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Healthcare costs of adverse drug reactions and potentially inappropriate prescribing in older adults: a population-based study

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ABSTRACT

Objectives To describe the distribution of costs based on potentially inappropriate prescribing (PIP) and adverse drug reaction (ADR) status in terms of total direct costs and costs caused by ADRs, among older adults.

Design A retrospective cohort study was conducted among older adults, identified from a random sample of the general Swedish population. PIP was identified based on the Screening Tool of Older Persons' Prescriptions (STOPP) criteria and ADRs were identified using the Howard criteria. Causality between PIP and ADRs was evaluated using Hallas' criteria. Prevalence-based direct healthcare costs were calculated for the 3-month study period, including the total cost for healthcare and drugs, and the cost caused by ADRs.

Setting All care levels, including primary care, other outpatient care and inpatient care.

Participants 813 adults ≥65 years.

Primary outcome measures The prevalence and cost of PIP and ADRs.

Results Total direct cost for persons with PIP was approximately twice the total cost of those without PIP (€1958 (€1428–€2616) vs €881 (€817–€1167), p=0.0020). The costs caused by ADRs was 10 times higher among persons with PIP, compared with those without PIP (€270 (€86–€545) vs €27 (€10–€61), p=0.047). For persons with ADRs caused by PIP, total direct costs were €4646 (€2617–€7931). This group represented 8% of the study population and used 25% of the costs. The main cost driver in all studied patient groups was healthcare contacts.

Conclusions Older persons with PIP and ADRs had high healthcare costs, particularly when ADRs were caused by PIP. Since these costs appear to be substantial, the potential savings by preventing their occurrence may, to a certain degree, cover the added cost of such activities. Further studies should be undertaken to provide further evidence on the costs of PIP, ADRs and ADRs caused by PIP.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study includes direct costs of potentially inappropriate prescribing (PIP), adverse drug reactions (ADRs) and ADRs caused by PIP in the general older population.
⇒ This study describes full healthcare costs, deviating from the previous focus on costs of drugs.
⇒ The study combines data from medical records with data from four administrative registers, and the application of three sets of validated clinical criteria (Screening Tool of Older Persons' Prescriptions/STOPP, Howard's and Hallas' criteria).
⇒ A limitation of the study is that the evaluation of PIP, ADRs and costs are based on a dataset generated in 2008.
⇒ All costs are provided in Euros 2020 value, and supplementary materials include the costs in SEK 2008 value to provide for cost translations.

INTRODUCTION

To tackle the challenges of prescribing in older adults and reducing potentially inappropriate prescribing (PIP), explicit prescribing criteria have been developed. The Screening Tool of Older Persons' Prescriptions (STOPP) criteria are screening tools developed to improve the quality and appropriateness of prescribing by reducing potentially inappropriate medications (PIMs).[1] Studies have reported that older patients prescribed PIMs had a twofold increase in odds of experiencing adverse drug reactions (ADRs),[2] and that the STOPP criteria are useful in linking PIMs to preventable ADRs, in a hospital[3–7] or community setting.[2 8 9]

The occurrence of ADRs generates high healthcare costs,[10] and the presence of PIMs is associated with increased healthcare utilisation.[9] Yet, several studies reporting costs of PIP in the older population solely include drug costs,[3 7 11–15] although some have addressed healthcare costs.[16–20] However, the relationship between PIP and costs resulting specifically from related ADRs represents a gap in the knowledge.

