrade). Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using logistic regression analysis in order to identify report, patient, drug or ADR-specific information provided more often in reports from physicians, pharmacists or consumers.

Results Within the study period the number of reports per year by physicians and pharmacists decreased steadily, while an opposite trend was observed for consumer reports. The proportion of female patients was higher in reports from pharmacists (64.4%) and consumers (64.8%) compared to those from physicians (55.3%). On average, patients in reports from pharmacists (58.7) were older compared to those from physicians (53.5) and consumers (52.6). As an example for the presence of specific information, the time to onset of the ADR could be calculated more often in consumer compared to physician (OR 1.9 [1.8–1.9]) and pharmacist reports (OR 1.7 [1.6–1.7]). In contrast, pharmacist (OR 0.5 [0.4–0.5]) and consumer (OR 0.5 [0.5–0.5]) reports included the indication of the suspected drug less often than physician reports. Physician reports on average (mean = 0.5) were slightly more complete according to the vigiGrade score compared to reports from consumers (mean = 0.4) and pharmacists (mean = 0.4).

Conclusion The ADR reports from consumers were comparable with regard to the completeness score with those from physicians and pharmacists underlining their value. Differences in completeness of specific information between the reporter types were found, suggesting that a common reporting of interactions between the three reporters may further improve the completeness of ADR reports. Furthermore, stratified analysis of ADR reports per reporter type may be helpful for certain objectives in scientific research.

Key Points

Throughout the period analysed, the annual number of reports from physicians and pharmacists steadily decreased, while the respective number of consumer reports increased.

Physicians' reports followed by consumers and pharmacists' reports were more complete with regard to relevant information according to an established score (vigi-Grade). In our analysis, physicians reported information regarding the indication of a drug more often, while the time period between the start of the drug therapy and the ADR occurrence (time to onset) could more often be calculated in reports from consumers.

Based on our analysis and existing literature, we suggest how the quality and number of spontaneous reports could be improved, by time-saving and streamlined assistance in the preparation of spontaneous reports by use of appropriate software.

1 Introduction

Spontaneous reports are one valuable tool used in pharmacovigilance practice for the detection of adverse drug reactions (ADRs) after marketing authorisation [1]. Initially, in Germany ADRs were mainly reported by physicians. Non-Health Care Professionals (non-HCPs, in the following "consumers") could also report ADRs, however, few consumer reports were received in the first years of recording. The first reports from pharmacists were recorded in 1986 [2].

In recent decades, various actions including legislative changes have been taken in the European Union (EU) to facilitate and draw attention to ADR reporting [3–7]. Among these were the possibility to report ADRs online and an appeal to report ADRs to the competent authorities in the package leaflet. Further on, since legislative changes in 2012 pharmaceutical companies are obliged to forward non-serious ADR reports (e.g., from consumers) to the competent authorities. These actions very likely contributed substantially to the enormous increase in the number of reports, especially from consumers [2, 8].

Meanwhile some studies and reviews have been published analysing the content and overall qualitative differences of spontaneous reports with regard to the reporting person's qualifications, most of which were carried out in Denmark, the UK and the Netherlands [9]. The vast majority of them focused on the reported drug(s) and/or ADR(s) and

identified differences and found that consumers and health-care professionals (HCPs)/physicians mentioned different ADRs. Notably, consumer reports complement HCP reports by covering different ADRs and drugs [9–12].

Very few of these studies focused on the quality of documentation and the type of information reported in relation to the reporters' qualification. This limited number of studies included, among others, datasets from France, the USA and the Netherlands [12–14]. Most of these studies used relatively small data sets and suggested additional investigations [9, 15].

The main aim of this study was to investigate and compare the amount and the type of information relevant for pharmacovigilance practice provided in reports from physicians, pharmacists and consumers in spontaneous reports from Germany contained in the European ADR database EudraVigilance. To the best of our knowledge, this represents the first study for Germany in this regard and, so far, only few studies investigated a dataset of this magnitude, comprising almost a quarter of a million reports. Finally, our analysis may provide scientific data which could be helpful for a discussion how the quality and therewith the value of spontaneous reports from various reporters could be improved.

2 Methods

2.1 EudraVigilance

ADRs are defined as noxious and unintended responses to medicinal products which can occur within or outside (e.g., off-label use) the terms of the marketing authorization [16]. Suspected cases of ADRs can be reported by healthcare professionals (HCPs) (e.g., pharmacists, physicians, nursing staff) as well as by non-healthcare professionals (non-HCPs) (e.g., consumers, lawyers) [17, 18]. Physicians and pharmacists, for example, are obliged to report suspected cases of ADRs according to their professional code of conduct [2, 18].

The ADR database EudraVigilance (EV), which is operated by the European Medicines Agency (EMA), contains ADR reports from all member states of the European Economic Area [17]. In EV drugs are coded with the EudraVigilance medicinal product dictionary and ADRs are coded in accordance with the MedDRA® (Medical Dictionary for Regulatory Activities) terminology [17, 19].

MedDRA® is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The MedDRA® trademark is owned by the International

Federation of Pharmaceutical Manufacturers and Associations (IFPMA) on behalf of the ICH.

Our analysis refers to spontaneous reports, these are unsolicited reports spontaneously reported in everyday practice, which are not collected in any organized data collection scheme such as clinical trials. Spontaneously submitted ADR reports have to include certain information to fulfil the minimum criteria (e.g., identifiable reporter and patient, at least one suspected drug and suspected ADR) [4]. Spontaneous ADR reports may contain structured and unstructured (free-text) information [20].

The primary source qualification (in the following “reporter type”) describes if the person who reported the ADR was an HCP or a non-HCP together with a more detailed specification (e.g., physician, consumer). Theoretically, one ADR report can contain several reporter types, for example, if information to the same case was reported by a physician and a consumer [4]. In order to analyse if there are differences between different reporter types, we restricted our analysis to those reports listing only one reporter type within the detailed specification. Note that despite that restriction, one ADR report may have been reported by more than one person of the same reporter type. We assume that the reporter type “pharmacists” also covers reports from other pharmacy staff such as pharmaceutical technical assistants (PTA). Further information regarding the reporting channels has been published elsewhere [2].

The designation of reports as “serious” or “non-serious” corresponds to the legal definition of the seriousness of the ADR reports, but not to its clinical severity. Therefore, all reports, including at least one ADR that was life-threatening, conferred lasting or significant disability or incapacity, led to death, required or prolonged hospitalization, led to congenital abnormalities, respectively birth defects, or endangered the patient and required medical or surgical intervention/treatment (“other”) are considered as serious [4].

2.2 Identification of Reports from Physicians, Pharmacists or Consumers

All spontaneous ADR reports from Germany received between 1 January 2018 and 31 December 2021 were extracted ($n = 548,347$) (see Fig. 1) from EV. In order to exclude the influence of reports referring to vaccines, all reports listing any vaccine as suspected/interacting drug were excluded ($n = 276,353$). As one example, COVID19 vaccines could have been subject to an overstimulated reporting, because they were subject to intense public debates [21]. Besides that, we excluded all reports containing hyposensitising solutions as suspected/interacting drugs ($n = 4579$) as well as duplicates, identified via equal case report identifiers ($n = 154$).

Only reports whose reporter type was exclusively specified as “physician” or “pharmacist” or “consumer” were further investigated ($n = 233,516$). Within these, 69,976 reports (30.0%) referred to physicians’, 42,396 (18.2%) to pharmacists’, and 121,144 (51.9%) to consumers.

2.3 Descriptive Analysis

All reports identified for physicians, pharmacists or consumers were analysed descriptively regarding their superordinate classification of seriousness (serious yes/no), year of receipt, and distribution of sex and age of the patients. Means, together with standard deviations ($\pm$ sd), and medians including their interquartile ranges (IQRs) were calculated for patients’ age and the quality of documentation (see below). For all other results, frequencies and percentages were calculated.

2.4 Quality of Documentation

An overall estimation of the quality of documentation was performed by applying a computer-based algorithm according to a published score (vigiGrade) [22]. This score, ranging from 0.07 to 1, was originally created to assess the provided information in the structured format of ADR reports in the global ADR database of the World Health Organization (WHO)—VigiBase [23]. According to the original publication, a report with a vigiScore > 0.8 is defined as “well documented”. For the assessment of the ADR reports in EV, the score was slightly adapted.

2.5 Consideration of Relevant Information

All sub-datasets were screened for the presence of certain information in the structured format of each ADR report. Please note that the quality of the information provided was not assessed.

The information provided was assigned to four categories: (1) report-related information, (2) patient-related information, (3) drug-related information, and (4) ADR-related information.

Sub-analyses of serious and non-serious ADR reports were performed.

2.6 Report-Related Information

The country of origin, report type, seriousness, and the narrative were categorized as report-related information. The country of origin (Germany), the report type (spontaneous report), and if the report was classified as serious (yes or no) was provided in each ADR report. In the narrative, the reporter has the option of supplying further information regarding the ADR in an unstructured free text format. In

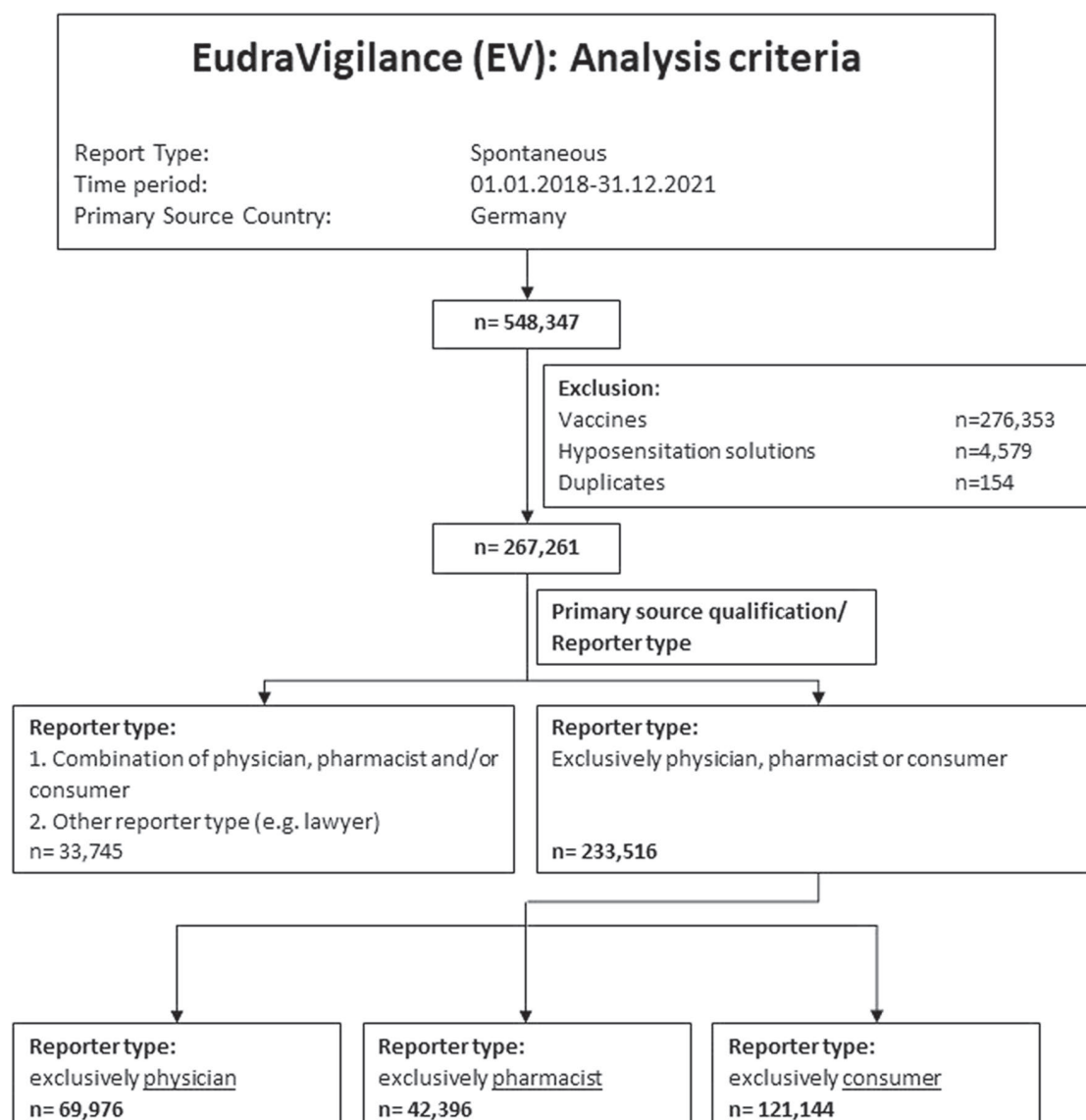


Fig. 1 Flowchart. Identification of adverse drug reaction (ADR) reports exclusively reported by physicians, pharmacists or consumers as reporter type in EudraVigilance (EV)

this case, we analysed if the respective reporter provided any further information as free text.

2.7 Patient-Related Information

Sex, age, height, weight and medical histories of the patients were categorized as patient-related information. Sex can be coded as female, male and not specified. Age, height and weight are numerical values or reported as not available. The medical history contains co-morbidities and previous conditions of the patients or is stated as not available. In this case, “not available” does not necessarily mean that the patient has no co-morbidities or previous conditions, it can

also indicate that the information was not reported. In our analyses, not specified in case of sex or not available in case of age, height, weight and medical history were considered as information not provided.

