The phenotype of adverse drug effects: Do emergency visits due to adverse drug reactions look different in older people? Results from the ADRED study

Katja S. Just1 | Harald Dormann2 | Marlen Schurig3 | Miriam Böhme3 | Michael Steffens3 | Bettina Plank-Kiegele2 | Kristin Ettrich4 | Thomas Seufferlein4 | Ingo Gräff5 | Svitlana Igel6 | Severin Schricker7 | Simon U. Jaeger6,8 | Matthias Schwab6,8,9 | Julia C. Stingl1

1Institute of Clinical Pharmacology, University Hospital of RWTH Aachen, Aachen, Germany
2Central Emergency Department, Hospital Fürth, Fürth, Germany
3Research Department, Federal Institute for Drugs and Medical Devices, Bonn, Germany
4Internal Medicine Emergency Department, Ulm University Medical Centre, Ulm, Germany
5Interdisciplinary Emergency Department (INZ), University Hospital of Bonn, Bonn, Germany
6Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, Germany
7Department of Internal Medicine, Division of General Internal Medicine and Nephrology, Robert-Bosch-Hospital, Stuttgart, Germany
8Department of Clinical Pharmacology, University of Tuebingen, Tuebingen, Germany
9Department of Pharmacy and Biochemistry, University of Tuebingen, Tuebingen, Germany

Aims: Older patients in particular suffer from adverse drug reactions (ADR) when presenting in the emergency department. We aimed to characterise the phenotype of those ADRs, to be able to recognise an ADR in older patients.

Methods: Cases of ADRs in emergency departments collected within the multicentre prospective observational study (ADRED) were analysed (n = 2215). We analysed ADR-associated diagnoses, symptoms and their risk profiles. We present frequencies and odds ratios (OR) with 95% confidence intervals for adults (18–64 years) compared to older adults (≥65 years; young–old 65–79, old–old ≥80 years) and regression coefficients (B) for each year of age.

Results: Most prominent differences were seen for drug-associated confusion, dehydration, and bradycardia (OR 6.70 [1.59–28.27], B .054; OR 6.02 [2.41–15.03], B .081, and 4.82 [2.21–10.54], B .040), more likely seen in older adults. Bleedings were reported in all age groups, but gastrointestinal bleedings occurred with more than doubled chance in older adults (OR 2.46 [1.77–3.41], B .030), likewise did other bleedings such as haemorrhage from respiratory passages (OR 2.89 [1.37–6.11], B.036). Falls were more likely in older adults (OR 2.84 [1.77–4.53], B .030), while dizziness was frequent in both age groups.

Conclusion: Our data point to differences in symptoms of ADRs between adults and older individuals, with dangerous drug-associated phenomena in the older adult such as bleedings or falls. Physicians should consider drug-associated origins of symptoms in older adults with an increased risk for serious health problems.

KEYWORDS
adverse drug reaction, emergency departments, network analysis, older adults, symptoms

The authors confirm that the PI for this paper is Julia C. Stingl and that she had direct clinical responsibility for patients.

German Clinical Trial Register: DRKS-ID: DRKS00008979.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2020 The Authors. British Journal of Clinical Pharmacology published by John Wiley & Sons Ltd on behalf of British Pharmacological Society
1 | INTRODUCTION

Adverse drug reactions (ADRs) are common, can lead to emergency department (ED) visits, and hospital admissions.1–9 Thereby ADRs can generate relevant health care costs.1,2 Moreover, ADRs can be harmful and followed by complications leading to morbidity or even death.5,6 Older adults are at especially high risk for experiencing ADRs as they are commonly multimedicated and vulnerable due to underlying conditions.1,3,10

With increasing age, a raising number of medications is commonly taken.11 This alters the risk for drug–drug interactions that can, amongst other problems, result in ADRs.12,13 The higher risk for ADRs in older adults may be further aggravated due to pharmacokinetic and pharmacodynamic changes that develop with aging.14

While many data exist about prevalence and drugs involved in ADRs, it is still not trivial to diagnose an ADR as it can present with many different symptoms such as allergic reactions, gastrointestinal bleeding or nausea.

Often most challenging when diagnosing an ADR is to differentiate the symptom as a response to a drug from a symptom as a sign of the underlying disease. Older adults take more drugs, have more comorbidities, more serious ADRs, tend to stay longer in hospitals, and have a higher risk of mortality compared to younger individuals presenting with side effects in an emergency.6,9 This challenge might be most prominent in the context of older multimorbid patients.6,15 Older adults have been reported to present to the ED with unspecific symptoms as a response to a drug.16 In addition, older adults are more often affected by medication errors that result in clinical symptoms, whereas younger adults do not necessarily react with severe symptoms to a medication error.17 The challenge to differentiate a symptom as a response to a drug from a symptom due to an underlying disease needs to be taken to increase an older adult’s health status and well-being, because the drug therapy might be modifiable in contrast to the presence of a chronic disease.

An ADR is often not presented by 1 specific symptom only but might rather be a complex syndrome presented by many symptoms according to severity. Therefore, analysing symptoms of ADRs might benefit from application of association rules and frequent set analyses. Frequent set analyses can thereby detect common combinations of symptoms, while association rule analyses could unmask combinations that arise more frequently than one would expect under statistical independence. Those methods were already used for example to assess comorbidity patterns in the elderly,18 use of drugs in the elderly,19 to identify patterns in gene expression data20 or to find combinatorial biomarkers for Alzheimer’s disease.21

Here, we present an analysis of the pivotal symptoms that patients presented during ED visits in this cohort of ADR cases. The aim of this analysis is to identify typical symptom profiles that may guide health professionals considering a potential association with drug therapy. We elaborated symptom and working diagnoses profiles in adults vs older patients and compared the nature and severity of the symptoms presented. The aim of this study is to understand common patterns of symptoms of ADRs leading to ED visits in adults and older adults.