The Drug-Related Morbidity in Sweden (DRUMS) project has previously investigated

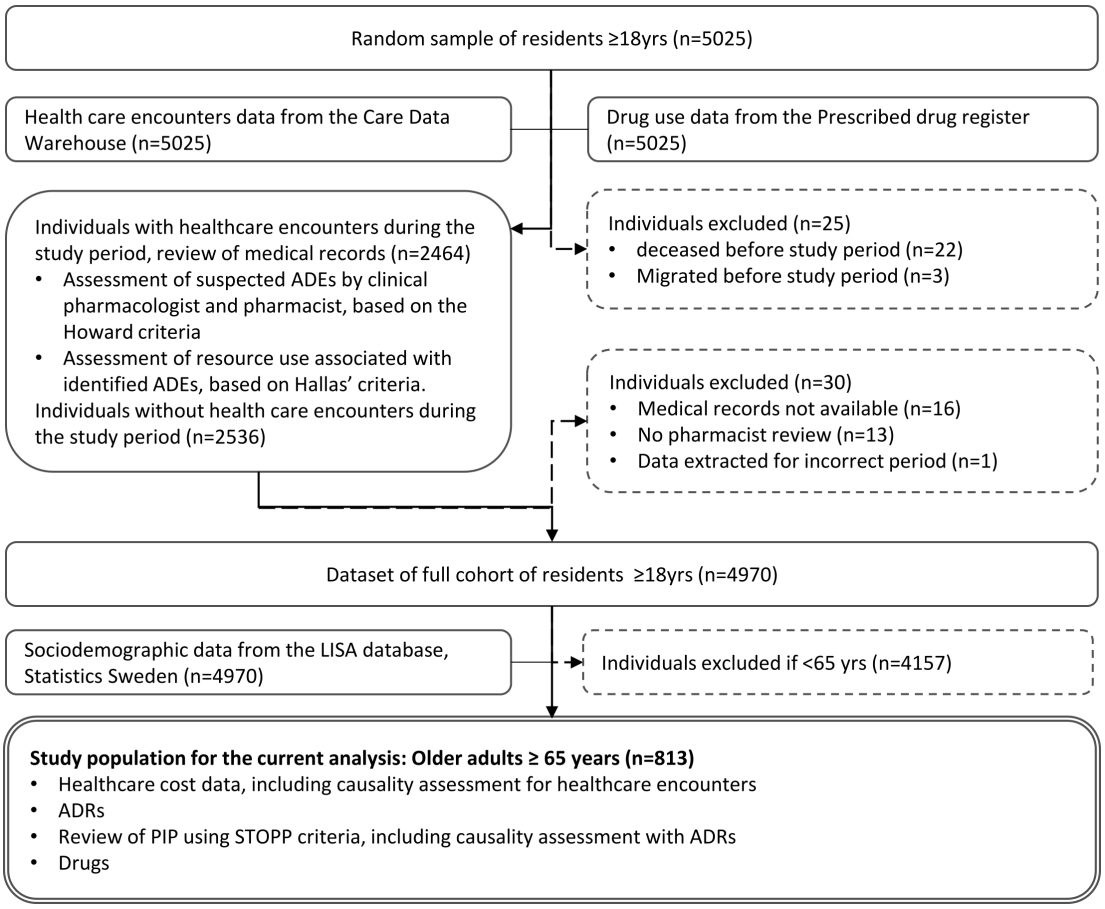

Figure 1 Study flow chart including data sources and clinical criteria employed. ADR, adverse drug reaction; ADR+, ADRs caused by PIP; ADE, adverse drug event; LISA, Longitudinal Integration Database for Health Insurance and Labour Market Studies; PIP, potentially inappropriate prescribing; STOPP, Screening Tool of Older Persons' Prescriptions.

the prevalence and economic impact of adverse drug events (ADEs), including ADRs, among the general population of Swedish adults.[10 21 22] This included studying the relationship between PIP and ADRs for the 813 older adults of the cohort.[2] However, a combined analysis of PIP, ADRs and costs was not undertaken. By revisiting the data from the DRUMS project, it is possible to provide a new and important knowledge and guide future studies aiming to close the identified knowledge gap. This study aims to describe the distribution of costs based on PIP and ADR status in terms of total direct costs and costs caused by ADRs among older adults. Specifically, the study compares costs between subgroups of the population with PIP vs without PIP, and the subgroup with ADRs vs the subgroup with ADRs caused by PIP.

METHODS

Study design and study population

A random sample of 5025 adults in the Swedish county Östergötland was identified by Statistics Sweden from the Total Population Register, of which 813 were older adults (≥65 years)[2] (figure 1). Data for the cohort were collected retrospectively from health registries and through a detailed review of medical records, including primary care, other outpatient care and inpatient care. Clinical criteria and causality criteria were applied, compiling information for the cohort about ADEs, drug use, healthcare use and costs for a 3-month period in 2008.[10 21] Thereafter, PIP and their potential contribution to ADRs were evaluated for the subcohort of older adults.[2]