2.8 Drug-Related Information

Drugs reported as suspected/interacting, action taken with the drug, applied dose of the drug, indication of the drug, reporting of suspected/interacting drugs classified as black triangle drugs and concomitant drugs were categorized as drug-related information. In accordance with the minimum criteria of ADR reports, at least one drug has to be reported

as suspected/interacting. Among others, action taken with the drug can be reported as withdrawn, continued, dose reduced, or information not available. The applied dose of the drug can be supplied as a numerical value with its unit name (e.g., milligram), as the number of applied dosage forms (e.g., one dose administered) or set to “not available”. The indication describes the underlying disease or condition for which the drug was taken by the patient or is reported as “not available”. The drugs classified as concomitant were not considered to be causative for the described ADR(s) by the reporter. In this category, all drugs taken concomitantly can be reported or set to “not available”. In this case, our data did not allow distinguishing whether the patient did not receive any concomitant medication or if the medication was not mentioned in the report.

If more than one drug was reported as suspected/interacting per ADR report, information regarding action taken with the drug, applied dose, and indication of the drug can be reported for each drug. Here, information was classified as available if action taken with drug, applied dose, or indication was reported for at least one drug.

Further on, we determined the number of drugs reported as suspected/interacting and reported as concomitant per ADR report.

In order to identify reports with at least one black triangle drug reported as suspected/interacting, the “list of medicinal products under additional monitoring” was used [24]. All active ingredients with a date of inclusion in 2022 were removed. Drugs labelled with a black triangle in the package leaflet or product information leaflet are subject to additional surveillance (e.g., new active ingredients, biologicals or drugs with conditional approvals).

2.9 Adverse Drug Reaction (ADR)-Related Information

The reported ADR(s), the outcome of the ADR(s), the time to onset of the ADR(s), as well as if the ADR is known or designated as a medically important event are categorized as ADR-related information. In accordance with the minimum criteria of ADR reports, at least one ADR has to be reported. The outcome describes, among others, if the ADR is *recovered/resolved*, *fatal* or *not recovered/not resolved* or *unknown*. The time to onset describes the time between the first intake of a drug and the occurrence of the ADR. It can be calculated based on the start date of the drug reported as suspected/interacting and the start date of the ADR. If multiple ADRs per report were mentioned, an outcome and a time to onset could be reported or calculated for each ADR. Information was counted as available if at least one outcome apart from unknown was reported, respectively, one time to onset could be calculated for one ADR. If the calculated time to onset was negative, the time to onset was classified as not

available (caused by, e.g., coding errors or if the suspected/interacting drug was taken after the ADR occurred).

The number of reported ADRs per ADR report was analysed.

All reports were analysed to determine if at least one ADR contained in the “designated medical event list” was reported. The list of designated medical events describes drug-related serious events defined by the EMA and is publicly available on the EMA’s website [25].

We determined whether at least one of the reported drug-ADR combinations per ADR report was already listed as known in SIDER. SIDER lists more than 140,000 known drug-ADR combinations based, for example, on information from package inserts. Further information on the content, data collection, and structure of SIDER can be found elsewhere [26, 27].

2.9.1 Logistic Regression Analyses

Logistic regression analyses were performed for the comparisons of physician versus consumer reports, physician versus pharmacist reports, pharmacist versus consumer reports, and serious versus non-serious reports of all reporter types. To this end, the reporter type, respectively, the classification serious/non-serious, was set as the outcome variable and all other variables, which were analysed in the consideration of relevant information as covariates. Country of origin, report type, and seriousness were not included as variables in the logistic regression models since all reports contained information on these three aspects. The results of the logistic regression analyses are presented as odds ratios (ORs) with 95% confidence intervals (CI) in square brackets [lower CI–upper CI].

All results of the logistic regression analyses are presented by mentioning the reference group last (e.g., in case of “physicians versus pharmacists”, pharmacists are considered as reference). Concerning the analyses of non-serious and serious reports within each reporter type, serious reports were always considered as the reference.

2.9.2 Reports per Physician, Pharmacist and Consumer

The number of reports from physicians and pharmacists was considered in relation to the number of practising physicians respectively pharmacists per year in Germany. For this purpose, the numbers of practising physicians in outpatient and hospital settings for each year were extracted from the “Ärzttestistik zum 31. Dezember 2021” provided by the *Bundesärztekammer* [28]. The numbers of practising pharmacists represents the number of pharmacists, pharmacists in internship (PhiP), pharmaceutical technical assistants (PTAs), pharmacy technicians and pharmacist assistants in

public pharmacies, and pharmacists working in hospital pharmacies, which were extracted for each year from “Die Apotheke - Zahlen Daten Fakten 2021/2022” published by the *Bundesvereinigung deutscher Apotheker-verbände* [29, 30]. In order to consider the number of reports from consumers in relation to the number of potentially drug-exposed inhabitants in Germany, we extracted the number of German inhabitants from statista “Bevölkerung—Einwohnerzahl von Deutschland 1990–2021” and subtracted the number of practising pharmacists and practicing physicians, as reports from these professionals were to be included in the respective categories [31]. The resulting number was multiplied with the proportion of Germans expected to take any medication according to a German survey [32].

Note that this is only an approximation since one pharmacist or physician or consumer can have submitted more than one ADR report and one ADR report can be reported by more than one pharmacist or physician.

3 Results

3.1 Descriptive Analysis

3.1.1 Report-Related Information

In total 233,516 reports were identified exclusively listing a physician, pharmacist or consumer as reporter type. The largest proportion of reports extracted referred to consumers (51.9%/n = 121,144), followed by physicians (30.0%/n = 69,976) and pharmacists (18.2%/n = 42,396) (Table 1).

Regarding the whole dataset, the lowest number of reports was received in 2021, whereas the number of reports between 2018 and 2020 was fairly similar. While the number of reports from physicians and pharmacists steadily decreased from 2018 to 2021 (physicians n = 20,633 to 12,759; pharmacists n = 14,036 to n = 7129), the number of reports from consumers increased steadily from 2018 to 2020 (n = 26,208 to n = 36,325) and decreased in 2021 (n = 27,753) compared to 2020.

Table 1 Descriptive analyses of adverse drug reaction (ADR) reports per reporter type of the total dataset and the sub-datasets (physician, pharma-

cist, consumer) with regard to the classification serious/non-serious, the receive year, and the demographical parameters (sex, age) of the patients

	Total (% total)	Physicians' reports (% of total/% of physicians' reports)	Pharmacists' reports (% of total/% of pharmacists' reports)	Consumer reports (% of total/% of consumers' reports)
<i>Number of reports</i>				
Number of reports per primary source qualification	233,516 (100%)	69,976 (30.0%/100%)	42,396 (18.2%/100%)	121,144 (51.9%/100%)
<i>Number of reports classified as serious^a</i>				
Yes	55,758 (23.9%)	32,039 (57.5%/45.8%)	7558 (13.6%/17.8%)	16,161 (29.0%/13.3%)
No	177,758 (76.1%)	37,937 (21.3%/54.2%)	34,838 (19.6%/82.2%)	104,983 (59.1%/86.7%)
<i>Number of reports received per year</i>				
2018	60,877 (26.1%)	20,633 (33.9%/29.5%)	14,036 (23.1%/33.1%)	26,208 (43.1%/21.6%)
2019	63,619 (27.2%)	20,289 (31.9%/29.0%)	12,472 (19.6%/29.4%)	30,858 (48.5%/25.5%)
2020	61,379 (26.3%)	16,295 (26.5%/23.3%)	8759 (14.3%/20.7%)	36,325 (59.2%/30.0%)
2021	47,641 (20.4%)	12,759 (26.8%/18.2%)	7129 (15.0%/16.8%)	27,753 (58.3%/22.9%)
<i>Number of reports per sex</i>				
Female	144,535 (61.9%)	38,706 (26.8%/55.3%)	27,320 (18.9%/64.4%)	78,509 (54.3%/64.8%)
Male	81,145 (34.7%)	28,049 (34.6%/40.1%)	13,687 (16.9%/32.3%)	39,409 (48.6%/32.5%)
Not specified	7836 (3.4%)	3221 (41.1%/4.6%)	1389 (17.7%/3.3%)	3226 (41.2%/2.7%)
	Total	Physician	Pharmacist	Consumer
<i>Age distribution</i>				
Mean (Sd) age	54.1 (± 21.4)	53.5 (± 21.8)	58.7 (± 20.5)	52.6 (± 21.2)
Median [IQR] age	57 [38–71]	56 [38–71]	62 [47–75]	54 [36–70]
Not specified	97,564	23,490	17,173	56,901

Sd standard deviation, IQR interquartile range

^aEach ADR report is classified as either serious or non-serious

Reports from physicians were more often classified as serious (45.8%/n = 32,039), i.e., comprising ADRs leading to hospitalization or prolongation thereof (19.6%/n = 13,706) or death (2.8%/n = 1967), compared to reports from pharmacists (serious: 17.8%/n = 7558; hospitalisation: 10.7%/n = 4523; death: 0.4%/n = 189) and consumers (serious: 13.3%/n = 16,161; hospitalisation: 2.9%/n = 3457; death: 0.3%/n = 419) (Table Appendix 1/Table Appendix 4; appendices are provided as Online Supplementary Material).

3.1.2 Patient-Related Information

Almost two-thirds of all consumer (64.8%) and pharmacists' (64.4%) reports referred to females, compared to slightly more than half of the physicians' reports (55.3%) (Table 1).

A substantial proportion of reports did not contain any information regarding the patients' age (total: 41.8%/n = 97,564; physician: 33.6%/n = 23,490; pharmacist: 40.5%/n = 17,173; consumer: 47.0%/n = 56,901). The mean and median age of the patients from all reports containing respective information were almost similar in reports from consumers (mean 52.6 ($\pm$ 21.2); median 54 [36–70]) and physicians (mean 53.5 ($\pm$ 21.8); median 56 [38–71]), while patients in the pharmacists' reports were slightly older (mean 58.7 ($\pm$ 20.5); median 62 [47–75]).

3.2 Quality of Documentation According to the vigiGrade Completeness Score

Overall, physicians' reports scored the highest vigiGrade score on average (mean 0.5 ($\pm$ 0.3); median 0.4 [0.2–0.6]), followed by consumer (mean 0.4 ($\pm$ 0.3); median 0.4 [0.2–0.6]) and pharmacists' reports (mean 0.4 ($\pm$ 0.3); median 0.3 [0.2–0.5]) (Fig. 2/Table Appendix 2). The scores for reports from physicians and consumers were more widely

dispersed and were more often greater than 0.5 than scores from pharmacists' reports.

No considerable differences regarding the quality of documentation for serious and non-serious reports for the three reporter types were observed (Table Appendix 2).

3.3 Analyses of Information Provided

3.3.1 Report-Related Information

The vast majority of the reports from all three reporter types contained a narrative, which was more often provided in consumer than in physicians' (OR 1.8 [1.7–1.9]) and pharmacists' (OR 1.9 [1.8–2.0]) reports, and less often provided in pharmacist versus physicians' reports' (OR 0.8 [0.8–0.9]) (Table 2; Fig. 4; Figure 4 is provided as Online Supplementary Material). Additionally, a narrative was less often present in reports classified as non-serious versus serious for all three reporter types (physicians: OR 0.2 [0.2–0.2]; pharmacist: OR 0.1 [0.1–0.2]; consumer OR 0.1 [0.1–0.2]) (Table Appendix 3/Table Appendix 4).

3.3.2 Patient-Related Information

Almost all reports contained information about the sex of the patient (Table 2/Fig. 3). It was more often reported in consumers' compared to physicians' (OR 2.2 [2.1–2.3]) and pharmacists' reports (OR 1.2 [1.1–1.3]) (Table 2/Fig. 4).