2 | METHODS

2.1 | Study population

The ADR case cohort of the multicentre prospective observational study trial named Adverse Drug Reactions in Emergency Departments (ADRED; DRKS-ID: DRKS00008979) was analysed. Within the ADRED study, we collected cases presenting with an ADR to 4 large hospital EDs of tertiary care and academic teaching hospitals in Germany. In general, in the study sites around 6.5% of ED visits can be attributed to ADRs. Within the feasibility study, it got evident that the enrolment of ADRs requiring informed consent was mostly possible in patients who stayed longer and were subsequently hospitalised. During short visits to the ED, it was mostly not possible to recruit patients for the ADRED study. Therefore, in the cohort of recognised ADR cases, most data are derived from hospitalised patients.6 Further details on enrolment and study design are published elsewhere.6,9

In brief, inclusion criteria were adult patients, presenting with symptoms that were seen in a possible, probable or certain relationship to a drug (ADR) according to the World Health Organization–Uppsala Monitoring Centre system for causality assessment by a trained physician or a pharmacist.22 Those personnel were experienced in emergency care, clinical pharmacy and drug safety, respectively. Regular telephone conferences were conducted for increasing consistency between study centres. Informed consent was assessed by study personnel. In patients who were not able to provide written informed consent due to the seriousness of the ADR (e.g. comatose,
intubated), only clinical data were included. All other participants agreed in participation and provided written informed consent. All cases that were enrolled between December 2015 and March 2018, were included in the analysis. The study was approved by the responsible ethical committee of the University of Bonn (202/15).

Within our previous analysis we showed that older adults are often affected by ADRs leading to ED presentation with a median age of 73 years with 2/3 being aged 65 years and older.

### 2.2 | Data collection

Demographic and clinical data (such as age, sex and seriousness of ADRs) were analysed. Current drug intake was investigated from the documented cases and causality assessment has been conducted by a physician or pharmacists for every drug taken per case.

All symptoms documented on arrival in the ED that were seen as related to the suspected drug were classified as low-level terms (LLTs) according to the medical terminology for drug regulatory authorities (MedDRA). The MedDRA terminology is organised as a hierarchy and LLTs are grouped and connected to a preferred term (PT). Likewise, a group of PTs is linked to an affected system organ class (SOC). Symptoms were defined on a LLT level and analysed on the PT and on the SOC level following the regulatory approach.

### 2.3 | Statistical analysis

Descriptive characteristics of the study population were calculated for adults (age <65 years), young-old (age 65–79 years), and old-old (age ≥80 years). Categorical variables are shown as absolute numbers and percentages. We checked for normality using Kolmogorov–Smirnov test. Continuous variables are presented as medians with interquartile ranges [IQR]. Continuous variables were compared using Kruskal–Wallis test and categorical variables were compared using Mantel–Haenszel test, with both testing for linear trends. Some patients already enrolled returned in the ED due to an ADR while the study trial was still ongoing (n = 122). This analysis refers to cases and not patients within the ADRED study.

Admission diagnoses and symptoms were analysed; symptoms on the PT and the SOC level. Frequency of admission diagnoses and of most common symptoms per organ class (SOC) found in >3% of older adults (age ≥ 65 years) were compared. The Mantel–Haenszel test was used testing for a linear trend over all 3 age groups. An odds ratio (OR) together with a 95% confidence interval (CI) was calculated for admission diagnoses and symptoms comparing adults and older adults in general. We calculated differences in frequencies in percentages between adults and older adults. If the relative frequency was equal, the odds would be 1. Odds above 1 signify a higher chance of presentation in older adults, and therefore a higher risk at older age. Therefore, the OR describes the chance to present to the ED due to an ADR with the admission diagnosis or the described symptom respectively as an older adult, compared to a younger adult. Further, we conducted logistic regression analyses for each admission diagnosis and symptom adjusting for age, sex, number of co-morbidities, and number of drugs taken. Thereby, we revealed regression coefficients for age. Regression coefficients can be interpreted as approximate extent in which the risk to present with a certain admission diagnosis or a symptom is changing with every year of age. The resulting significant OR and 95% CI for age per admission diagnoses and symptom are shown in a figure.

Frequency set analysis was done to detect common combinations of symptoms and to compare all 3 age groups. For the symptom pairs found in >2% of older adults, ORs and 95% CI were calculated showing the chance for being affected as an older adult by a symptom pair compared to an adult. We conducted an association rule analysis to detect also less frequent but interesting combinations of symptoms in all 3 age groups. Thereby, we analysed the dataset for symptom combinations per age group that occurred more frequently than expected by chance. This means, that the lift was defined as ≥1. The support, which represents the frequency of combination of symptoms, was set to 1% to detect also associations with low prevalence.

As we saw that those patients who died during the following hospital stay were in median 77 years old, we took a closer look at patients with death as outcome vs patients who could be discharged.

Association rule and frequent set analyses were performed using Python Version 3.7 with the frequent patterns tool of the Python library Mixtend (machine learning extensions). Results of characteristics and regression analyses were discussed nominally without correction for multiple testing. All analyses were undertaken using IBM SPSS Statistics Version 21.

### 3 | RESULTS

In total, 2215 ADR cases, 731 (33.0%) cases from adult patients (aged 18–64 years), 880 (39.7%) from young-old, and 604 (27.3%) cases from old-old patients were analysed. Characteristics of the study population are displayed in Table 1.

In all 3 age groups, the median number of symptoms that were documented when presenting to the ED was 2. There was a significant tendency towards having more comorbidities, intake of more drugs, more serious ADRs, and a more often seen and longer hospitalisation with raising age groups. Diseases of the circulatory and the genitourinary system became more common with increasing age. Likewise, the use of drugs used to treat diseases of the circulatory or the genitourinary system such as urologicals, β-blocking agents, diuretics, angiotensin converting enzyme inhibitors and angiotensin antagonists, cardiac glycosides and antithrombotics were more frequently taken with increasing age group. In contrast, infections, neoplasms, diseases of the nervous system, and mental and behavioural disorders were more common in younger adults, with antibiotics, antineoplastic and immunomodulating agents, systemic glucocorticoids, and antiepileptics taken more often by younger adults.