Data sources

The unique personal identification number was used to link microdata between registers, including sociodemographics collected from the Longitudinal Integration Database for Health Insurance and Labour Market Studies, administered by Statistics Sweden. Healthcare use during the study period was identified through the Regional Care Data Warehouse, in Östergötland County, covering all public and most private healthcare encounters in the county.[23] Healthcare costs were identified from the Cost Per Patient Register from Östergötland County Council, providing information about costs divided by resource types.[10] Prescribed and dispensed medications and their costs were identified from the Swedish Prescribed Drug Register,[24 25] and defined as the reimbursement costs to the counties and the patient out-of-pocket cost. The study population and data collection have been previously described in detail elsewhere.[2 10]

Identification of PIP

A research pharmacist (KH) identified PIP using the first version of the STOPP criteria, including drug–drug and drug–disease interactions, unnecessary therapeutic duplication and drugs which can increase the risks of cognitive decline and falls in older patients.[26] PIP was identified from the Swedish Prescribed Drug Register,[24] and the medical records for a period of 6 months, starting 3 months prior the study period for the 813 older adults (figure 1).

Identification of ADRs and ADRs caused by PIP

In this study, ADRs were defined according to the WHO as 'a response to a drug which is noxious and unintended, and which occurs at doses normally used in man'.[27] Medical records were reviewed for suspected ADEs, including ADRs, for a period of 15 months, starting 9 months prior to the study period and ending 3 months after. A standardised data collection sheet was used by research pharmacists to extract information necessary for the assessment and evaluation. ADRs and causal relationship with used medication were independently assessed in a separate process by two expert reviewers; a clinical pharmacologist and a pharmacist, in a stepwise manner using the Howard criteria.[28] ADRs assessed to have at least possible causality were considered ADRs. Ongoing ADRs with causal contribution from identified PIP[2] are hereafter referred to as ADR+.

Identification of costs

Prevalence-based direct costs for healthcare and drug use during the 3-month study period were calculated, both as the total cost for all healthcare encounters and dispensed drugs, and as the cost caused by ADRs employing the resource use method.[29] The ADR costs were derived from a study evaluating costs of ADEs, in mutually exclusive categories including ADRs, and their contribution to healthcare encounters.[10] The reviewers were instructed that the ADE contributing most to costs should be listed first. Costs caused by ADRs were costs for identifying, monitoring and treating ADRs, derived by evaluating the association with the prevalent ADRs for each healthcare encounter, using a method developed from the Hallas' criteria.[10 29] The evaluation was as follows: a healthcare encounter was categorised as dominantly caused by ADRs if one or more ADRs were the main reason for the encounter. Further, ADRs could be partly contributing (ie, ADRs had a substantial contribution to the encounter), less important (ie, ADRs had a minor or uncertain contribution to the encounter) or not contributing (ie, other symptoms/circumstances were the main reason for the encounter). Healthcare costs caused by ADRs were the full costs of healthcare encounters dominantly caused by ADRs. For other encounters caused at least partially by ADRs (partly contributing or less important) and for drug costs resulting from ADRs, the specific costs used for diagnosing, treating and monitoring ADRs were identified.

Statistical analyses

The characteristics of the population subgroups were reported with descriptive statistics; those with and without PIP, persons with or without ADRs and persons with ADR+. The subgroups were compared using z-test of proportions.

Overall mean costs were described and compared between subgroups with or without PIP and with or without ADRs. Costs caused by ADRs were described and compared between subgroups where applicable. Costs caused by ADR+ were also described. All cost estimates were described with bias corrected 95% CIs calculated by bootstrap, to account for skewed cost data.[30] Results were translated to Euro (€) in 2020 value using the Swedish healthcare inflation index (price index with quality adjusted wages for the county, including medicines),[31] and the 2020 exchange rate.[32]

We also conducted a sensitivity analysis omitting the 12 criteria that had been excluded from the second version of the STOPP criteria published after the data collection was conducted.[33]

Statistical analyses were performed using STATA V.14.2. This work followed The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[34] Definition of terms used in this study is provided in online supplemental table S1.

Patient and public involvement

This project did not include patient or public involvement in developing the research questions, design, conduct, choice of outcome measures or recruitment.