Two-thirds of reports from physicians contained information regarding the patient's age (66.4%). Age was similarly often provided in reports from pharmacists (OR 1.0 [0.9–1.0]) and less often reported by consumers (OR 0.6 [0.6–0.6]) compared to physicians. Concerning all three reporter types, the age of the patient was less often included in non-serious versus serious reports (physician: OR 0.7

Fig. 2 Boxplots of VigiGrade completeness scores per adverse drug reaction (ADR) report from physicians, pharmacists and consumers. Medians are visualized by the bar and means by the white dot within the boxplot. The lower and upper borders of the boxplot indicate the first (25%) and third quartile (75%) of the scores, respectively. The whiskers indicate the minimum and maximum of the scores. Black dots indicate outliers

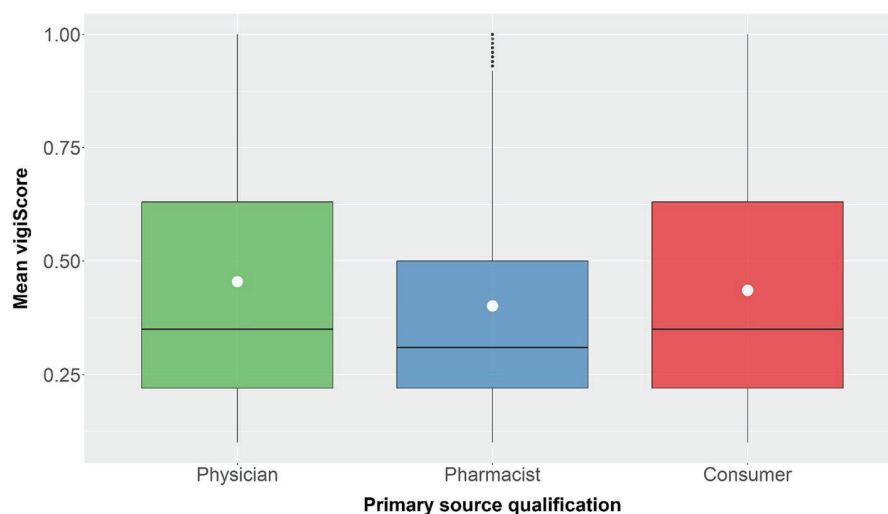


Table 2 Number of reports with report, patient, drug and adverse drug reaction (ADR)-related information

Observation	Number of reports with information			Logistic regression analysis		
	Physicians reports (n = 69,976)	Pharmacists reports (n = 42,396)	Consumer reports (n = 121,144)	OR [$\pm$ 95.0% CI], p value consumer versus physician (reference)	OR [$\pm$ 95.0% CI], p value pharmacist versus physician (reference)	OR [$\pm$ 95.0% CI], p value consumer versus pharmacist (reference)
<i>Report-related factors</i>						
Report type ^a	69,976 [100%]	42,396 [100%]	121,144 [100%]	–	–	–
Seriousness ^b	69,976 [100%]	42,396 [100%]	121,144 [100%]	–	–	–
Country ^a	69,976 [100%]	42,396 [100%]	121,144 [100%]	–	–	–
Narrative	66,534 [95.1%]	40,356 [95.2%]	117,958 [97.4%]	1.8 [1.7–1.9]***	0.8 [0.8–0.9]***	1.9 [1.8–2.0]***
<i>Patient-related factors</i>						
Sex	66,755 [95.4%]	41,007 [96.7%]	117,918 [97.3%]	2.2 [2.1–2.3]***	1.8 [1.7–1.9]***	1.2 [1.1–1.3]***
Age	46,486 [66.4%]	25,223 [59.5%]	64,243 [53.0%]	0.6 [0.6–0.6]***	1.0 [0.9–1.0]**	0.6 [0.6–0.6]***
Height	20,854 [29.8%]	9390 [22.1%]	37,851 [31.2%]	1.5 [1.4–1.6]***	2.0 [1.9–2.2]***	0.6 [0.6–0.7]***
Weight	22,188 [31.7%]	9294 [21.9%]	38,510 [31.8%]	0.6 [0.6–0.6]***	0.4 [0.4–0.5]***	1.8 [1.6–1.9]***
Medical history	40,269 [57.5%]	14,927 [35.2%]	61,545 [50.8%]	1.0 [1.0–1.0]	0.5 [0.5–0.6]***	1.9 [1.8–1.9]***
<i>Drug-related factors</i>						
Action taken with drug	40,365 [57.7%]	20,948 [49.4%]	52,469 [43.3%]	0.6 [0.6–0.6]***	0.9 [0.9–1.0]***	0.6 [0.6–0.6]***
Dose	38,320 [54.8%]	18,052 [42.6%]	66,747 [55.1%]	1.2 [1.2–1.2]***	0.8 [0.8–0.8]***	1.5 [1.4–1.5]***
Indication	49,178 [70.3%]	19,353 [45.6%]	61,211 [50.5%]	0.5 [0.5–0.5]***	0.5 [0.4–0.5]***	1.1 [1.1–1.1]***
Concomitant drugs	19,678 [28.1%]	11,153 [26.3%]	24,059 [19.9%]	0.7 [0.7–0.7]***	1.1 [1.1–1.2]***	0.6 [0.6–0.6]***
<i>ADR-related factors</i>						
Outcome	38,890 [55.6%]	19,925 [47.0%]	66,332 [54.8%]	1.2 [1.2–1.3]***	1.1 [1.1–1.1]***	1.2 [1.2–1.2]***
Time to onset	25,832 [36.9%]	13,033 [30.7%]	56,224 [46.4%]	1.9 [1.8–1.9]***	1.2 [1.2–1.3]***	1.7 [1.6–1.7]***

Number of reports and the proportion of reports with information of the categories investigated grouped into report-, patient-, drug- and ADR-related information. In addition, logistic regression analyses were performed for physician versus consumer reports, physician versus pharmacist reports and pharmacist versus consumer reports including patient, drug- and ADR-related information as covariables. Note that if the upper CI was lesser than 1, we assumed that the observation was more frequently reported for physicians (consumers vs. physicians, pharmacists vs. physicians) and pharmacists (consumers vs. pharmacists). If the lower CI was greater than 1 we assumed that the observation was more frequently reported for consumers (consumers vs. physicians, consumers vs. pharmacists) and pharmacists (pharmacists vs. physicians)

OR odds ratio, CI confidence interval

p values coded as: 0 ‘***’; 0.001 ‘***’; 0.01 ‘*’; 0.05 ‘.’; 0.1 ‘.’ 1

^aCategory was part of the filter criteria

^bAutomatically assigned to all reports

[0.7–0.7]; pharmacist: OR 0.4 [0.4–0.4]; consumer: OR 0.4 [0.4–0.4]) (Table Appendix 3/Table Appendix 4).

Consumers (0.6 [0.6–0.7]) and physicians (pharmacist vs. physician OR 2.0 [1.9–2.2]) less likely provided information about patients’ height compared to pharmacists (height: 22.1%, weight: 21.9%), whereas the opposite applies to the weight (consumer versus pharmacist OR 1.8 [1.6–1.9]; pharmacist versus physician OR 0.4 [0.4–0.5]) (Table 2/Fig. 3).

The medical history of the patients was clearly less often reported in pharmacists’ (35.2%) compared to physicians’ (OR 0.5 [0.5–0.6]) and consumer reports (consumer vs. pharmacist OR 1.9 [1.8–1.9]) (Table 2/Fig. 4). Across all three reporter types, reports classified as serious more frequently included a medical history compared to non-serious reports (Table Appendix 3/Table Appendix 4). Physicians

(25.0%) and consumers (16.6%) also more often provided more than two medical histories compared to pharmacists (8.6%) (Table 3).

3.3.3 Drug-Related Information

Physicians (20.9%) more often reported more than one suspected/interacting drug than pharmacists (10.7%) and consumers (11.8%) (Table 4).

Information regarding the action taken with at least one of the suspected/interacting drugs was less frequently reported by pharmacists (OR 0.9 [0.9–1.0]) and consumers (OR 0.6 [0.6–0.6]) compared to physicians (57.7%) (Table 2; Figs. 3 and 4). Slight differences between non-serious and serious reports concerning the proportion of reports with this

Fig. 3 Radar chart of the proportion of reports with information on the categories investigated per reporter type. Categories analysed are listed anti-clockwise in alphabetical order. The more distant the dot is from the centre of the radar chart, the higher the number of reports that included information on the respective category

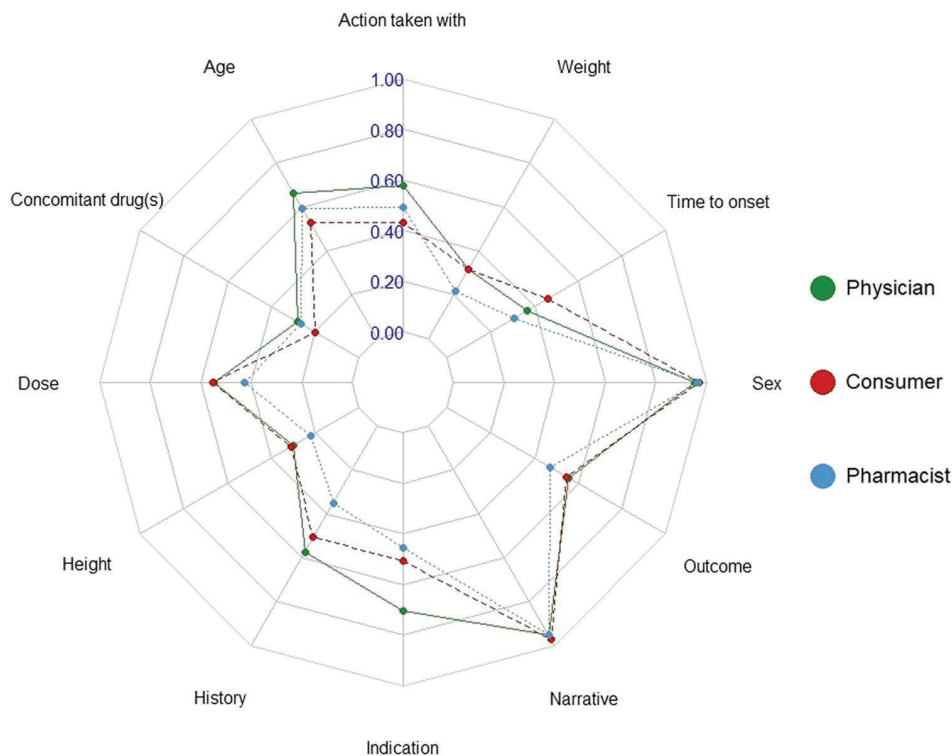


Table 3 Number of reported medical histories per adverse drug reaction (ADR) report and their percentage share in reports from physicians, pharmacists and consumer

Count medical history	Number of reported medical histories					
	Physicians reports (<i>n</i> = 69,976)		Pharmacist reports (<i>n</i> = 42,396)		Consumer reports (<i>n</i> = 121,144)	
	Number of reports [%]	Sum of reports with $\geq$ count of medical histories [%]	Number of reports [%]	Sum of reports with $\geq$ count of medical histories [%]	Number of reports [%]	Sum of reports with $\geq$ count of medical histories [%]
No medical history	29,707 [42.5%]	69,976 [100%]	27,469 [64.8%]	42,396 [100%]	59,599 [49.2%]	121,144 [100%]
1	15,213 [21.7%]	40,269 [57.6%]	8329 [19.6%]	14,927 [35.2%]	28,411 [23.5%]	61,545 [50.9%]
2	7645 [10.9%]	25,056 [35.9%]	2988 [7.0%]	6598 [15.6%]	13,047 [10.8%]	33,134 [27.4%]
3	5475 [7.8%]	17,411 [25.0%]	1473 [3.5%]	3610 [8.6%]	7676 [6.3%]	20,087 [16.6%]
4	3584 [5.1%]	11,936 [17.2%]	808 [1.9%]	2137 [5.1%]	4645 [3.8%]	12,411 [10.3%]
5	2351 [3.4%]	8352 [12.1%]	453 [1.1%]	1329 [3.2%]	2764 [2.3%]	7766 [6.5%]
> 5	6001 [8.7%]	6001 [8.7%]	876 [2.1%]	876 [2.1%]	5002 [4.2%]	5002 [4.2%]

information from the three reporter types were observed (Table Appendix 3/Table Appendix 4).

The dose of at least one drug classified as suspected/interacting was more often present in physician (pharmacist vs. physician OR 0.8 [0.8–0.8]) and consumer (1.5 [1.4–1.5]) reports compared to pharmacists' reports (42.6%) (Table 2; Figs. 3 and 4).

Consumers (OR 0.5 [0.5–0.5]) and pharmacists (OR 0.5 [0.4–0.5]) clearly less often specified an indication for at

least one drug reported as suspected/interacting than physicians (70.3%).

The proportion of reports with at least one black triangle drug reported as suspected/interacting was higher in physicians' (21.5%) than in reports from pharmacists (10.6%) and consumers (9.9%) (Table 4).

Concomitant drugs were reported less often in consumers' reports (19.9%) compared to physicians' (OR 0.7 [0.7–0.7]) and pharmacists' (0.6 [0.6–0.6]) reports

Table 4 The number of suspected/interacting and concomitant drugs per adverse drug reaction (ADR) report and the number of reports with at least one black triangle drug listed as suspected/interacting

drug with their percentage share in reports from physicians, pharmacists and consumers

Drug-related information						
Observation	Physicians reports (<i>n</i> = 69,976)		Pharmacists reports (<i>n</i> = 42,396)		Consumer reports (<i>n</i> = 121,144)	
Number of reported suspected/interacting drugs						
Count of sus- pected/interacting drugs	Number of reports [%]	Sum of reports with ≥ count of suspected/interact- ing drugs [%]	Number of reports [%]	Sum of reports with ≥ count of suspected/interact- ing drugs [%]	Number of reports [%]	Sum of reports with ≥ count of suspected/inter- acting drugs [%]
1	55,367 [79.1%]	69,976 [100%]	37,864 [89.3%]	42,396 [100%]	106,719 [88.1%]	121,144 [100%]
2	9215 [13.2%]	14,609 [20.9%]	3282 [7.7%]	4532 [10.7%]	10,758 [8.9%]	14,425 [11.8%]
3	2859 [4.1%]	5394 [7.7%]	731 [1.7%]	1250 [3.0%]	2237 [1.8%]	3667 [2.9%]
4	1236 [1.8%]	2535 [3.6%]	277 [0.7%]	519 [1.3%]	761 [0.6%]	1430 [1.1%]
5	540 [0.8%]	1299 [1.8%]	113 [0.3%]	242 [0.6%]	271 [0.2%]	669 [0.5%]
>5	759 [1.0%]	759 [1.0%]	129 [0.3%]	129 [0.3%]	398 [0.3%]	398 [0.3%]
Reports with black triangle drug in suspected/interacting drug						
Black triangle drug in suspected/ interacting drug	Physicians reports (n = 69,976) Number of reports [%]		Pharmacists reports (n = 42,396) Number of reports [%]		Consumer reports (n = 121,144) Number of reports [%]	
At least one	15,067 [21.5%]		4482 [10.6%]		11,976 [9.9%]	
None	54,909 [78.5%]		37,914 [89.4%]		109,168 [90.1%]	
Number of reported concomitant drugs						
Count of reported concomitant drugs	Number of reports [%]	Sum of reports with ≥ count of concomitant drugs [%]	Number of reports [%]	Sum of reports with ≥ count of concomitant drugs [%]	Number of reports [%]	Sum of reports with ≥ count of con- comitant drugs [%]
0	50,298 [71.9%]	69,976 [100%]	31,243 [73.7%]	42,396 [100%]	97,085 [80.1%]	121,144 [100%]
1	5909 [8.4%]	19,678 [28.0%]	3048 [7.2%]	11,153 [26.2%]	10,841 [8.9%]	24,059 [19.7%]
2	3585 [5.1%]	13,769 [19.6%]	1878 [4.4%]	8105 [19.0%]	5232 [4.3%]	13,218 [10.8%]
3	2531 [3.6%]	10,184 [14.5%]	1443 [3.4%]	6227 [14.6%]	2986 [2.5%]	7986 [6.5%]
4	1888 [2.7%]	7653 [10.9%]	1179 [2.8%]	4784 [11.2%]	1716 [1.4%]	5000 [4.0%]
5	1334 [1.9%]	5765 [8.2%]	893 [2.1%]	3605 [8.4%]	1114 [0.9%]	3284 [2.6%]
>5	4431 [6.3%]	4431 [6.3%]	2712 [6.3%]	2712 [6.3%]	2170 [1.7%]	2170 [1.7%]

(Table 2; Fig. 3). According to the logistic regression analyses concomitant drugs were more likely reported from pharmacists than physicians (OR 1.1 [1.1–1.2]) (Table 2; Fig. 4). For all three reporter types, concomitant drugs were less often included in non-serious versus serious reports (pharmacists: 0.2 [0.2–0.2]; physicians: 0.4 [0.4–0.5]; consumer: 0.2 [0.2–0.2]) (Table Appendix 3/Table Appendix 4). Regarding the number of concomitant drugs per ADR report, physicians (28.0%) and pharmacists (26.2%) more frequently reported more than one concomitant drug compared to consumers (19.7%) (Table 4).