The International Classification of Diseases 10 level 2 diagnoses of adults, young-old and old-old patients causing the admission to
### TABLE 1  Characteristics of the study population (n = 2215) according to age group

|                          | Adults, n = 731 | Young-old, n = 880 | Old-old, n = 604 | Significance |
|--------------------------|-----------------|--------------------|-----------------|--------------|
| Age (y)                  | 51 [38, 58]     | 74 [70, 77]        | 84 [82, 87]     |              |
| Sex (male), n (%)        | 360 (49.2%)     | 495 (56.3%)        | 260 (43.0%)     | .048         |
| Hospitalized, n (%)      | 576 (78.8%)     | 823 (93.5%)        | 571 (94.5%)     | <.001        |
| No of drugs              | 3 [2, 8]        | 8 [5, 11]          | 8 [6, 10]       | <.001        |
| No of suspected drugs    | 1 [1, 2]        | 2 [1, 2]           | 1 [1, 2]        | <.001        |
| No of admission diagnoses| 1 [1, 2]        | 1 [1, 2]           | 2 [1, 2]        | .003         |
| No of comorbidities      | 3 [1, 5]        | 5 [3, 8]           | 5 [4, 7]        | <.001        |
| Length of stay (days)    | 3 [0, 7]        | 6 [3, 10]          | 6 [3, 9]        | <.001        |
| Seriousness, n (%)       |                |                    |                | <.001        |
| Non-serious harm         | 165 (22.6%)     | 58 (6.6%)          | 38 (6.3%)       |              |
| Hospitalization required | 525 (71.8%)     | 775 (88.1%)        | 537 (88.9%)     |              |
| Life-threatening          | 37 (5.1%)       | 45 (5.1%)          | 25 (4.1%)       |              |
| Persistent disability    | 0 (0.0%)        | 1 (0.1%)           | 1 (0.2%)        |              |
| Death                    | 4 (0.5%)        | 1 (0.1%)           | 3 (0.5%)        |              |
| Condition at discharge, n (%) |          |                    |                | .433         |
| Recovered                | 23 (3.1%)       | 34 (3.9%)          | 10 (1.7%)       |              |
| Not recovered            | 61 (8.3%)       | 65 (7.4%)          | 50 (8.3%)       |              |
| Condition improved       | 601 (82.2%)     | 703 (79.9%)        | 491 (81.3%)     |              |
| Persistent harm          | 2 (0.3%)        | 9 (1.0%)           | 6 (1.0%)        |              |
| Death                    | 11 (1.5%)       | 39 (4.4%)          | 25 (4.1%)       |              |
| Unknown                  | 33 (4.5%)       | 30 (3.4%)          | 22 (3.6%)       |              |
| No. of symptoms (preferred terms) | 2 [2, 4] | 2 [1, 4]          | 2 [1, 3]       | .005         |

### Drug classes taken

| Drug classes taken                                                 | Adults | Young-old | Old-old |
|-------------------------------------------------------------------|--------|-----------|---------|
| Antineoplastic and immunomodulating agents                        | 315 (8.6%) | 326 (4.4%) | 51 (1.1%) |
| Antithrombotics                                                   | 250 (6.8%) | 809 (10.9%) | 597 (12.3%) |
| Antibiotics                                                       | 133 (3.6%) | 75 (1.0%) | 46 (0.9%) |
| Systemic glucocorticoids                                          | 74 (2.0%) | 90 (1.2%) | 32 (0.7%) |
| Antipsychotics                                                    | 48 (1.4%) | 54 (0.7%) | 74 (1.5%) |
| Antidepressants                                                   | 130 (3.6%) | 210 (2.8%) | 143 (2.9%) |
| Antiparkinsonian medications                                     | 15 (0.4%) | 49 (0.7%) | 48 (1.0%) |
| Opioids                                                           | 93 (2.6%) | 151 (2.0%) | 105 (2.2%) |
| Non-opioid analgesics                                             | 219 (6.0%) | 260 (3.5%) | 208 (4.3%) |
| Antiepileptics                                                    | 81 (2.2%) | 125 (1.7%) | 64 (1.3%) |
| Hypnotics, sedatives and anxiolytics                              | 49 (1.3%) | 78 (1.1%) | 59 (1.2%) |
| Beta blocking agents                                              | 171 (4.7%) | 537 (7.2%) | 367 (7.5%) |
| Other cardiac preparations                                        | 27 (0.7%) | 55 (0.7%) | 41 (0.8%) |
| Cardiac glycosides and antiarrhythmics                            | 33 (0.9%) | 188 (2.5%) | 150 (3.1%) |
| Diuretics                                                         | 147 (4.0%) | 586 (7.9%) | 473 (9.7%) |
| ACE inhibitors and angiotensin antagonists                        | 184 (5.0%) | 483 (6.5%) | 390 (8.0%) |
| Calcium channel blockers                                          | 79 (2.2%) | 234 (3.2%) | 166 (3.4%) |
| Drugs used in diabetes                                            | 127 (3.5%) | 387 (5.2%) | 191 (3.9%) |
| Drugs for constipation                                            | 45 (1.2%) | 108 (1.5%) | 98 (2.0%) |
| Urologicals                                                       | 22 (0.6%) | 129 (1.7%) | 92 (1.9%) |
| Drugs for obstructive airway diseases                             | 129 (3.5%) | 287 (3.9%) | 138 (2.8%) |
| Drugs for acid related disorders                                  | 240 (6.6%) | 484 (6.5%) | 322 (6.6%) |
| Thyroid therapy                                                   | 128 (3.5%) | 243 (3.3%) | 136 (2.8%) |
the ED due to an ADR are pictured in table 2 (all with a prevalence of >3% in older adults).

Age had highest impact on being admitted for volume depletion and heart failure in ADR-cases. The adjusted regression coefficient (B) for age was .064 ($P < .001$, OR$_{age}$ 1.04 [1.02–1.07]) for volume depletion, meaning that the chance to present with ADR-associated volume depletion raises by approximately 6.4% for each year of age. The odds to present with volume depletion were significantly higher for older compared with younger adults (OR 4.32 [1.86–10.05]). The regression coefficient for heart failure was B .041 ($P = .002$, OR$_{age}$ 1.041 [1.02–1.07]) making a increase in chance by approximately 4.1% for each year of age and resulting in an OR of 5.10 [1.83–14.22]. Furthermore, the chances to present with ADR-associated bleeding got higher the older people were (haemorrhage from respiratory passages B .036, $P = .001$, OR$_{age}$ 1.04 [1.02–1.07] and OR 2.89 [1.37–6.11]; other anaemias B .034 ($P = .001$), OR$_{age}$ 1.03 [1.01–1.56] and OR 2.85 [1.51–5.41]; and gastrointestinal bleeding B .030, $P < .001$, OR$_{age}$ 1.03 [1.02–1.04] and OR 2.46 [1.77–3.41] (unspecified