RESULTS

In total 46% (375 of all 813 older adults) had one or more PIP (table 1) and 20% (159 of 813) experienced one or more ADRs. Among them, 62 persons experienced ADR+, representing 39% of persons experiencing ADRs (62 of 159) and 17% of persons receiving PIP (62 of 375). Significantly fewer individuals in the youngest age group received a PIP, as opposed to the oldest age group, where significantly more individuals received a PIP. Polypharmacy appeared to be equally common regardless of PIP and ADR status. The use of multidose dispensing, an adherence aid widely used in the Nordic countries with machine dispensed disposable sachets individually packaged for the intended time of administration,[35] was more common in the subgroup with PIP compared with the subgroup without PIP, and in the subgroup with ADR+ compared with the total subgroup with ADRs. Healthcare use, including primary care visits and hospitalisations, was more common among individuals with PIP compared with those without PIP.

Table 2 shows included costs and quantities for healthcare encounters dominantly associated with ADRs and dominantly associated with ADR+. In the total population, nurse visits and other outpatient were the most frequent type of healthcare encounters, followed by

Table 1 Descriptive statistics of the study population (N=813)

Characteristics	Population with PIP(N = 375) N (%)	Population without PIP(N = 438) N (%)	Population with ADRs(N = 159) N (%)	Population without ADRs(N = 654) N (%)	Population with ADR+(N = 62) N (%)	Total population(N=813) N (%)
Age (years)						
Median, range	76, 65-98	73, 65-97	77, 65-94	74, 65-98	80, 65-94	75, 65-98
65–74	160 (43) ***	241 (55)	61 (38)**	340 (52)	21 (34)	401 (49)
75–84	143 (38)	146 (33)	65 (41)	224 (34)	24 (39)	289 (36)
≥85	72 (19) **	51 (12)	33 (21)*	90 (14)	17 (27)	123 (15)
Sex						
Female	218 (58)	240 (55)	93 (58)	365 (56)	35 (56)	458 (56)
Dispensed prescribed medications†						
Median, range	7, 0-25	4, 0-17	8, 0-25	5, 0-25	10, 1-25	5, 0-25
0	2 (1) ***	43 (10)	3 (2)*	42 (6)	0 (0)	45 (6)
1	87 (23)	81 (18)	50 (31)***	118 (18)	18 (29)	168 (21)
2–5	97 (26)	101 (23)	33 (21)	165 (25)	13 (21)	198 (24)
6–9	82 (22)	93 (21)	35 (22)	140 (21)	15 (24)	175 (22)
≥10	107 (29)	120 (27)	38 (24)	189 (29)	16 (26)	227 (28)
Multidose dispensing	62 (17)****	23 (5)	30 (19)***	55 (8)	21 (34)*	85 (10)
Level of healthcare use‡						
Primary care	209 (56)**	195 (45)	109 (69)****	295 (45)	41 (66)	404 (50)
Specialized care	148 (39)	145 (33)	84 (53)****	209 (32)	34 (55)	293 (36)
Hospitalization	67 (18)**	45 (10)	53 (33)****	59 (9)	19 (31)	112 (14)

Percentages were rounded.
P values comparing the population with PIP to the population without PIP, the population with ADRs to the population without ADRs, and the population with ADR+ to the population with ADRs.
*P<0.05 **p**p<0.01 ***p***p<0.001 ****p****p<0.0001.
†Three months prior the study period.
‡Defined by diagnosis related group weights.
ADR, adverse drug reaction; ADR+, ADR caused by PIP; PIP, potentially inappropriate prescribing.

Table 2 Overview of the included quantities and costs for healthcare encounters dominantly caused by ADRs and ADR+ by types of encounters

Encounters	Average direct costs for encounters, total population			Average direct costs for encounters dominantly caused by ADRs*			Average direct costs for encounters dominantly caused by ADR+ *		
	Encounters n (%)	Cost per encounter mean (95% CI), €		Encounters n (%)	Cost per encounter mean (95% CI), €		Encounters n (%)	Cost per encounter mean (95% CI), €	
Telephone contacts	124 (14)	16	(10 to 26)	34 (14)	25	(9 to 57)	8 (10)	30	(7 to 66)
Nurse visits	191 (22)	52	(45 to 63)	57 (24)	36	(30 to 43)	20 (24)	40	(29 to 52)
Physician visits	111 (13)	179	(162 to 198)	43 (18)	112	(78 to 151)	15 (18)	105	(54 to 161)
Specialist physician visits	86 (10)	370	(319 to 426)	38 (16)	298	(237 to 357)	14 (17)	340	(235 to 455)
Home healthcare	130 (15)	166	(133 to 209)	33 (14)	316	(176 to 474)	16 (19)	107	(82 to 137)
Other outpatient visits	190 (22)	15	(11 to 22)	14 (6)	67	(5 to 164)	9 (11)	0	(–)
Hospitalisations	45 (5)	4610	(3446 to 6080)	17 (7)	4921	(3500 to 6355)	2 (2)	9216	(–)

CIs were bias corrected using bootstrap.
*The cost of the entire encounter included in the direct costs caused by ADRs. Excluding encounters in private healthcare when not included in the Cost Per Patient Register.
ADR, adverse drug reaction; ADR+, ADR caused by PIP; PIP, potentially inappropriate prescribing.