3.3.4 ADR-Related Information

A higher proportion of reports from physicians (44.7%) contained only one ADR compared to reports from pharmacists (36.4%) and consumers (36.6%) (Table 5).

At least one outcome per ADR report was more often provided in physicians' (55.6%) and consumers' (54.8%) than in pharmacists' (47.0%) reports (Table 2; Fig. 3). However, logistic regression analyses showed that the information was more often included in consumer (OR 1.2 [1.2–1.3]) and pharmacist (OR 1.1 [1.1–1.1]) compared to physicians' reports (Table 2; Fig. 4).

Table 5 Number of reported adverse drug reactions (ADRs) per ADR report, the number of reports describing an ADR from the designated medical events list and containing at least one known ADR-drug combination contained in SIDER with their percentage share in reports from physicians, pharmacists and consumers

ADR-related information						
Observation	Physicians reports (<i>n</i> = 69,976)		Pharmacists reports (<i>n</i> = 42,396)		Consumer reports (<i>n</i> = 121,144)	
Number of reported ADR						
Count of reported ADR	Number of reports [%]	Sum of reports with ≥ count of reported ADR [%]	Number of reports [%]	Sum of reports with ≥ count of reported ADR[%]	Number of reports [%]	Sum of reports with ≥ count of reported ADR [%]
1	31,279 [44.7%]	69,976 [100%]	15,419 [36.4%]	42,396 [100%]	44,329 [36.6%]	69,976 [100%]
2	17,293 [24.7%]	38,697 [55.3%]	12,488 [29.5%]	26,977 [63.7%]	29,718 [24.5%]	38,697 [63.5%]
3	9443 [13.5%]	21,404 [30.6%]	7101 [16.7%]	14,489 [34.2%]	18,740 [15.5%]	21,404 [39.0%]
4	5037 [7.2%]	11,961 [17.1%]	3501 [8.3%]	7388 [17.5%]	10,666 [8.8%]	11,961 [23.5%]
5	2752 [3.9%]	6924 [9.9%]	1737 [4.1%]	3887 [9.2%]	6188 [5.1%]	6924 [14.7%]
>5	4172 [6.0%]	4172 [6.0%]	2150 [5.1%]	2150 [5.1%]	4172 [9.6%]	4172 [9.6%]
Reports listing a designated medical event as ADR						
	Physicians reports (n = 69,976)		Pharmacists reports (n = 42,396)		Consumer reports (n = 121,144)	
	Number of reports [%]		Number of reports [%]		Number of reports [%]	
At least one	3380 [4.8%]		484 [1.1%]		874 [0.7%]	
None	66,596 [95.2%]		41,912 [98.9%]		120,270 [99.3%]	
Reports containing at least one known ADR-drug combination (SIDER)						
	Physicians reports (n = 69,976)		Pharmacists reports (n = 42,396)		Consumer reports (n = 121,144)	
	Number of reports [%]		Number of reports [%]		Number of reports [%]	
At least one	14,376 [20.5%]		7217 [17.0%]		21,219 [17.5%]	
None	55,600 [79.5%]		35,179 [83.0%]		99,925 [82.5%]	

The time to onset based on the information of the start date of drug therapy and the ADR occurrence could be calculated more often in reports from consumers (46.4%) compared to reports from physicians (OR 1.9 [1.8–1.9]) and pharmacists (OR 1.7 [1.6–1.7]) (Table 2; Figs. 3 and 4).

Designated medical important events were mentioned in only a few reports and in proportion were more often contained in physician (4.8%) than in pharmacist (1.1%) and consumer (0.7%) reports (Table 5).

In total about 10% of the drugs reported in our dataset were included in SIDER. For these drugs a slightly greater proportion of reports from physicians (20.5%) included drug-ADR combinations already known in SIDER compared to reports of pharmacists (17.0%) and consumers (17.5%).

3.4 Number of Reports per Physicians, Pharmacists and Drug-Exposed Inhabitants in Germany

Despite the increase of the number of practicing physicians and pharmacists between 2018 and 2021, the number of

ADR reports from both decreased (Table 6). Thus, the calculated numbers of reports per 100 practicing physicians and pharmacists decreased, too. Without consideration that one physician/pharmacist could have reported more than one ADR per year, six per 100 practicing physicians and 11 per 100 practicing pharmacists reported an ADR in 2018 compared to three per 100 practicing physicians and six per 100 practicing pharmacists in 2021. The number of reports from consumers per 10,000 potentially drug-exposed inhabitants increased continuously from 2018 to 2020 and slightly decreased in 2021.

4 Discussion

Our analysis revealed several differences among reports from the three reporter types. Among others, the time to onset could be calculated more often in consumer reports and, details about the patients' medical history and the indications of the suspected drugs were more likely to be found

Table 6 Number of reports per 100 practicing physicians/pharmacists and 10,000 potentially drug-exposed inhabitants in Germany

Year	Physician reports (<i>n</i> = 69,976)			Pharmacist reports (<i>n</i> = 42,396)			Consumer reports (<i>n</i> = 121,144)		
	Reports per year	Practicing physicians per year ^a	Reports per 100 practicing physicians	Reports per year	Pharmacists (pharmaceutical staff) per year ^b	Reports per 100 pharmacists (pharmaceutical staff)	Reports per year	Potentially drug exposed inhabitants per year ^c	Reports per 10,000 potentially drug exposed inhabitants
2018	20,633	359,099	5.7	14,036	128,309	10.9	26,208	45,310,393	5.8
2019	20,289	367,100	5.5	12,472	130,308	9.6	30,858	45,387,253	6.8
2020	16,295	373,304	4.4	8759	130,755	6.7	36,325	45,378,112	8.0
2021	12,759	378,650	3.4	7129	130,463	5.5	27,753	45,419,257	6.1

^aCorresponds to the total number of physicians in outpatient and hospital settings from “Ärztstatistik zum 31. Dezember 2021” provided by the Bundesärztekammer [28]

^bCorresponds to the total number of pharmacists, pharmacists in internship (PhIP), pharmaceutical technical assistants (PTAs), pharmacy technician in public pharmacies, pharmacist assistants and pharmacists working in hospital pharmacies from “Die Apotheke - Zahlen Daten Fakten 2021/2022” published by the Bundesvereinigung deutscher Apothekerverbände [29, 30]

^cCorresponds to the share of potentially drug-exposed inhabitants in Germany according to a German survey. The number of German inhabitants was taken from statista “Bevölkerung—Einwohnerzahl von Deutschland 1990–2021” [31]. The percentual share of potentially drug-exposed inhabitants was taken from “Prütz, Franziska, et al. “Inanspruchnahme ambulanter medizinischer Leistungen in Deutschland—Ergebnisse der Studie GEDA 2019/2020-EHIS.” (2021)” [32]

in physicians' reports compared to the other reporter types, respectively. According to the *vigiGrade* score, physicians' reports scored marginally better than those from pharmacists and consumers.

4.1 Descriptive Analysis

Further explanations for the increasing numbers of consumer reports besides the already mentioned legislative changes in forwarding non-serious reports by marketing authorization holders, are an increased awareness of ADR reporting systems, how to report ADRs and facilitation of reporting. In contrast, the decline of reports from physicians and pharmacist in general might be associated with the increased reporting of consumers themselves. Further on, the decline of ADR reports from physicians in 2020 and 2021 might correlate with the fact that patients consulted physicians less frequently during the first year of the COVID-19-pandemic [33]. Similarly, pharmacist-consumer contacts might have been reduced as well.

In summary, reports from the three reporter types appear to represent different populations of patients and thereby complement each other. A study covering ADR reports from the European Economic Area performed in EudraVigilance showed that patients in consumer reports were on average younger compared to those in HCP reports (physicians and pharmacists combined), too [8]. Possibly, consumers more often report their ADRs online and this approach might be used more often by younger than older consumers. In addition, older adults in general consult physicians more often than younger adults, probably also regarding drug-related problems. Additionally, serious ADRs requiring

medical contact might occur more often in older compared to younger adults [2, 34, 35]. Pharmacies in Germany offer low-threshold services regarding medication analyses. This might be an important point of contact to recognize ADRs especially in older polymedicated patients [36].

The higher proportion of reports referring to females from all three reporter types, which was also described in other studies, could generally reflect that females consult physicians more often, suffer from ADRs more often, report ADRs more frequently, and, especially, in case of younger females, take more drugs compared to males [8, 9, 35, 37, 38].

4.2 Completeness Score (*vigiGrade*)

In a previous study (2007–2012) performed in *VigiBase*, the *VigiGrade* completeness score differed, dependent on the country of origin, between the three reporter types [22]. Concerning the analysed reports from Germany, the reports from physicians were clearly more often classified as “well documented” than those from pharmacist and consumers in this study. However, these results may no longer reflect the current situation. As in our study, a current study from South Africa showed only minor differences between all reporter types, suggesting that physicians' reports were slightly more complete [39].

4.3 Information Provided in Reports from Physicians, Pharmacists and Consumers

Our analysis revealed that information on patients' age, weight, height and medical history were not available in a

large number of the reports. However, the age of the patient is a highly relevant information regarding the analyses of ADR reports, since ADRs might differ between younger (e.g., children) and older patients. Information regarding the weight and height of the patient may not only be relevant for correct dosing in children, but also give a hint regarding the body composition, which may impact on pharmacokinetics and pharmacodynamics of specific drugs. Thus, these information may be important to identify specific patients with a higher risk to develop certain ADRs [40]. The same applies to the medical history of the patient, since certain comorbidities have been shown to be a decisive (co-)factor in the occurrence of specific ADRs [41].

Information regarding the dose, action taken with the drug and the indication of drug therapy were partially missing in more than 50% of the reports. In addition, the number of reports with sufficient information to calculate a time to onset was also low for all three reporter types (< 50%). However, the latter could be calculated more often in reports from consumers than from physicians and pharmacists. As already seen in a US study, consumers may know the exact start date of their drug therapy and date of the ADR more accurately than physicians and pharmacists [13]. In summary, information concerning drug therapy, as well as the start date of the ADR are highly relevant for the assessment of the causal relationship between the intake of a drug and the occurrence of an ADR as well as the further course of the ADR.

The absence of the aforementioned information in approximately every second ADR report is a relevant important finding in terms of pharmacovigilance. It should encourage further studies to elucidate the underlying reasons since it bears the potential to significantly increase the relevance and impact of submitted ADR reports.

As in an Italian and a US Study, a higher proportion of reports from physicians (and pharmacists) listed at least one concomitant drug compared to consumers. In our study, this could be attributed to the older average age of the patient's in the reports from physicians and pharmacists, possibly associated with more drugs taken in these age groups compared to those of consumers [35]. However, the proportions of reports with concomitant drugs were rather low for all three reporter types in our analysis (< 30%). This could reflect patients not taking any co-medications, reporters not distinguishing between concomitant and suspected/interacting drugs or information not being provided.

Nearly twice as many reports from physicians than from consumers and pharmacists listed at least one black triangle drug as suspected/interacting. Possibly, physicians and pharmacists are more aware about the additional monitoring processes and the meaning of the black triangle symbol than patients [41, 42]. In fact, according to a Finish study physicians were more likely to report ADRs if they were aware

of the additional monitoring process [41]. Furthermore, in a German study, physicians more often reported ADRs to newly authorised drugs which may be more frequently labelled with a black triangle than older ones. Additionally the Finish study indicated that pharmacists did not see their relevance in the process of additional monitoring, which might also apply to our results [41].

In contrast to other studies, we could not confirm that consumers more likely reported known ADRs compared to physicians and pharmacists [8, 43]. However, we only considered one database, namely SIDER, for the detection of known ADRs and only about 10% of the drugs reported in our dataset were included in SIDER clearly limiting the value of our results. Given that SIDER is based on drug labels, especially new ADRs not yet included therein could not be covered in this analysis.