### TABLE 1 (Continued)

| Drug classes taken            | Adults     | Young-old | Old-old |
|-------------------------------|------------|-----------|---------|
| Lipid modifying agents        | 129 (3.5%) | 400 (5.4%)| 270 (5.5%)|
| Antigout preparations         | 39 (1.1%)  | 150 (2.0%)| 104 (2.1%)|
| Vitamins                      | 86 (2.4%)  | 134 (1.8%)| 86 (1.8%)|
| Mineral supplements           | 72 (2.0%)  | 168 (2.3%)| 107 (2.2%)|
| Antinaemic preparations       | 61 (1.7%)  | 101 (1.4%)| 84 (1.7%)|

| ICD-10                      | Medical history of cases | Adults     | Young-old | Old-old |
|-------------------------------|--------------------------|------------|-----------|---------|
| A-B                          | Certain infectious and parasitic diseases | 32 (2.0%)  | 39 (1.2%) | 22 (1.0%)|
| C                            | Neoplasms                | 129 (7.9%) | 200 (6.3%)| 56 (2.6%)|
| D                            | Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism | 69 (4.2%)  | 118 (3.7%)| 86 (4.0%)|
| E                            | Endocrine, nutritional, and metabolic diseases | 263 (16.1%)| 547 (17.1%)| 355 (16.7%)|
| F                            | Mental and behavioural disorders | 117 (7.2%) | 128 (4.0%)| 100 (4.7%)|
| G                            | Diseases of the nervous system | 77 (4.7%)  | 145 (4.5%)| 79 (3.7%)|
| H                            | Diseases of the eye and adnexa/ear and mastoid process | 13 (0.8%)  | 23 (0.7%) | 16 (0.8%)|
| I                            | Diseases of the circulatory system | 286 (17.6%)| 702 (22.0%)| 530 (24.9%)|
| J                            | Diseases of the respiratory system | 88 (5.4%)  | 202 (6.3%)| 99 (4.7%)|
| K                            | Diseases of the digestive system | 100 (6.1%) | 148 (4.6%)| 116 (5.5%)|
| L                            | Diseases of the skin and subcutaneous tissues | 21 (1.3%)  | 18 (0.6%) | 18 (0.8%)|
| M                            | Diseases of the musculoskeletal system and connective tissue | 58 (3.6%)  | 115 (3.6%)| 78 (3.7%)|
| N                            | Diseases of the genitourinary system | 62 (3.8%)  | 224 (7.0%)| 179 (8.4%)|
| O                            | Pregnancy, childbirth, and puerperium | 2 (0.1%)   | -         | -        |
| Q                            | Congenital malformations, deformations and chromosomal abnormalities | 4 (0.2%)   | 7 (0.2%)  | 6 (0.3%)  |
| R                            | Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified | 64 (3.9%)  | 120 (3.8%)| 103 (4.8%)|
| S-T                          | Injury, poisoning and certain other consequences of external causes | 35 (2.1%)  | 51 (1.6%) | 36 (1.7%)|
| U                            | Codes for special purposes | 12 (2.1%)  | 15 (0.5%) | 9 (0.4%)  |
| V, X, Y                      | External causes of morbidity and mortality | 4 (0.2%)   | 6 (0.2%)  | 3 (0.1%)  |
| Z                            | Factors influencing health status and contact with health services | 193 (11.8%)| 389 (12.2%)| 234 (11.0%)|

Adults: age 18–64 years; young-old: age 65–79 years; old-old: age ≥80 years.

Continuous variables are shown as median [interquartile ranges] and categorical variables are shown in absolute numbers (%); level of significance shown by $P$-values resulted from Kruskal–Wallis test for continuous and from Mantel–Haenszel test for categorical variables testing for linear trend; significant $P$-values (<.05) in bold text.

Frequencies given in absolute number (percentages). Absolute numbers of drugs refer to number of drugs within the respective drug class per age group. Percentages refer to the total number of drugs in respective drug classes in the respective age group. Absolute numbers of comorbidities refer to number of comorbidities on level 1 of ICD-10 per age group. Percentages refer to the total number of comorbidities on level 1 of ICD-10 in the respective age group.

ACE, angiotensin converting enzyme; ICD, International Classification of Diseases
**TABLE 2**  Frequency and odds of adverse drug reaction-associated admission diagnoses according to age group

| Admission diagnosis, n (%) | ICD 10 code | Adults   | Young-old | Old-old | OR [95% CI]  | Regression coefficient (B) | Significance |
|---------------------------|-------------|----------|-----------|---------|-------------|---------------------------|--------------|
| Volume depletion          | E86         | 6 (0.8%) | 23 (2.6%) | 34 (5.6%) | 4.32 [1.86–10.05] | .064                      | <.001        |
| Heart failure             | I50         | 4 (0.6%) | 29 (3.3%) | 16 (2.6%) | 5.10 [1.83–14.22] | .041                      | .002         |
| Haemorrhage from respiratory passages | R04 | 8 (1.1%) | 32 (3.6%) | 19 (3.1%) | 2.89 [1.37–6.11] | .036                      | .001         |
| Other anemias             | D64         | 11 (1.5%) | 34 (3.9%) | 35 (5.8%) | 2.85 [1.51–5.41] | .034                      | <.001        |
| Atrial fibrillation and flutter | I48 | 19 (2.6%) | 37 (4.2%) | 27 (4.5%) | 1.54 [0.92–2.59] | .033                      | <.001        |
| Other diseases of digestive system | K92 | 45 (6.2%) | 109 (12.4%) | 112 (18.5%) | 2.46 [1.77–3.41] | .030                      | <.001        |
| Syncope and collapse      | R55         | 30 (4.1%) | 51 (5.8%) | 49 (8.1%) | 1.51 [1.00–2.29] | .023                      | <.001        |
| Acute posthaemorrhagic anaemia | D62 | 12 (1.6%) | 28 (3.2%) | 20 (3.3%) | 1.80 [0.95–3.41] | .018                      | .103         |
| Essential (primary) hypertenion | I10 | 29 (4.1%) | 33 (3.8%) | 21 (3.5%) | 0.80 [0.51–1.26] | .009                      | .217         |
| Other disorders of fluid, electrolyte and acid–base balance | E87 | 12 (1.9%) | 30 (3.4%) | 26 (4.3%) | 1.75 [0.99–3.09] | .008                      | .360         |
| Dizziness and giddiness   | R42         | 27 (3.7%) | 32 (3.6%) | 23 (3.8%) | 0.91 [0.57–1.45] | .003                      | .738         |
| Acute renal failure       | N17         | 20 (2.7%) | 45 (5.1%) | 25 (4.1%) | 1.58 [0.96–2.61] | .001                      | .864         |
| Abnormalities of breathing | R06 | 27 (3.7%) | 59 (6.7%) | 23 (3.8%) | 1.37 [0.88–2.13] | -.002                     | .801         |
| Other gastroenteritis and colitis of infectious and unspecified origin | A09 | 35 (4.8%) | 23 (2.6%) | 20 (3.3%) | 0.57 [0.36–0.89] | -.007                     | .325         |
| Nausea and vomiting       | R11         | 27 (3.7%) | 36 (4.1%) | 19 (3.1%) | 0.91 [0.57–1.45] | -.009                     | .184         |

Frequency is shown by absolute numbers (percentages). Percentages refer to amount of population with given diagnosis as cause for admission in the respective age group.  

