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

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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.

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 data[20] 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.

What is already known about this subject

- Older patients are affected by adverse drug reactions (ADR) that lead to emergency department visits.
- They present with more drugs, comorbidity and, possibly, more serious ADRs.
- It is challenging to differentiate a symptom as a response to a drug from a sign of an underlying disease.

What this study adds

- Differences in symptoms of ADRs between adults and older individuals exist.
- Especially dangerous drug-associated phenomena such as bleedings, confusion or falls are more prominent in 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 the in 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).[23] 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).[24–26] 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, antineoplasic 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	**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%)	

(Continues)

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%)
Antianaemic 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

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} 1.06 [1.04–1.09]) 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} 1.04 [1.02–1.97]) 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 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 anaemias	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) hypertension	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 seen more 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], respectively), 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 –.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.

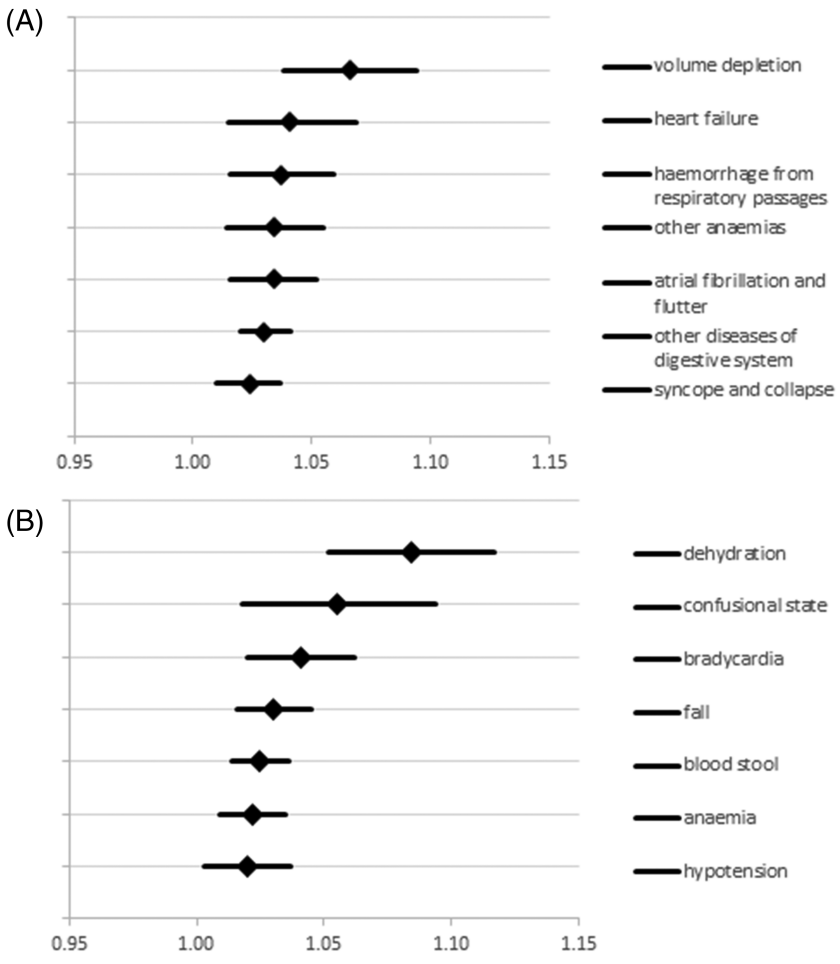

FIGURE 1 Odds ratios with 95% confidence intervals for adverse drug reaction-associated admission diagnoses A, and adverse drug reaction-associated symptoms B, significantly associated with age

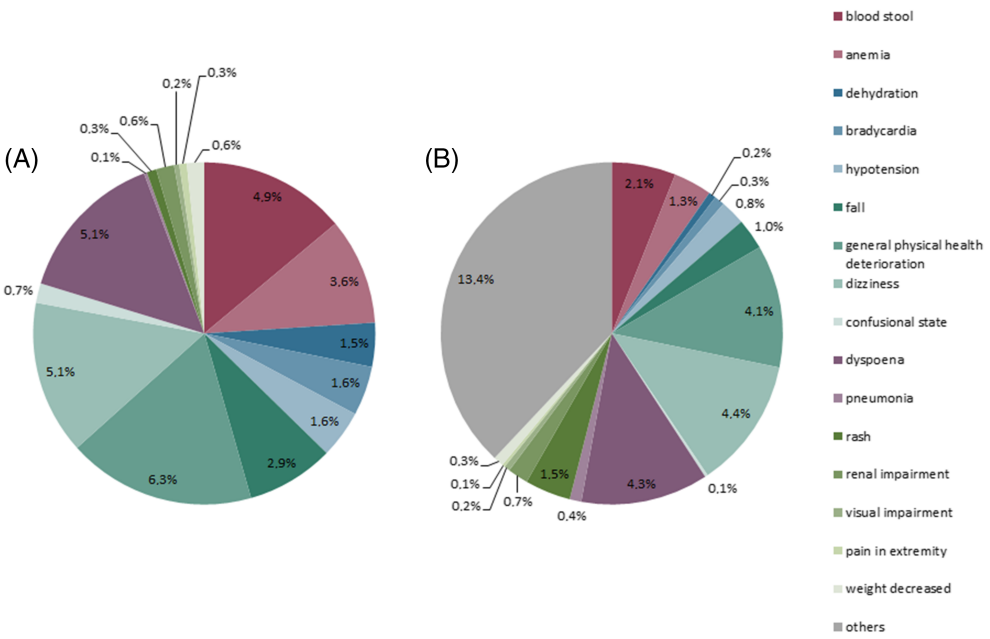

FIGURE 2 Frequencies of adverse drug reaction-associated symptoms in percentages in older adults A, and adults B

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 impairment[a]	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
Pneumonia[b]	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
[a]visual impairment was seen 4 times in adults. Likewise, was plasma cell myeloma and hyperthyroidism.
[b]pneumonia 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. Volume depletion, heart failure, cardiac arrest, abnormalities of breathing and diabetes mellitus were more often coded as admission diagnosis in patients subsequently dying.

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.[1,8,10] 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.[27–29] 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.[30,31] However, when adjusting for sex, number of drugs taken, and number of comorbidities, 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,[32] while there is still a lack of enrolment of older and multi-morbid adults to clinical trials for cardiovascular and antithrombotic medicines,[33] 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 for 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.[34] 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.[35] 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.[36] 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.[9]

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 ¼ 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.[37]

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.[38] 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[9] 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.[16,39] 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.[1,8] Also trigger lists for study enrolment have been used widely which might not transport the initial picture on ED presentation.[4] 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 4 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.

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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.Schu., M.St. and K.J. conducted the statistical analyses. M.Schu. coordinated the study. H.D., T.S., I.G. and M.Schw. 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.

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SUPPORTING INFORMATION

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

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