ADRs listed as designated medical events were more often provided in reports from physicians (and pharmacists) compared to consumers which is in line with another study. The lower proportions of reports with designated medical events found in our study (< 5%) compared to the aforementioned study (40–50%), might be caused by the fact that in that study the “MedDRA® list of serious events” was additionally considered. Further, the higher proportion of non-serious reports in our analysis may have contributed to the lower proportion of reports with designated medical events.

4.4 Suggestions

The results of our analysis could serve as a basis for further initiatives aiming to improve the quality and therewith the value of spontaneous reports from each reporter type.

In order to maintain the positive trend of increasing numbers of consumer reports further campaigns to inform consumers about the possibility and the importance to report ADRs could be helpful [11]. In this regard it could also be highlighted which information is particularly relevant (e.g., the time to onset) and why they should be provided. Thereby, the quality of documentation and the value of their reports could be increased [43]. Meanwhile, physicians and pharmacists should be reminded of the possibility and importance of spontaneous reporting, for example, via appeals in their professional journals to encourage ADR reporting [44, 45].

In order to distinguish between patients without any medical histories/co-medications and reports in which a respective medical history/co-medication is not provided, the introduction of additional coding, i.e., “the patient has no medical history/concomitant drug”, could be helpful. In this respect, online reporting tools could be designed to precisely query these situations with drop-down menus allowing to select the appropriate answer “yes/no/unknown” [44].

Minimising the amount of time spent on reporting could possibly counteract the decreasing number of reports and may

improve the completeness of information provided by physicians and pharmacists [43, 45, 46]. Among other factors, the entry of information to a web based or printout reporting format requires a considerable amount of time. Therefore, spontaneous reporting systems allowing simple creations of reports via interfacing with practice/pharmacy software applications thereby sharing personal data already stored in one system albeit still meeting data protection requirements could be valuable tools. In this respect, automatic transfer of relevant data to an optional ADR reporting file would only require a final check before electronic submission [43, 44, 47].

A more interactive exchange between all three reporter types may further increase the quality of documentation of their reports [44, 48]. As already suggested by Hadi et al., granting pharmacists access to certain patient data could be useful in order to enhance the value of the pharmacists' reports [49]. However, in the EU and Germany, strict data protection regulations have to be considered which could complicate the implementation of such applications.

5 Strengths and Limitations

Our analysis provides the current status of the quality of ADR reports from different reporter types especially after the changes in legal requirements.

However, the inherent limitations to analyses performed in spontaneous reporting systems have to be taken into account. One of the major limitations is the unknown amount of under-reporting that may differ, among others, between the analysed reporter types, as well as for serious and non-serious ADR reports.

Furthermore, we only considered if specific information were provided. The quality or relevance of the information provided for pharmacovigilance was not assessed. However, this would be difficult to quantify as a basis for a comparison.

In addition, we could not distinguish between initial reports and reports with follow-ups that might be submitted on request, and thus, may have influenced the completeness of the respective reports. Consumer reports in particular, if submitted via a pharmaceutical company, could contain additional information as a result of explicit inquiries by specifically trained employees. Additionally, possibly at the time of analysis not all follow-up reports, especially those from 2021 may have been received.

Please note that the calculations of reporting rates per 100 physicians/pharmacists and 10,000 potentially drug-exposed inhabitants are estimations since one physician or pharmacist may also have reported more than one ADR.

Our analysis only covers ADR reports related to drugs, thus, the results may not be transferrable to vaccines. We

only considered reports coded with one primary source qualification. It may be possible that some of these reports were reported by more than one reporter type but not encoded as such. However, we assume that this would only apply to a small number of our reports and, therefore, should not affect our results substantially. In addition, the number of reports coded with more than one reporter type was rather low (7.7%, 20,473/267,261 reports of total dataset) and should not substantially affect our observations.

6 Conclusion

In terms of the overall completeness, the ADR reports from consumers were comparable with regard to the information provided to those from physicians and pharmacists highlighting their value to gain further information on ADRs. Besides further campaigns to continuously increase the awareness towards ADR reporting systems, a more intense interacting among all three reporter types may further improve the completeness of ADR reports.

Finally, since reports from consumers, physicians and pharmacist may differ in terms of presence of certain information, the population of patients covered, and the reported drugs/ADRs, stratified analysis of ADR reports per reporter type dependent on the research question are recommended [2, 9–12].

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40264-023-01355-8>.

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Declarations

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Conflict of interest MS and DD were supported by the ANKA project, which is funded by own resources of the German Federal Institute for Drugs and Medical Devices (BfArM) and own resources of the Institute for Medical Biometry, Informatics and Epidemiology (IMBIE) at the University Hospital of Bonn (V-2020.2/68502/2020–2024). The analyses and results presented in this manuscript constitute a subproject within the ANKA project. The remaining authors have no other conflicts of interest that are directly relevant to the content of this manuscript.

Data availability statement The pseudonymised ADR reports from EudraVigilance are not publicly accessible due to data protection requirements. Distinct levels of access are provided for various stakeholders (<https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance/access-eudravigilance-data>). Being one of the competent authorities in Germany, the highest level of access is granted to the Federal Institute for Drugs and Medical Devices (BfArM). Nevertheless, even with the lowest access level, researchers can perform the same analysis in EudraVigilance (EV) with aggregated data (public access: www.adrreports.eu/en/index.html). For further information regarding the processing of personal data in the context of the operation of EudraVigilance Human we refer to the European Medicines Agency's Data Protection Notice for EudraVigilance Human.

Ethics approval The presented study is a retrospective analysis of pseudonymised reports of adverse drug reactions. According to the local ethics committee of the Medical Faculty of Bonn no ethics approval is needed for this study (file no. 100/21).

Consent for publication Not applicable.

Consent to participate Not applicable.

Code availability Not applicable.

Author contributions PC, DD and BS contributed to the conception and design of the study. PC performed the data analysis. PC, DD and MS selected the statistical methods. PC, DD and BS performed the evaluation and discussion of the analysis results. PC, DD and BS wrote the first drafts of the manuscript. PC, DD, BS and MS commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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References

- Moore N, Berdai D, Blin P, Droz C. Pharmacovigilance—the next chapter. *Therapies*. 2019. <https://doi.org/10.1016/j.therap.2019.09.004>.
- Dubral D, Schmid M, Alešik E, Paeschke N, Stingl J, Sachs B. Frequent adverse drug reactions, and medication groups under suspicion. *Deutsches Ärzteblatt Int*. 2018. <https://doi.org/10.3238/arztebl.2018.0393>.
- Borg J-J, Aislaitner G, Pirozynski M, Mifsud S. Strengthening and rationalizing pharmacovigilance in the EU: where is Europe heading to?: A review of the new EU legislation on pharmacovigilance. *Drug Saf*. 2011. <https://doi.org/10.2165/11586620-00000-00000-00000>.
- European Medicines Agency and Heads of Medicines Agencies. Guideline on good pharmacovigilance practices (GVP) Module VI: collection, management and submission of reports of suspected adverse reactions to medicinal products [EMA/873138/2011 Rev 2]. 2017. www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/08/WC500232767.pdf. Accessed 9 Dec 2022.
- European Commission. Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010. <https://link.springer.com/content/pdf/10.1007/s40264-018-0647-1.pdf?pdf=button>. Accessed 9 Dec 2022.
- European Commission. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001. <https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:311:0067:0128:en:PDF>. Accessed 9 Dec 2022.
- European Commission. Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02004R0726-20220128>. Accessed 9 Dec 2022.
- Banovac M, Candore G, Slattery J, Houyez F, Haerry D, Genov G, et al. Patient reporting in the EU: analysis of EudraVigilance data. *Drug Saf*. 2017. <https://doi.org/10.1007/s40264-017-0534-1>.
- Inácio P, Cavaco A, Airaksinen M. The value of patient reporting to the pharmacovigilance system: a systematic review. *Br J Clin Pharmacol*. 2017. <https://doi.org/10.1111/bcp.13098>.
- Al Dweik R, Kohen D, Stacey D, Yaya S. Adverse drug reaction reporting in Canada: consumer versus physician reports. *Drugs Ther Perspect*. 2020. <https://doi.org/10.1007/s40267-020-00762-6>.
- Härmark L, Van Hunsel F, Grundmark B. ADR reporting by the general public: lessons learnt from the Dutch and Swedish systems. *Drug Saf*. 2015. <https://doi.org/10.1007/s40264-015-0264-1>.
- Kheloufi F, Default A, Roubey F, Laugier-Castellan D, Boyer M, Rodrigues B, et al. Informativeness of patient initial reports of adverse drug reactions. Can it be improved by a pharmacovigilance centre? *Eur J Clin Pharmacol*. 2017. <https://doi.org/10.1007/s00228-017-2254-y>.
- Toki T, Ono S. Assessment of factors associated with completeness of spontaneous adverse event reporting in the United States: a comparison between consumer reports and healthcare professional reports. *J Clin Pharm Ther*. 2020. <https://doi.org/10.1111/jcpt.13086>.
- Rolfes L, Van Hunsel F, Wilkes S, Van Grootheest K, Van Puijenbroek E. Adverse drug reaction reports of patients and healthcare professionals—differences in reported information. *Pharmacoepidemiol Drug Saf*. 2015. <https://doi.org/10.1002/pds.3687>.
- Jobski K, Bantel C, Hoffmann F. Characteristics and completeness of spontaneous reports by reporter's role in Germany: an analysis of the EUDRAVIGILANCE database using the example of opioid-associated abuse, dependence, or withdrawal. *Pharmacol Res Perspect*. 2023. <https://doi.org/10.1002/prp2.1077>.
- World Health Organization. International drug monitoring: the role of the hospital, report of a WHO meeting [held in Geneva from 18 to 23 November 1968]. 1969.
- European Medicines Agency. EudraVigilance - European database of suspected adverse drug reaction reports. https://www.adrreports.eu/en/data_source.html. Accessed 12 Dec 2022.
- Kommas E, Lex D, Huber M, Paeschke N. Verdachtsfälle melden—Warum am behördlichen Nebenwirkungsmelde-System kein Weg vorbeiführt. *Deutsche ApothekerZeitung*. 2019;37:44.