\( n = 731 \) adults with 262 different diagnoses given 1167 times on admission;  \( n = 880 \) young-old with 285 different diagnoses given 1544 times on admission;  \( n = 604 \) old-old with 208 different diagnoses given 1065 times on admission.

The table shows admission diagnoses given in >3% of cases in older age (age ≥ 65 years). The odds ratio (OR) and 95% confidence intervals (CI) show the chance be admitted due to a certain diagnosis on emergency department presentation when being an older adult (any age ≥ 65 years) compared to an adult. The regression coefficient shows the difference of the chance presenting with a certain admission diagnosis per year of age adjusted for sex, number of comorbidities, and number of drugs taken.
gastrointestinal bleeding [melena and haematemesis]). In addition, the adjusted chance to present with an ADR-associated atrial fibrillation or flutter and with syncope or collapse increased with age (B.033, \( P < .001 \), OR\(_{age} \) 1.03 [1.02–1.05] and B.023, \( P < .001 \), OR\(_{age} \) 1.02 [1.01–1.04] respectively). The corresponding significant OR\(_{age} \) and 95% CI for a certain admission diagnosis are shown in Figure 1A.

The majority of ADR symptoms affected comparable organ systems in both age groups. Gastrointestinal disorders, general and administrations site disorders, and nervous system disorders were most often found as affected organ systems presented by symptoms (each in >25% of the total population). However, drug-associated injuries, poisoning and procedural complications, and blood and lymphatic system disorders were more often than 2 times more often in older adults (OR 2.53 [1.72–3.71] and OR 2.14 [1.50–3.06], respectively). Further, metabolism and nutrition disorders and vascular system disorders were more often found leading to ED presentation in older adults (OR 1.65 [1.23–2.23] and OR 1.31 [1.02–1.68], respectively). In contrast, adults presented more often with symptoms affecting the skin and subcutaneous tissues, infections and infestations, and other, specific disorders than older adults (OR 0.35 [0.26–0.49], OR 0.38 [0.24–0.59], and OR 0.42 [0.28–0.64], respectively) (data not shown).

In older adults, most common symptoms per affected organ class presented 35.4% of all symptoms reported on ED admission. In adults, the same symptoms presented 21.9% of all symptoms reported in that age group. Figure 2 shows percentages of symptoms reported for adults and older adults.

Table 3 shows the odds for presenting with an ADR-associated symptom (PT) per affected organ class (per SOC) per age group and adjusted regression coefficients for age in years.

Age showed highest impact on presentation with drug-associated dehydration (B .081, \( P < .001 \), OR\(_{age} \) 1.08 [1.05–1.12] and OR 6.02 [2.41–15.03]). Likewise confusion and bradycardia became more common with rising age (B .054, \( P = .003 \), OR\(_{age} \) 1.05 [1.02–1.09] and OR 6.70 [1.59–28.27], and B .040, \( P < .001 \), OR\(_{age} \) 1.04 [1.02–1.06] and OR 4.82 [2.21–10.54], respectively). With every year of age, the chance to present with a drug-associated fall increased by approximately 3% (B .030, \( P < .001 \), OR\(_{age} \) 1.03 [1.02–1.05] and OR 2.84 [1.77–4.53]). The chance to present with anaemia or blood stool was more than doubled in older adults (2.78 [1.82–4.25], and OR 2.30 [1.65–3.22]), with increasing chance of around 2.2–2.5% for each year of age (B .022, \( P = .001 \), OR\(_{age} \) 1.02 [1.01–1.04] and B.025, \( P < .001 \), OR\(_{age} \) 1.03 [1.01–1.04]). A comparable effect was seen for ADR-associated hypotension, which became more likely with rising age (B .020, \( P = .020 \), OR\(_{age} \) 1.02 [1.00–1.04] and OR 1.91 [1.12–3.28]). In contrast, the chance to present with pneumonia was reduced with rising age (B -0.044, \( P = .007 \), and OR 0.26 [0.08–0.85]). The corresponding significant OR\(_{age} \) and 95% CI for a certain ADR-associated symptom are shown in Figure 1B.

**FIGURE 1** Odds ratios with 95% confidence intervals for adverse drug reaction-associated admission diagnoses A, and adverse drug reaction-associated symptoms B, significantly associated with age.
**FIGURE 2** Frequencies of adverse drug reaction-associated symptoms in percentages in older adults A, and adults B

**TABLE 3** Frequency and odds of adverse drug reaction-associated symptoms (preferred terms) per affected organ class and age group

| Symptom                        | Adults  | Young–old | Old–old | OR [95% CI] | Regression coefficient (B) | Significance |
|--------------------------------|---------|-----------|---------|-------------|-----------------------------|--------------|
| Dehydration                    | 5 (0.7%)| 20 (2.3%) | 38 (6.3%)| 6.02 [2.41–15.03] | .081 | <.001 |
| Confusional state              | 2 (0.3%)| 12 (1.4%) | 14 (2.3%)| 6.70 [1.59–28.27] | .054 | .003 |
| Bradycardia                    | 7 (1.0%)| 32 (3.6%) | 33 (5.5%)| 4.82 [2.21–10.54] | .040 | <.001 |
| Fall                           | 21 (2.9%)| 51 (5.8%) | 63 (10.4%)| 2.84 [1.77–4.53] | .030 | <.001 |
| Blood stool                    | 43 (5.9%)| 99 (11.3%)| 89 (14.7%)| 2.30 [1.65–3.22] | .025 | <.001 |
| Anaemia                        | 26 (3.6%)| 75 (8.5%) | 63 (10.4%)| 2.78 [1.82–4.25] | .022 | .001 |
| Hypotension                    | 17 (2.3%)| 37 (4.2%) | 26 (4.3%)| 1.91 [1.12–3.28] | .020 | .020 |
| Weight decreased               | 7 (1.0%)| 14 (1.6%) | 9 (1.5%) | 1.69 [0.72–3.94] | .010 | .475 |
| Pain in extremity              | 2 (0.3%)| 6 (0.7%) | 4 (0.7%) | 2.57 [0.56–11.73] | .005 | .833 |
| General physical health deterioration | 81 (11.1%)| 158 (18.0%)| 79 (13.1%)| 1.53 [1.18–1.98] | .005 | .244 |
| Dizziness                      | 86 (11.8%)| 115 (13.1%)| 81 (13.4%)| 1.18 [0.91–1.53] | .001 | .884 |
| Dyspnoea                       | 84 (11.5%)| 152 (17.3%)| 62 (10.3%)| 1.02 [0.93–1.71] | −.002 | .673 |
| Visual impairmenta             | 4 (0.6%)| 5 (0.6%) | 2 (0.3%) | 0.90 [0.26–3.07] | −.010 | .556 |
| Renal impairment               | 14 (1.9%)| 13 (1.5%) | 11 (1.8%) | 0.88 [0.45–1.70] | −.017 | .140 |
| Rash                           | 31 (4.2%)| 12 (1.4%) | 1 (0.2%) | 0.21 [0.11–0.41] | −.018 | .082 |
| Pneumoniab                     | 8 (1.1%)| 4 (0.5%) | -       | 0.26 [0.08–0.85] | −.044 | .007 |

Frequency is shown by absolute numbers (percentages). Percentages refer to amount of population presenting with the symptom. OR: odds ratio; CI: confidence interval

aVisual impairment was seen 4 times in adults. Likewise, was plasma cell myeloma and hyperthyroidism.
bPneumonia was seen 4 times in older adults. Likewise, was febrile infection, systemic infection, and localized infection reported in 4 older adults each.

The table shows the most often reported symptom (preferred term) in older adults (age ≥65 years) per affected organ class (per system organ class). The OR shows the chance of showing a symptom on emergency department presentation when being an older adult. The regression coefficient shows the difference of the chance presenting with a certain admission diagnosis per year of age adjusted for sex, number of co-morbidities, and number of drugs taken.

The affected organ classes (depicted by system organ class) for the list of symptoms: confusional state—psychiatric disorder, dehydration—metabolism and nutrition disorder, bradycardia—cardiac disorder, fall—injury, poisoning and procedural complications, anaemia—blood and lymphatic system disorder, pain in extremity—musculoskeletal and connective tissue disorder, blood stool—gastrointestinal disorder, hypotension—vascular disorder, weight decreased—investigation, general physical health deterioration—general and administration site disorders, dyspnoea—respiratory, thoracic and mediastinal disorder, dizziness—nervous system disorder, visual impairment—other, renal impairment—renal and urinary disorder, pneumonia—infection and infestation, rash—skin and subcutaneous tissue disorder.
Analysing symptom pairs by frequent set analysis, nausea and vomiting were most often reported together in all age groups (in 5.5% of adults, and 3.6% of older adults with 3.3% in young-old and 4.0% in old-old). Frequencies of symptom pairs are shown in Supplement 1. In general, the chance for presenting with nausea and vomiting was higher for adults than older adults (OR 0.42 [0.27–0.63]). Likewise, chances were higher for presenting as an adult with dizziness and nausea, and with fever and general physical health deterioration compared to older adults (OR 0.57 [0.34–0.95], and 0.49 [0.28–0.87], respectively). No chance for presenting with a symptom pair was higher in older adults compared to adults, but there were trends for presenting more often with anaemia and blood stool (1.2% of younger adults, 2.2% of young-old and 2.6% of old-old patients), and blood stool and general physical health deterioration with higher age (0.8% for younger adults, 2.0% for young-old and 2.8% for old-old).

Analysing symptom pairs by association rule analysis revealed combinations of symptoms that were frequent and strongly associated within our groups. Within the group of adults, 25.6% presented with just 1 symptom, 26.7% of young-old patients, and 31.8% of old-old patients. Injuries such as falls, together with wounds and with fractures, were seen in older adults (young-old fracture and fall: lift 14.6 (support 1.25%), and old-old wound and fall: lift 9.6 (support 2.65%). This means that fracture and fall were reported 14.6 times more often together in young-old patients than one would expect by chance. In contrast in adults, erythema and pruritus were more often reported together (lift 16.1, support 1.23%; Supplement 2).

A table showing characteristics of patients who were discharged and those who died during hospital stay after admission can be found in Supplement 3.

The numbers of symptoms and admission diagnoses were higher in death cases. The hospital stay was prolonged in patients who died subsequently. In death cases at least 1 antineoplastic or immunomodulating drug was more often suspected than in others. In death cases, the hospital stay was prolonged in patients who died subsequently. In fact, those patients dying during subsequent stay were older. However, our sample was too small to draw any concrete conclusions.

4 | DISCUSSION

This study shows the distinct differences in ADRs causing ED presentations of older adults compared to adults. It is likely that older adults present with specific drug-associated symptoms such as confusion, dehydration or bradycardia to the ED. Likewise, older adults are prone to any kind of drug-associated bleeding events such as gastrointestinal bleedings. Further, falls are typical ADRs causing ED presentation of older adults, whereas younger adults might present more often with symptoms such as erythema or infections.

Drug-associated gastrointestinal bleeding events were within the most frequent symptoms in older age groups, which is in line with other studies on ADRs in the ED and supports the fact that diseases of the circulatory system and the use of antithrombotics was more frequent in older adults. In our study, the chance of presenting with a bleeding event of any kind was 2–3 times higher in older adults. This finding emphasises again the importance of age as a risk factor for drug-associated bleedings that was also shown to increase fatality. As older adults took more medication, we cannot differentiate whether this is an effect of age or maybe of drug–drug or drug–disease interactions that are known to increase drug-associated bleeding risks. However, when adjusting for sex, number of drugs taken, and number of co-morbidities, the chance to present with a drug-associated bleeding event still increased with each year of age. Therefore, our study shows an alarming tendency towards drug-associated bleeding in older adults. As low-dose aspirin as a primary prevention strategy for cardiovascular events was not shown to be effective in apparently healthy older adults, while there is still a lack of enrolment of older and multi-morbid adults to clinical trials for cardiovascular and antithrombotic medicines, a sustainable indication for treating an older adult with antithrombotic drugs is strongly recommended.