19. MedDRA. Medical dictionary for regulatory activities. www.meddra.org/how-to-use/support-documentation. Accessed 12 Dec 2022.
20. European Medicines Agency. EudraVigilance user manual. https://www.ema.europa.eu/en/documents/regulatory-procedural-guide-line/eudravigilance-user-manual-marketing-authorisation-holders_en.pdf. Accessed 1 Dec 2022.
21. European Medicines Agency. 2021 Annual Report on EudraVigilance for the European Parliament, the Council and the Commission. https://www.ema.europa.eu/en/documents/report/2021-annual-report-eudravigilance-european-parliament-council-commission_en.pdf. Accessed 9 Dec 2022.
22. Bergvall T, Norén GN, Lindquist M. vigiGrade: a tool to identify well-documented individual case reports and highlight systematic data quality issues. *Drug Saf*. 2014. <https://doi.org/10.1007/s40264-013-0131-x>.
23. Uppsala Monitoring Center. About VigiBase -The unique global resource at the heart of the drive for safer use of medicines. <https://who-umc.org/vigibase/>. Accessed 12 Dec 2022.
24. European Medicines Agency. List of medicines under additional monitoring. <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/medicines-under-additional-monitoring/list-medicines-under-additional-monitoring>. Accessed 11 Aug 2022.
25. European Medicines Agency. Designated medical events. <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/signal-management#designated-medical-events-section>. Accessed 11 Aug 2022.
26. Kuhn M, Letunic I, Jensen LJ, Bork P. The SIDER database of drugs and side effects. *Nucleic Acids Res*. 2016. <https://doi.org/10.1093/nar/gkv1075>.
27. Kuhn M, Campillos M, Letunic I, Jensen LJ, Bork P. A side effect resource to capture phenotypic effects of drugs. *Mol Syst Biol*. 2010. <https://doi.org/10.1038/msb.2009.98>.
28. Bundesärztekammer. Ergebnisse der Ärzttestistik zum 31.12.2021. <https://www.bundesaeztekammer.de/baek/ueber-uns/aerzttestistik/aerzttestistik-2021>. Accessed 12 Aug 2022.
29. Bundesvereinigung Deutscher Apothekerverbände (ABDA). Die Apotheke 2021: Zahlen, Daten, Fakten. https://www.abda.de/fileadmin/user_upload/assets/ZDF/ZDF21/ABDA_ZDF_2021_Broschuere.pdf. Accessed 20 Jul 2022.
30. Bundesvereinigung Deutscher Apothekerverbände (ABDA). Die Apotheke 2022: Zahlen, Daten, Fakten. <https://www.abda.de/aktuelles-und-presse/publikationen/detail/die-apotheke-zahlen-daten-fakten-2022/>. Accessed 20 Jul 2022.
31. Statista. Bevölkerung - Einwohnerzahl von Deutschland von 1990 bis 2022. <https://de.statista.com/statistik/daten/studie/2861/umfrage/entwicklung-der-gesamtbewoelkerung-deutschlands/>. Accessed 1 Mar 2022.
32. Prütz F, Rommel A, Thom J, Du Y, Sarganas G, Starker A. Inanspruchnahme ambulanter medizinischer Leistungen in Deutschland – Ergebnisse der Studie GEDA 2019/2020-EHIS. Robert Koch-Institut; 2021; <https://doi.org/10.25646/8554>
33. Jördens MS, Loosen SH, Seraphin T, Luedde T, Kostev K, Roderburg C. Impact of the COVID-19 pandemic on consultations and diagnoses in gastroenterology practices in Germany. *Front Med*. 2021. <https://doi.org/10.3389/fmed.2021.684032>.
34. Dubrall D, Just KS, Schmid M, Stingl JC, Sachs B. Adverse drug reactions in older adults: a retrospective comparative analysis of spontaneous reports to the German Federal Institute for Drugs and Medical Devices. *BMC Pharmacol Toxicol*. 2020. <https://doi.org/10.1186/s40360-020-0392-9>.
35. Knopf H, Prütz F, Du Y. Use of medicines by adults in Germany. *J Health Monit*. 2017. <https://doi.org/10.17886/RKI-GBE-2017-130>.
36. Sell R, Schaefer M. Prevalence and risk factors of drug-related problems identified in pharmacy-based medication reviews. *Int J Clin Pharm*. 2020. <https://doi.org/10.1007/s11096-020-00976-8>.
37. De Langen J, Van Hunsel F, Passier A, De Jong-van Den Berg L, Van Grootheest K. Adverse drug reaction reporting by patients in The Netherlands: three years of experience. *Drug Saf*. 2008. <https://doi.org/10.2165/00002018-200831060-00006>.
38. Thiessard F, Roux E, Miremont-Salamé G, Fourrier-Réglat A, Haramburu F, Tubert-Bitter P, et al. Trends in spontaneous adverse drug reaction reports to the French Pharmacovigilance System (1986–2001). *Drug Saf*. 2005. <https://doi.org/10.2165/00002018-200528080-00007>.
39. Matlala MF, Lubbe MS, Steyn H. The completeness of adverse drug reaction reports in South Africa: an analysis in VigiBase®. *Afr J Primary Health Care Fam Med*. 2023. <https://doi.org/10.4102/phcfm.v15i1.3659>.
40. De Baerdemaeker LE, Mortier EP, Struys MM. Pharmacokinetics in obese patients. *Contin Educ Anaesth Crit Care Pain*. 2004. <https://doi.org/10.1093/bjaceaccp/mkh042>.
41. Sandberg A, Ehlers P, Torvinen S, Sandberg H, Siven M. Regulation awareness and experience of additional monitoring among healthcare professionals in Finland. *Healthcare*. 2021. <https://doi.org/10.3390/healthcare9111540>.
42. Januskiene J, Segec A, Slattery J, Genov G, Plueschke K, Kurz X, et al. What are the patients' and health care professionals' understanding and behaviors towards adverse drug reaction reporting and additional monitoring? *Pharmacoepidemiol Drug Saf*. 2021. <https://doi.org/10.1002/pds.5162>.
43. Alomar M, Tawfiq AM, Hassan N, Palaian S. Post marketing surveillance of suspected adverse drug reactions through spontaneous reporting: current status, challenges and the future. *Ther Adv Drug Saf*. 2020. <https://doi.org/10.1177/2042098620938595>.
44. Hohl CM, Small SS, Peddie D, Badke K, Bailey C, Balka E. Why clinicians don't report adverse drug events: qualitative study. *JMIR Public Health Surveill*. 2018. <https://doi.org/10.2196/publichealth.9282>.
45. Vallano A, Cereza G, Pedròs C, Agustí A, Danés I, Aguilera C, et al. Obstacles and solutions for spontaneous reporting of adverse drug reactions in the hospital: obstacles and solutions for reporting adverse drug reactions. *Br J Clin Pharmacol*. 2005. <https://doi.org/10.1111/j.1365-2125.2005.02504.x>.
46. Ribeiro-Vaz I, Santos C, Da Costa-Pereira A, Cruz-Correia R. Promoting spontaneous adverse drug reaction reporting in hospitals using a hyperlink to the online reporting form: an ecological study in Portugal. *Drug Saf*. 2012. <https://doi.org/10.2165/11597190-000000000-00000>.
47. Güner MD, Ekmekci PE. Healthcare professionals' pharmacovigilance knowledge and adverse drug reaction reporting behavior and factors determining the reporting rates. *J Drug Assess*. 2019. <https://doi.org/10.1080/21556660.2019.1566137>.
48. Matos C, Härmak L, Van Hunsel F. Patient reporting of adverse drug reactions: an international survey of national competent authorities' views and needs. *Drug Saf*. 2016. <https://doi.org/10.1007/s40264-016-0453-6>.
49. Hadi MA, Neoh CF, Zin RM, Elrggal M, Cheema E. Pharmacovigilance: pharmacists' perspective on spontaneous adverse drug reaction reporting. *IPRP*. 2017. <https://doi.org/10.2147/IPRP.S105881>.

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3.3.1 Supplemental information: Comparative Analysis of Information Provided in German Adverse Drug Reaction Reports Sent by Physicians, Pharmacists and Consumers

1 [Supplementary information:](#)

2 [Article information:](#)

3 [Article title:](#)

4 Comparative Analysis of Information Provided in German Adverse Drug Reaction Reports sent by
5 Physicians, Pharmacists and Consumers

6 [Journal name](#)

7 Drug Safety

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19 Supplementary tables and figures

20 Table Appendix 1: Further descriptive analysis of ADR reports per reporter type.

	Total (%total)	Physicians' reports (% of total / %of physicians' reports)	Pharmacists' reports (% of total / %of pharmacists' reports)	Consumer reports (% of total / %of consumers' reports)
Number of reports coded with seriousness hospitalisation				
Yes	21,686 (9.3%)	13,706 (63.2%/19.6%)	4,523 (20.9%/10.7%)	3,457 (15.9%/2.9%)
No	82,027 (35.1%)	21,489 (26.2%/30.7%)	14,563 (17.8%/34.3%)	45,975 (56.0%/38.0%)
Not Available	129,803 (55.6%)	34,781 (26.8%/49.7%)	23,310 (18.0%/55.0%)	71,712 (55.2%/59.2%)
Number of reports coded with seriousness death				
Yes	2,575 (1.1%)	1,967 (76.4%/2.8%)	189 (7.3%/0.4%)	419 (16.3%/0.3%)
No	85,737 (36.7%)	23,745 (27.7%/33.9%)	14,877 (17.4%/35.1%)	47,115 (55.0%/38.9%)
Not Available	145,204 (62.2%)	44,264 (30.5%/63.3%)	27,330 (18.8%/64.5%)	73,610 (50.7%/60.8%)
Number of reports per agegroup				
0-9 years	3,890 (1.7%)	1,660 (42.7%/2.4%)	604 (15.5%/1.4%)	1,626 (41.8%/1.3%)
10-19 years	5,385 (2.3%)	2,352 (43.7%/3.4%)	676 (12.6%/1.6%)	2,357 (43.8%/1.9%)
20-29 years	11,574 (5.0%)	3,388 (29.3%/4.8%)	1,337 (11.6%/3.2%)	6,849 (59.2%/5.7%)
30-39 years	14,820 (6.3%)	4,909 (33.1%/7.0%)	1,898 (12.8%/4.5%)	8,013 (54.1%/6.6%)
40-49 years	15,778 (6.8%)	5,346 (33.9%/7.6%)	2,582 (16.4%/6.1%)	7,850 (49.8%/6.5%)
50-59 years	22,957 (9.8%)	8,015 (34.9%/11.5%)	4,200 (18.3%/9.9%)	10,742 (46.8%/8.9%)
60-69 years	22,689 (9.7%)	8,175 (36.0%/11.7%)	4,727 (20.8%/11.1%)	9,787 (43.1%/8.1%)
70-79 years	23,407 (10.0%)	7,610 (32.5%/10.9%)	5,352 (22.9%/12.6%)	10,445 (44.6%/8.6%)
80-89 years	13,713 (5.9%)	4,387 (32.0%/6.3%)	3,381 (24.7%/8.0%)	5,945 (43.4%/4.9%)
90-99 years	1,702 (0.7%)	629 (37.0%/0.9%)	454 (26.7%/1.1%)	619 (36.4%/0.5%)
>99 years	37 (0%)	15 (40.5%/0%)	12 (32.4%/0%)	10 (27.0%/0%)
Not Specified	97,564 (41.8%)	23,490 (24.1%/33.6%)	17,173 (17.6%/40.5%)	56,901 (58.3%/47.0%)
Age distribution				
	Total	Physician	Pharmacist	Consumer
Minimum age	0	0	0	0
First quartile	38	38	47	36
Median age	57	56	62	54
Third quartile	71	71	75	70
Maximum age	112/120 ¹	112/120 ¹	105	105

¹ one case with the age 120 years was found. This case may be coded incorrectly. The second highest value was 112 years.

24 Legend Table Appendix 1. Table Appendix 1 shows further descriptive analysis of the total dataset
25 and the sub-datasets (physician, pharmacist, consumer) with regard to the classification seriousness
26 death, seriousness hospitalisation, the number of reports per age group and further specification of
27 the age of the patients.

28 *Table Appendix 2: vigiGrade completeness scores for all reports, serious reports and non serious reports from all three reporter types*

	Total			Physicians' reports			Pharmacists' reports			Consumer reports		
	All	Serious		All	Serious		All	Serious		All	Serious	
		Yes	No		Yes	No		Yes	No		Yes	No
Number of reports	233,516	55,758	177,758	69,976	32,039	37,937	42,396	7,558	34,838	121,144	16,161	104,983
Mean vigiScore	0.4	0.5	0.4	0.5	0.5	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Standard deviation of vigiScores	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.2	0.3	0.3	0.2	0.3
Minimum vigiScore	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
First quartile	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Median vigiScore	0.4	0.4	0.4	0.4	0.4	0.4	0.3	0.2	0.3	0.4	0.4	0.4
Third quartile	0.6	0.6	0.6	0.6	0.7	0.5	0.5	0.4	0.5	0.6	0.6	0.6
Maximum vigiScore	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Interquartile range Vigiscores	0.4	0.4	0.4	0.4	0.4	0.3	0.3	0.2	0.4	0.4	0.4	0.4

29

30 Table appendix 2 legend: Table appendix 2 shows the distribution of the vigiGrade completeness score calculated for all reports, serious reports and non-

31 serious reports altogether and for each reporter type (physician, pharmacist and consumer).

32 *Table Appendix 3: Number of serious and non-serious reports for each reporter type with report,*
 33 *patient, drug and ADR related information.*

Which Information reported									
	Physician [%]			Pharmacist [%]			Consumer [%]		
	All	Serious		All	Serious		All	Serious	
Observation		Yes	No		Yes	No		Yes	No
Report related factors									
Report Type ¹	69,976 [100%]	32,039 [100%]	37,937 [100%]	42,396 [100%]	7,558 [100%]	34,838 [100%]	121,144 [100%]	16,161 [100%]	104,983 [100%]
Seriousness ²	69,976 [100%]	32,039 [100%]	37,937 [100%]	42,396 [100%]	7,558 [100%]	34,838 [100%]	121,144 [100%]	16,161 [100%]	104,983 [100%]
Country ¹	69,976 [100%]	32,039 [100%]	37,937 [100%]	42,396 [100%]	7,558 [100%]	34,838 [100%]	121,144 [100%]	16,161 [100%]	104,983 [100%]
Narrative	66,534 [95.1%]	31,479 [98.3%]	35,055 [92.4%]	40,356 [95.2%]	7,493 [99.1%]	32,863 [94.3%]	117,958 [97.4%]	16,076 [99.5%]	101,882 [97.0%]
Patient related factors									
Sex	66,755 [95.4%]	30,895 [96.4%]	35,860 [94.5%]	41,007 [96.7%]	7,423 [98.2%]	33,584 [96.4%]	117,918 [97.3%]	15,651 [96.8%]	102,267 [97.4%]
Age	46,486 [66.4%]	23,517 [73.4%]	22,969 [60.5%]	25,223 [59.5%]	6,008 [79.5%]	19,215 [55.2%]	64,243 [53.0%]	9,228 [57.1%]	55,015 [52.4%]
Height	20,854 [29.8%]	10,886 [34.0%]	9,968 [26.3%]	9,390 [22.1%]	2,443 [32.3%]	6,947 [19.9%]	37,851 [31.2%]	4,718 [29.2%]	33,133 [31.6%]
Weight	22,188 [31.7%]	11,664 [36.4%]	10,524 [27.7%]	9,294 [21.9%]	2,500 [33.1%]	6,794 [19.5%]	38,510 [31.8%]	4,921 [30.4%]	33,589 [32.0%]
Medical history	40,269 [57.5%]	20,685 [64.6%]	19,584 [51.6%]	14,927 [35.2%]	2,855 [37.8%]	12,072 [34.7%]	61,545 [50.8%]	9,630 [59.6%]	51,915 [49.5%]
Drug related factors									
Action taken with	40,365 [57.7%]	18,166 [56.7%]	22,199 [58.5%]	20,948 [49.4%]	3,292 [43.6%]	17,656 [50.7%]	52,469 [43.3%]	7,918 [49.0%]	44,551 [42.4%]
Dose	38,320 [54.8%]	17,924 [55.9%]	20,396 [53.8%]	18,052 [42.6%]	2,709 [35.8%]	15,343 [44.0%]	66,747 [55.1%]	8,965 [55.5%]	57,782 [55.0%]
Indication	49,178 [70.3%]	23,028 [71.9%]	26,150 [68.9%]	19,353 [45.6%]	2,644 [35.0%]	16,709 [48.0%]	61,211 [50.5%]	9,908 [61.3%]	51,303 [48.9%]
Concomitant drugs	19,678 [28.1%]	12,398 [38.7%]	7,280 [19.2%]	11,153 [26.3%]	4,254 [56.3%]	6,899 [19.8%]	24,059 [19.9%]	4,016 [24.8%]	20,043 [19.1%]
ADR related factors									
Outcome	38,890 [55.6%]	18,658 [58.2%]	20,232 [53.3%]	19,925 [47.0%]	2,881 [38.1%]	17,044 [48.9%]	66,332 [54.8%]	9,406 [58.2%]	56,926 [54.2%]
Time to onset	25,832 [36.9%]	13,791 [43.0%]	12,041 [31.7%]	13,033 [30.7%]	1,806 [23.9%]	11,227 [32.2%]	56,224 [46.4%]	7,766 [48.1%]	48,458 [46.2%]