Dizziness and syncope were frequent in both age groups. However, the chance of syncope or a fall was up to 2.8 times higher in older adults. Our study shows for the first time a connection of drug-associated falls with age, whereas this connection is apparently not visible with drug-associated dizziness; while in general, comparable drug groups are taken and underlying diseases present. This confirms further findings on drug-associated falls as reason for unplanned hospitalisations in older adults. In addition, this might point to the importance of a physiological reserve for fall prevention, because the chance to present with drug-associated dizziness was independent of age. This could put the frail old adult at high risk for drug-associated falls and injuries. This hypothesis is in line with findings that falls in frail older adults are associated with fewer fall-risk increasing drugs than in robust older adults. Notably, those falls can be connected to injuries such as wounds or fractures increasing severity, as shown in this dataset. The altered risk for drug-associated falls of older adults might be seen in the context of a marked higher chance for presenting with dehydration, confusion or bradycardia. Interestingly, neurological diseases and mental and behavioural disorders were more frequent underlying diseases in younger adults, whereas the use of substances affecting the central nervous system was comparable over all age groups. This might point to a broader use of central nervous agents for other indications than mental diseases in older adults such as antidepressants to treat sleep disorders or antipsychotics to treat agitation. Notably, agents acting on the central nervous system such as antidepressants or antipsychotics are suspected to be more likely to cause the ED presentation compared to their general use.

The chance of being admitted due to volume depletion or heart failure in the context of an ADR was 4–5 times higher in older adults, which is in line with cardiovascular diseases being more frequent in older adults. What is striking is that those admission diagnoses might be linked to deaths during subsequent hospital stay. In fact, those patients dying during subsequent stay were older. However, our sample was too small to draw any concrete conclusions.

We assumed ADRs as a combination of symptoms. While this can be underlined by a median of 2 symptoms seeing on ED presentation, and just around 1/4 to 1/3 of cases presenting with just 1 symptom, we
decided to conduct frequent pair and association rule analyses. As our study group was small for that kind of analyses and heterogeneous, we found already well-known combinations of symptoms. The small study group is for example represented by little support numbers. This shows, that even with small sample sizes, frequent set and association rule analyses work properly and underline the importance of drug associated bleedings and falls in older adults. Furthermore, we do think that those analyses might be valuable for understanding common patterns of medication intake and symptoms that might be associated with an ADR especially in older adults, where cases become complex and in bigger study samples. As those patients who were dying in the following hospital stay presented with more symptoms and more diagnoses causing admission, we expect the number of symptoms representing more severe, more complex cases. Therefore, it is reasonable to focus on leading symptoms or chief complaints of ADRs in both age groups and to use triage and acuity scales for drug-associated problems in the ED. 

Dermal allergic reactions to drugs such as erythema, pruritus or rash were found to be important in younger adults in this dataset. It is possible, that in older adults, allergic skin reactions decrease and therefore would not lead to ED presentations. Likewise, in this dataset, adults were more likely to present with drug-associated infections such as pneumonia or gastroenteritis or colitis than older adults. This might be a consequence of medication as antineoplastic and immunomodulating agents being commonly taken in this cohort of ADRs and neoplasms more often underlying diseases of younger adults.

We were able to replicate findings about older adults presenting with unspecific symptoms such as general physical health deterioration to the ED. Nonetheless, our data show that several specific symptoms appear more likely in older adults such as bleedings or falls. Therefore, an ADR is most often a concrete phenomenon affecting older adults. It might have sense to consider drug treatment as a cause in those cases in the older adult.

A strength of our study is the collection of all ADR-associated symptoms in the ED. Previous studies so far often focused on diagnoses and missed the initial presentation. Also trigger lists for study enrolment have been used widely which might not transport the initial picture on ED presentation. The inclusion of all ADR-associated symptoms on ED admission offers the potential to characterise those serious ADRs better.

There are also some potential limitations to this study. First, patients who were not able to provide written informed consent were not consequently enrolled over the full time of the study and in all centres. Therefore first, the serious ADRs resulting in unresponsiveness and deaths maybe underrepresented. Second, this might also be true for patients who were treated as outpatients and not admitted to the hospital. We expect those outpatients to be underrepresented in our dataset. Therefore, our sample might be valid mostly for severe ADRs that needed hospitalisation. And third, those analyses of combination of symptoms do not concern all cases and do not represent the whole study population.

We showed that concrete drug-associated phenomena such as falls, syncope, confusion and bleedings bring older adults to present as an emergency. While ADRs have a substantial impact on older adults’ health and health care utilisation, physicians should consider drug treatment especially in those cases in older adults. Further, we need to focus on benefit-risk ratios when prescribing drugs as those might differ in older adults with an increased risk for serious ADRs.

ACKNOWLEDGEMENTS
This work has not been published elsewhere. This work was supported by the framework of the AMTS focus of the German Federal Ministry of Health (BMG), grant number ZMVI5–2514ATA004. The work was in parts supported by the Robert Bosch Stiftung, Stuttgart, Germany. Open access funding enabled and organized by Projekt DEAL. [Correction added on 22 July 2020, after first online publication: Projekt Deal funding statement has been added.]

COMPETING INTERESTS
There are no competing interests to declare.

CONTRIBUTORS
K.J. conducted the analyses and drafted the manuscript. J.S. designed the ADRED study and supervised all analyses and coordination. M.B., M.Schau., M.St. and K.J. conducted the statistical analyses. M.Schau. coordinated the study. H.D., T.S., I.G. and M.Schaw. supervised the identification of ADR cases at clinical sites. B.P.K., K.E., S.I., S.S. and S.J. participated in identification of ADR cases at clinical sites. All authors collaborated in writing and approved the final manuscript.

DATA AVAILABILITY STATEMENT
The datasets analysed during the current study are available from the corresponding author on reasonable request.

ORCID
Katja S. Just [https://orcid.org/0000-0002-6782-8078]
Julia C. Stingl [https://orcid.org/0000-0002-1566-8156]

REFERENCES
1. Pirmohamed M, James S, Meakin S, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ. 2004;329(7456):15-19.
2. Schneeweiss S, Hasford J, Gottler M, Hoffmann A, Riethling AK, Avorn J. Admissions caused by adverse drug events to internal medicine and emergency departments in hospitals: a longitudinal population-based study. Eur J Clin Pharmacol. 2002;58(4):285-291.
3. van der Hooft CS, Dieleman JP, Siemes C, et al. Adverse drug reaction-related hospitalisations: a population-based cohort study. Pharmacoeconomics Drug Saf. 2008;17(4):365-371.
4. Leendertse AJ, Egberts AC, Stoker LJ, van den Beemt PM. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Arch Intern Med. 2008;168(17):1890-1896.
5. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 1998;279(15):1200-1205.
6. Schurlig AM, Bohme M, Just KS, et al. Adverse drug reactions (ADR) and emergencies. Dtsch Arztebl Int. 2018;115(15):251-258.
7. Budnitz DS, Pollock DA, Weidenbach KN, Mendelsohn AB, Schroeder TJ, Annest JL. National surveillance of emergency department visits for outpatient adverse drug events. JAMA. 2006;296(15):1858-1866.

8. van Der Hoot C, Sturkenboom MC, van Grootheest K, Kingma HJ, Stricker BHC. Adverse drug reaction-related hospitalisations. Drug Saf. 2006;29(2):161-168.

9. 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. 2019Dec 12;76(3):439-448. https://doi.org/10.1007/s00228-019-02797-9 [Epub ahead of print]

10. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. N Engl J Med. 2011;365(21):2002-2012.

11. Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey. JAMA. 2002;287(3):337-344.

12. Hohl CM, Dankoff J, Colacane A, Afflalo M. Polypharmacy, adverse drug-related events, and potential adverse drug interactions in elderly patients presenting to an emergency department. Ann Emerg Med. 2001;38(6):666-671.

13. Nguyen JK, Fouts MM, Kotabe SE, Lo E. Polypharmacy as a risk factor for adverse drug reactions in geriatric nursing home residents. Am J Geriatr Pharmacother. 2006;4(1):36-41.

14. McLean JD, Le Couteur DG. Aging biology and geriatric clinical pharmacology. Pharmacol Rev. 2004;56(2):163-184.

15. Lavan AH, Gallagher P. Predicting risk of adverse drug reactions in older adults. Ther Adv Drug Saf. 2016;7(1):11-22.

16. Nickel CH, Ruedinger JM, Messmer AS, et al. Drug-related emergency department visits by elderly patients presenting with non-specific complaints. Scand J Trauma Resusc Emerg Med. 2013;21(1):15.

17. Meier F, Maas R, Sonst A, et al. Adverse drug events in patients admitted to an emergency department: an analysis of direct costs. Pharmacoeconom Drug Saf. 2015;24(2):176-186.

18. Held FP, Blyth F, Gnjidic D, et al. Association rules analysis of comorbidity and multimorbidity: the Concord health and aging in men project. J Gerontol A Biol Sci Med Sci. 2016;71(5):625-631.

19. Held F, Le Couteur DG, Blyth FM, et al. Polypharmacy in older adults: association rule and frequent-set analysis to evaluate concomitant medication use. Pharmacol Res. 2017;116:39-44.

20. Creighton C, Hanash S. Mining gene expression databases for association rules. Bioinformatics. 2003;19(1):79-86.

21. Szalai B, Grolmusz VK, Grolmusz VI. Identifying combinatorial biomarkers by association rule mining in the CAMD Alzheimer’s database. Arch Gerontol Geriatr. 2017;73:300-307.

22. Uppsala Monitoring Centre. The WHO-UMC System. [https://www.who-umc.org/media/2768/standardised-case-causality-assessment.pdf]. Accessed June, 12 2017.

23. Wood K. The medical dictionary for drug regulatory affairs (MEDDRA) project. Pharmacoeconom Drug Saf. 1994;3:7-13.

24. Menec VH, Chipperfield JG. The interactive effect of perceived control and functional status on health and mortality among young-old and old-old adults. J Gerontol B Psychol Sci Soc Sci. 1997;52:P118-P126.

25. Zizza CA, Ellison KJ, Wernette CM. Total water intakes of community-living middle-old and oldest-old adults. J Gerontol A Biol Sci Med Sci. 2009;64:481-486.

26. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56:M146-M157.

27. Hernández-Díaz S, Rodríguez LAG. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s. Arch Intern Med. 2000;160(14):2093-2099.

28. Hernández I, Baik SH, Pihera A, Zhang Y. Risk of bleeding with dabigatran in atrial fibrillation. JAMA Intern Med. 2015;175(1):18-24.

29. Li L, Geraghty OC, Mehta Z, Rothwell PM, Study OV. Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study. Lancet. 2017;390:490-499.

30. Gasse C, Hollowell J, Meier CR, Haefeli WE. Drug interactions and risk of acute bleeding leading to hospitalisation or death in patients with chronic atrial fibrillation treated with warfarin. Thromb Haemost. 2005;94(3):537-543.

31. Delaney JA, Opatrny L, Brophy JM, Suisa S. Drug-drug interactions between antithrombotic medications and the risk of gastrointestinal bleeding. CMAJ. 2007;177(4):347-351.

32. McNeil JJ, Wolfe R, Woods RL, et al. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. N Engl J Med. 2018;379(16):1509-1518.

33. Cerreta F, Padrao A, Skibicka-Stepien I, Strampelli A, de Orbe Izquierdo MS. Medicines for older people: assessment and transparancy at the European medicines agency regarding cardiovascular and antithrombotic medicinal products. Eur Geriatr Med. 2018;9(4):415-418.

34. Chan M, Nicklason F, Vial JH. Adverse drug events as a cause of hospital admission in the elderly. Intern Med J. 2001;31(4):199-205.

35. Clegg A, Young J, lilffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013;381:752-762.

36. Bennett A, Gnjidic D, Gillett M, et al. Prevalence and impact of fall-risk-increasing drugs, polypharmacy, and drug-drug interactions in robust versus frail hospitalised falls patients: a prospective cohort study. Drugs Aging. 2014;31(3):225-232.

37. Bullard MJ, Unger B, Spence J, Grafstein E, Group CNW. Revisions to the Canadian emergency department triage and acuity scale (CTAS) adult guidelines. CJEM. 2008;10:136-142.

38. Skassa-Brociek W, Manderscheid J-C, Michel F-B, Bousquet J. Skin test reactivity to histamine from infancy to old age. J Allergy Clin Immunol. 2007;177(4):347-351.

39. Quinn K, Herman M, Lin D, Supapol W, Worster A. Common diagnosis and treatment for a phenotype. J Gerontol A Biol Sci Med Sci. 2019;76(3):439-448. https://doi.org/10.1111/jgs.14304

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

How to cite this article: Just KS, Dormann H, Schurig M, et al. The phenotype of adverse drug effects: Do emergency visits due to adverse drug reactions look different in older people? Results from the ADRED study. Br J Clin Pharmacol. 2020;86: 2144–2154. https://doi.org/10.1111/bcp.14304