34 ¹Category was part of the filter criteria

35 ²Automatically assigned to all reports

36 Legend table appendix 3: OR= Odds Ratio; CI= 95% confidence interval

37 *Table Appendix 4: Logistic regression analysis of serious and non-serious reports by each reporter type*

Logistic regression analysis			
Observation	OR [+/- 95.0% CI], p-value physician serious (reference) vs. Physician non serious	OR [+/- 95.0% CI], p-value pharmacist serious (reference) vs. pharmacist non serious	OR [+/- 95.0% CI], p-value consumer serious (reference) vs. consumer non serious
Report related factors			
Narrative	0.2 [0.2-0.2]***	0.1 [0.1-0.2]***	0.1 [0.1-0.2]***
Patient related factors			
Sex	0.9 [0.8-0.9]***	0.9 [0.7-1.1]	0.9 [0.7-1.1]
Age	0.7 [0.7-0.7]***	0.4 [0.4-0.4]***	0.4 [0.4-0.4]***
Height	1.1 [1.0-1.3]**	1.1 [0.9-1.3]	1.1 [0.9-1.3]
Weight	0.8 [0.7-0.8]***	0.5 [0.4-0.6]***	0.5 [0.4-0.6]***
Medical history	0.7 [0.7-0.7]***	0.8 [0.8-0.9]***	0.8 [0.8-0.9]***
Drug related factors			
Action taken with drug	1.3 [1.3-1.4]***	1.2 [1.1-1.2]***	1.2 [1.1-1.2]***
Dose	1.2 [1.1-1.2]***	1.4 [1.3-1.4]***	1.4 [1.3-1.4]***
Indication	1.1 [1.0-1.1]***	1.9 [1.8-2.1]***	1.9 [1.8-2.1]***
Concomitant drugs	0.4 [0.4-0.5]***	0.2 [0.2-0.2]***	0.2 [0.2-0.2]***
ADR related factors			
Outcome	1.0 [1.0-1.1]	1.7 [1.6-1.8]***	1.7 [1.6-1.8]***
Time to onset	0.7 [0.7-0.7]***	1.5 [1.4-1.6]***	1.5 [1.4-1.6]***

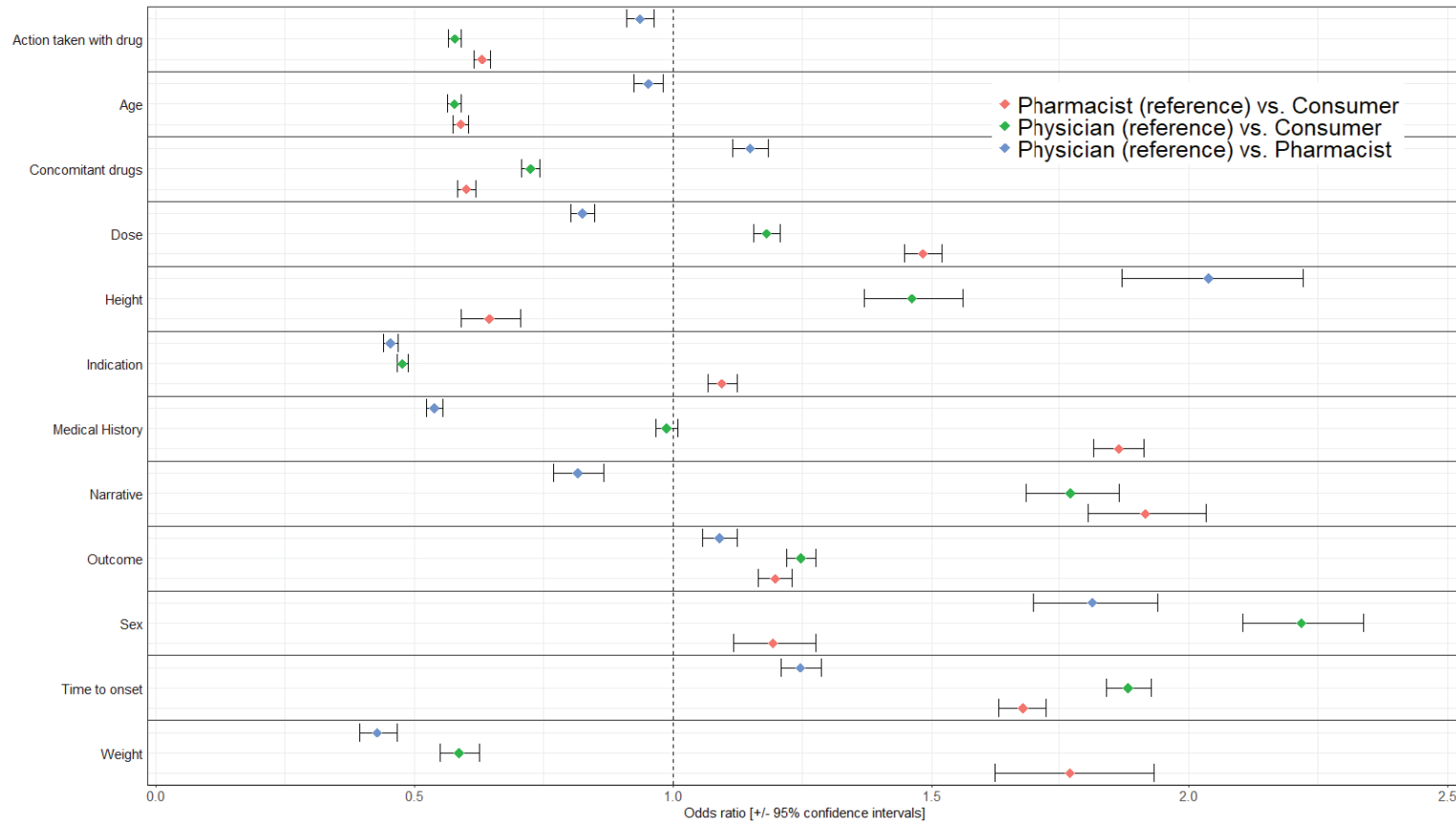
38

39 p-values coded as: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

40 OR= Odds Ratio; CI= 95% confidence interval

41 Legend table appendix 4: Table appendix shows the results of the logistic regression analyses for
 42 serious vs. non-serious reports for physicians', consumers' and pharmacists' reports including report,
 43 patient, drug and ADR related information as co-variables. Note, that if the upper CI was lesser than
 44 1, we assumed that the observation was more frequently reported for the serious reports. If the
 45 lower CI was greater than 1 we assumed that the observation was more frequently reported in non-
 46 serious reports.

47 *Figure 4: Forest plot of the results of the logistic regression analyses for each comparison.*



48

49 Figure 4 legend: Figure 4 shows the odds ratio (OR) and their 95% confidence intervals (CI) for each logistic regression analysis (pharmacist versus consumer,
 50 physician versus consumer, physician versus pharmacist). The x-axis indicates the value of the OR and the 95% CI. Y-axis indicates the information observed. All
 51 three different comparisons are indicated by different colours of the OR (pharmacists versus consumers= red OR ; physicians versus consumers= green OR;
 52 physicians versus pharmacists blue OR)

4. Discussion with references

The analyses described within this dissertation provide substantial insights into ADR in children, females and males as well as on the information contained in spontaneous reports by different reporter types. Chosen key findings as well as exemplary selected correlations between the individual analyses are presented below.

4.1 Sex, drugs and ADR

In our study regarding sex-specific differences of reported ADR, the overall share of both sexes was well balanced in the two data sets analysed. Therein we were able to identify certain aspects being more frequently reported either for females or males. These referred to different suspected drugs, ADR and drug-ADR combinations. Among them no clear pattern was observed, indicating either females or males being affected more often. Eventually, after considering the prescription data, a higher number of drug-ADR combinations remained for males compared to females. These findings do not directly correspond with the findings of various studies concluding that females were more prone to experience an ADR in general (Evans et al., 2005; Madla et al., 2021; Martin et al., 1998; Pont et al., 2014; Yadesa et al., 2021; Zopf et al., 2008). But this discrepancy could be related to our focus on reports describing a hospitalisation or a prolongation of it. Consequently our analysis focussed on serious reports. Thus it rather tends to strengthen the results of a review by Brabete et al. (2022). They found that females seem to have more ADR in general, but especially serious ADR were more often found in male patients.

Similar patterns potentially supporting this hypothesis could be derived from our analysis of the information included in the reports. Therein especially reports from pharmacists and consumers, mainly classified as non-serious, considerably referred to more female than male patients. Contrary, the distribution of both sexes was almost equal in reports from physicians, in which almost every second report was classified as serious. However, these findings might also be influenced by other factors. Among these are, for example, a higher use of drugs by females, along with higher willingness of females to report ADR themselves (Leone et al., 2013; Madla et al., 2021; Watson et al., 2019).

A rather well-balanced sex distribution, partially including more male patients, was found in our analysis of ADR related hospitalisations in children. Here, solely in the group of 13-

to 17-year-olds considerably more females were included. This finding could be affected by the fact that females within this age group use drugs more frequently than males (Knopf et al., 2019). Further, it could be attributable to the circumstance that drug related suicide attempts are most frequent in this particular age group (Dubrall et al., 2021) and females more often tend to suicide in this age (Zygo et al., 2019).

A main advantage of our study on sex-specific differences lays in the correlation with prescription data. Most identified sex-specific drug-ADR combinations did not remain more frequently reported either for females (21 of 31 drug-ADR combinations) or males (19 of 40) after the connection with them. This indicates that a large proportion of ADR related hospitalisation or its prolongation are attributable to sex-specific higher prescribing frequencies of certain drugs. Rodenburg et al. (2011) demonstrated this likewise. Those drug-ADR combinations found to be sex-specific i) in both data sources and ii) remaining sex-specific after correlation with prescription data, indicate a substantial probability to be attributable to sex related physiological factors (Farkouh et al., 2020; Madla et al., 2021). For these combinations, potential causes were identifiable in the scientific literature (chapter 3.1). The findings of this study emphasize the importance to investigate sex-specific ADR. Further studies are needed to identify the underlying conditions and to enable efficient measures for prevention.

4.2 Children and ADR

Similarly, in our study on ADR in children, we identified several identical, frequently reported suspected drugs and related reactions in both data sets observed. For instance, Methylphenidate and Insulin Aspart were among the five most frequently suspected drugs. For the latter mentioned it was striking that a large proportion of these reports described conditions such as application problems indicating a medication error. Studies have shown that a standardised process of insulin administration in hospitals, double-checking the calculated dose (Lawson et al., 2022) and appropriate training of children and their parents are effective measures to avoid these specific medication errors (Baharvand and Hormozi, 2019; Zysberg and Lang, 2015). Therefore it seems important to repeatedly draw attention to this problem (Rinke et al., 2014). Not only this medication error appears to occur specifically often among children, but the exact frequency of medication errors remains to be uncertain so far (Azar et al., 2021; Ghaleb et al., 2006; Kaushal, 2001; Miller

et al., 2007). Based on these insights, it seems imperative to further investigate medication errors among children in more depth.

4.3 Information included in spontaneous reports from physicians, pharmacists and consumers

In our analysis of the information included in the reports from physicians, pharmacists and consumers (chapter 3.3) we investigated a fairly up-to-date and largely complete data set of German spontaneous reports from EudraVigilance. Both studies described above clearly highlighted the advantage to narrow down spontaneous reports into specific subgroups. As a result, it is possible to identify groups at higher risk more accurately, subsequently develop targeted root cause analyses and measures (Moore et al., 2019). From this perspective most reports in our analysis of the information included in the reports were suitable for sex stratification as they contained a respective information thereon (95.4% - 97.3%). However, age was reported in scarcely more than half of all reports from consumers (53.0%) and in a slightly higher share in those from pharmacists (59.5%) and physicians (66.4%). Considering the special characteristics of different demographic groups already described in detail, a lack of this information constitutes a remarkable limitation to the further utilisation of the spontaneous reports in this regard.

Additionally, we were able to identify differences in the overall presence of information relevant for pharmacovigilance within the reports of physicians, pharmacists or consumers. As an example, physicians more often mentioned the indication of a suspected drug in their reports (70.3%) compared to consumers (50.5%) and pharmacists (45.6%). Based on these findings encouragement specifically addressed to each group in order remind them of the importance of the spontaneous reporting system is recommended. Alongside, the essential need for reports to be as comprehensive as possible should be highlighted (Al Dweik et al., 2017; Alomar et al., 2020; Costa et al., 2023; Durrieu et al., 2016; Gonzalez-Gonzalez et al., 2013; Hasford et al., 2002; Li et al., 2020; Inch et al. 2012). As a possible hypothesis, the interdisciplinary exchange of physicians, pharmacists and consumers could enhance the amount of information included (Leone et al., 2013; Nicol et al., 2019). In addition, a simplification of the reporting process, for instance by allowing direct transmission of data from electronic patient data to the reports, could be helpful. These measures could minimise the time required for

reporting, which is often described as a burden, especially for healthcare professionals (Hohl et al., 2018; Li et al., 2020; Routledge and Bracchi, 2023).

4.4 Further strengths and limitations

Besides the advantages already mentioned, the two analyses described in chapter 3.1 and chapter 3.2 highlight the benefits resulting from a comparative analysis of two data sets collected with different methodological approaches. Thus, findings emerging from two different sources appear to contribute to a more comprehensive understanding than those obtained from one source alone (Lavertu et al., 2021; Trifirò et al., 2018). A similar approach of analysing two differently collected data sets could on the one hand be suitable to investigate specific types of reactions representing ADR, for example anaphylactic reactions (Christ et al., 2023, 2024). On the other hand it might be helpful to evaluate new data sources, for example insurance data, for their subsequent use in the context of pharmacovigilance (Christ et al., 2022).

Despite all the benefits of our methodological approaches, the findings presented are subject to certain limitations. An inherent limitation of spontaneous reports is underreporting, which depends on factors such as if the ADR is already known or not and if the drug under suspicion has been approved for a long time or just recently. But its exact extent remains unknown (Al Dweik et al., 2017; García-Abeijon et al., 2023; Hazell and Shakir, 2006; Lopez-Gonzalez et al., 2009). Another limitation of the studies shown is that, with the exception of a random sample of the spontaneous reports from the study on ADR in children, we considered and analysed only those information that was available in a structured, tabular format. Information solely available in free text form, as it can be provided in the spontaneous reports' narratives, was not taken into account. Approaches based on natural language processing, as shown by Kim et al. (2023), could enable and facilitate to incorporate such information in the future. Furthermore, except for several reports within the analysis on ADR in children, we did not assess the causality between the suspected drug and the potential ADR (Edwards et al., 1990; UMC and WHO, 2013). The main reason for this was that a causality assessment, especially for data sets this large, requires a very time-consuming evaluation on a single report level. Artificial intelligence approaches might once again become a valuable instrument in this context henceforward (Cherkas et al., 2022).

4.5 References

Al Dweik R, Stacey D, Kohen D, Yaya S. Factors affecting patient reporting of adverse drug reactions: a systematic review. *Br J Clin Pharmacol* 2017; 83: 875–883

Alomar M, Tawfiq AM, Hassan N, Palaian S. Post marketing surveillance of suspected adverse drug reactions through spontaneous reporting: current status, challenges and the future. *Ther Adv Drug Saf* 2020; 11: 1–11

Azar C, Allué D, Valnet-Rabier MB, Chouchana L, Rocher F, Durand D, Grené-Lerouge N, Saleh N, Maison P. Patterns of medication errors involving pediatric population reported to the French Medication Error Guichet. *Pharm Pract (Granada)* 2021; 19: 2360

Baharvand P, Hormozi M. Can parents' educational level and occupation affect perceived parental support and metabolic control in adolescents with type 1 diabetes? *J Educ Health Promot* 2019; 8: 11

Banovac M, Candore G, Slattery J, Houyez F, Haerry D, Genov G, Arlett P. Patient Reporting in the EU: Analysis of EudraVigilance Data. *Drug Saf* 2017; 40: 629–645

Brabete AC, Greaves L, Maximos M, Huber E, Li A, Lê ML. A Sex- and Gender-Based Analysis of Adverse Drug Reactions: A Scoping Review of Pharmacovigilance Databases. *Pharmaceuticals (Basel)* 2022; 15: 298

Cherkas Y, Ide J, Van Stekelenborg J. Leveraging Machine Learning to Facilitate Individual Case Causality Assessment of Adverse Drug Reactions. *Drug Saf* 2022; 45: 571–582

Christ P, Dubrall D, Dölle-Bierke S, Francuzik W, Schmid M, Worm M, Sachs B. Abstracts of the 18th German Allergy Congress, Bonn, September 14–16, 2023 – P7.04 Arzneimittel-assoziierte anaphylaktische Reaktionen in Deutschland: Komplementäre deskriptive Analyse von Fällen des Anaphylaxie-Registers und Spontanberichten der Europäischen Nebenwirkungsdatenbank. *Allergo J Int* 2023; 32: 220–221

Christ P, Dubrall D, Schmid M, Dölle-Bierke S, Francuzik W, Worm M, Sachs B. 9th German Pharm-Tox Summit 2024 – P170 Drug-associated anaphylactic reactions in Germany: A complementary descriptive analysis of cases from the Anaphylaxis-Registry and spontaneous reports from the European Adverse Reaction Database (EudraVigilance). *Naunyn-Schmiedeberg's Arch Pharmacol* 2024; 397(Suppl1): 59

Christ P, Rischke N, Dubrall D, Scholle O, Stausberg J, Haug U, Sachs B, 2022. 29th Annual Meeting of the German Drug Utilisation Research Group (GAA) – WOLGA: Further development, optimization and application of an algorithm for the detection of serious adverse drug reactions based on claims data - first results of a sub-analysis focusing on clostridium difficile infections. <https://doi.org/10.3205/22GAA07> (date accessed: 08.08.2024)

Costa C, Abeijon P, Rodrigues DA, Figueiras A, Herdeiro MT, Torre C. Factors associated with underreporting of adverse drug reactions by patients: a systematic review. *Int J Clin Pharm* 2023; 45: 1349–1358

Dubrall D, Leitzen S, Toni I, Stingl J, Schulz M, Schmid M, Neubert A, Sachs B. Descriptive analysis of adverse drug reaction reports in children and adolescents from Germany: frequently reported reactions and suspected drugs. *BMC Pharmacol Toxicol* 2021; 22: 56

Durrieu G, Jacquot J, Mège M, Bondon-Guitton E, Rousseau V, Montastruc F, Montastruc JL. Completeness of Spontaneous Adverse Drug Reaction Reports Sent by General Practitioners to a Regional Pharmacovigilance Centre: A Descriptive Study. *Drug Saf* 2016; 39: 1189–1195

Edwards IR, Lindquist M, Wiholm BE, Napke E. Quality criteria for early signals of possible adverse drug reactions. *Lancet* 1990; 336: 156–158

Evans RS, Lloyd JF, Stoddard GJ, Nebeker JR, Samore MH. Risk Factors for Adverse Drug Events: A 10-Year Analysis. *Ann Pharmacother* 2005; 39: 1161–1168

Farkouh A, Riedl T, Gottardi R, Czejka M, Kautzky-Willer A. Sex-Related Differences in Pharmacokinetics and Pharmacodynamics of Frequently Prescribed Drugs: A Review of the Literature. *Adv Ther* 2020; 37: 644–655

García-Abeijon P, Costa C, Taracido M, Herdeiro MT, Torre C, Figueiras A. Factors Associated with Underreporting of Adverse Drug Reactions by Health Care Professionals: A Systematic Review Update. *Drug Saf* 2023; 46: 625–636

Ghaleb MA, Barber N, Franklin BD, Yeung VW, Khaki ZF, Wong IC. Systematic Review of Medication Errors in Pediatric Patients. *Ann Pharmacother* 2006; 40: 1766–1776

Gonzalez-Gonzalez C, Lopez-Gonzalez E, Herdeiro MT, Figueiras A. Strategies to Improve Adverse Drug Reaction Reporting: A Critical and Systematic Review. *Drug Saf* . 2013; 36: 317–328

Hasford J, Goettler M, Munter KH, Müller-Oerlinghausen B. Physicians' knowledge and attitudes regarding the spontaneous reporting system for adverse drug reactions. *J Clin Epidemiol* 2002; 55: 945–950

Hazell L, Shakir SAW. Under-Reporting of Adverse Drug Reactions: A Systematic Review. *Drug Saf* 2006; 29: 385–396

Hohl CM, Small SS, Peddie D, Badke K, Bailey C, Balka E. Why Clinicians Don't Report Adverse Drug Events: Qualitative Study. *JMIR Public Health Surveill* 2018; 4: e21

Inch J, Watson MC, Anakwe-Umeh S, Yellow Card Study Collaboration. Patient versus Healthcare Professional Spontaneous Adverse Drug Reaction Reporting: A Systematic Review. *Drug Saf* 2012; 35: 807–818

Kaushal R, Bates DW, Landrigan C, McKenna KJ, Clapp MD, Federico F, Goldmann DA. Medication Errors and Adverse Drug Events in Pediatric Inpatients. *JAMA* 2001; 285: 2114-2120

Kim S, Kang T, Chung TK, Choi Y, Hong Y, Jung K, Lee H. Automatic Extraction of Comprehensive Drug Safety Information from Adverse Drug Event Narratives in the Korea Adverse Event Reporting System Using Natural Language Processing Techniques. *Drug Saf* 2023; 46: 781–795

Knopf H, Sarganas G, Grams D, Du Y, Poethko-Müller C. Anwendung von Arznei- und Nahrungsergänzungsmitteln im Kindes- und Jugendalter in Deutschland: Ergebnisse aus KiGGS Welle 2. *Bundesgesundheitsbl* 2019; 62: 1215–1224

Lavertu A, Vora B, Giacomini KM, Altman R, Rensi S. A New Era in Pharmacovigilance: Toward Real-World Data and Digital Monitoring. *Clin Pharmacol Ther* 2021; 109: 1197–1202

Lawson SA, Hornung LN, Lawrence M, Schuler CL, Courter JD, Miller C. An Initiative to Reduce Insulin-Related Adverse Drug Events in a Children's Hospital. *Pediatrics* 2022; 149: e2020004937

Leone R, Moretti U, D'Incau P, Conforti A, Magro L, Lora R, Velo G. Effect of Pharmacist Involvement on Patient Reporting of Adverse Drug Reactions: First Italian Study. *Drug Saf* 2013; 36: 267–276

Li R, Zaidi STR, Chen T, Castelino R. Effectiveness of interventions to improve adverse drug reaction reporting by healthcare professionals over the last decade: A systematic review. *Pharmacoepidemiol Drug Saf* 2020; 29: 1–8

Lopez-Gonzalez E, Herdeiro MT, Figueiras A. Determinants of Under-Reporting of Adverse Drug Reactions: A Systematic Review. *Drug Saf* 2009; 32: 19–31

Madla CM, Gavins FKH, Merchant HA, Orlu M, Murdan S, Basit AW. Let's talk about sex: Differences in drug therapy in males and females. *Adv Drug Deliv Rev* 2021; 175: 113804

Martin RM, Biswas PN, Freemantle SN, Pearce GL, Mann RD. Age and sex distribution of suspected adverse drug reactions to newly marketed drugs in general practice in England: analysis of 48 cohort studies. *Br J Clin Pharmacol* 1998; 46: 505–511

Miller MR, Robinson KA, Lubomski LH, Rinke ML, Pronovost PJ. Medication errors in paediatric care: a systematic review of epidemiology and an evaluation of evidence supporting reduction strategy recommendations. *Qual Saf Health Care* 2007; 16: 116–126

Moore N, Berdaï D, Blin P, Droz C. Pharmacovigilance – The next chapter. *Therapie* 2019; 74: 557–567

Nicol C, Moulis F, Bondon-Guitton E, Durrieu G, Montastruc JL, Bagheri H. Does spontaneous adverse drug reactions' reporting differ between different reporters? A study in Toulouse Pharmacovigilance Centre. *Therapie* 2019; 74: 521–525

Pont L, Alhawassi T, Bajorek B, Krass I. A systematic review of the prevalence and risk factors for adverse drug reactions in the elderly in the acute care setting. *Clin Interv Aging* 2014; 9: 2079–2086

Rinke ML, Bundy DG, Velasquez CA, Rao S, Zerhouni Y, Lobner K, Blanck JF, Miller MR. Interventions to Reduce Pediatric Medication Errors: A Systematic Review. *Pediatrics* 2014; 134: 338–360

Rodenburg EM, Stricker BHC, Visser LE. Sex-related differences in hospital admissions attributed to adverse drug reactions in the Netherlands. *Br J Clin Pharmacol* 2011; 71: 95–104

Routledge PA, Bracchi R. Improving the spontaneous reporting of suspected adverse drug reactions: An overview of systematic reviews. *Br J Clin Pharmacol* 2023; 89: 2377–2385

Trifirò G, Sultana J, Bate A. From Big Data to Smart Data for Pharmacovigilance: The Role of Healthcare Databases and Other Emerging Sources. *Drug Saf* 2018; 41: 143–149

Uppsala Monitoring Centre (UMC), World Health Organization (WHO), 2013: The use of the WHO-UMC system for standardised case causality assessment. <https://www.who.int/publications/m/item/WHO-causality-assessment> (date accessed: 08.08.2024)

Watson S, Caster O, Rochon PA, Den Ruijter H. Reported adverse drug reactions in women and men: Aggregated evidence from globally collected individual case reports during half a century. *EClinicalMedicine* 2019; 17

Yadesa TM, Kitutu FE, Deyno S, Ogwang PE, Tamukong R, Alele PE. Prevalence, characteristics and predicting risk factors of adverse drug reactions among hospitalized older adults: A systematic review and meta-analysis. *SAGE Open Med* 2021; 9: 1–14

Zopf Y, Rabe C, Neubert A, Gaßmann KG, Rascher W, Hahn EG, Brune K, Dormann H. Women encounter ADRs more often than do men. *Eur J Clin Pharmacol* 2008; 64: 999–1004

Zygo M, Pawłowska B, Potembska E, Dreher P, Kapka-Skrzypczak L. Prevalence and selected risk factors of suicidal ideation, suicidal tendencies and suicide attempts in young people aged 13–19 years. *Ann Agric Environ Med* 2019; 26: 329–336

Zysberg L, Lang T. Supporting parents of children with type 1 diabetes mellitus: a literature review. *Patient Intell* 2015; 7: 21–31

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