Table 3 Comparing direct costs over a 3-month period among older adults with and without PIP, and with and without ADRs, respectively

	Population with PIP (N=375)		Population without PIP (N=438)		Cost difference		
	Cost per patient		Cost per patient		Cost per patient		
	Mean	(95% CI), €	Mean	(95% CI), €	Mean	(95% CI), €	
Direct cost, total	1958	(1428 to 2616)	981	(817 to 1167)	977	(448 to 1685)	**
Cost caused by ADRs	270	(86 to 545)	27	(10 to 61)	243	(43 to 526)	*
Cost caused by ADR+	75	(16 to 218)	NA		NA		
Persons with ADRs (n=159)	(**n=110**)		(**n=49**)				
Direct cost, total	4084	(2714 to 6239)	2193	(1527 to 3028)	1891	(130 to 4033)	NS
Cost caused by ADRs	921	(278 to 1928)	240	(102 to 491)	681	(3 to 1624)	NS
Cost caused by ADR+	254	(51 to 776)	NA		NA		
Persons with ADR+ (n=62)	(**n=62**)		(**n=0**)				
Direct cost, total	4646	(2617 to 7931)	NA		NA		
Cost caused by ADRs	919	(129 to 2431)	NA		NA		
Cost caused by ADR+	451	(105 to 1365)	NA		NA		
	Population with ADR (N=159)		Population without ADR (N=654)		Cost difference		
					Mean	(95% CI), €	
Direct cost, total	3501	(2564 to 5134)	929	(775 to 1121)	2572	(1503 to 4121)	****
Cost caused by ADRs	711	(274 to 1338)	NA		NA		
Cost caused by ADR+	176	(41 to 549)	NA		NA		
Persons with PIPs (n=375)	(**n=110**)		(**n=265**)				
Direct cost, total	4084	(2714 to 6239)	1076	(825 to 1550)	3008	(1462 to 5153)	**
Cost caused by ADRs	921	(278 to 1928)	NA		NA		
Cost caused by ADR+	254	(51 to 776)	NA		NA		
Persons with ADR+ (n=62)	(**n=62**)		(**n=0**)				
Direct cost, total	4646	(2618 to 7932)	NA		NA		
Cost caused by ADRs	919	(129 to 2431)	NA		NA		
Cost caused by ADR+	451	(97 to 1362)	NA		NA		

Costs were rounded and presented in 2020 value €.
CIs were bias corrected using bootstrap.
P values for the cost difference between groups.
*p<0.05;**p<0.01;***p<0.001;****p<0.0001.
ADR, adverse drug reaction; ADR+, ADR caused by PIP; NA, not applicable; NS, not significant; PIP, potentially inappropriate prescribing.

home healthcare visits, physician visits and telephone contacts. A similar distribution could be observed among the encounters caused by ADRs and ADR+. Hospitalisations dominantly associated with ADR+ were about twice the cost of hospitalisations caused by ADRs regardless of PIP status, although this represented very few hospitalisations overall.

In table 3, the direct costs of persons with or without PIP and with or without ADRs are detailed. In the total population, the total direct cost for persons with PIP was approximately double compared with those without PIP (€1958 (€1428–€2616) vs €881 (€817–€1167), p=0.002). The cost caused by ADRs was 10 times higher among the population with PIP, compared with the population without PIP (€270 (€86–€545) vs €27 (€10–€61), p=0.047). In the subgroup with ADRs, there was a tendency towards higher total costs among persons with PIP, although not statistically significant (€4084 (€2714–€6239) vs €2193 (€1527–€3028), p=0.058). For the total population, total direct costs for the subgroup with ADRs was almost four times the total cost of those without ADRs (€3501 (€2564–€5134) vs €929 (€775–€1121), p=0.0001). For persons with ADR+, total direct costs were €4646 (€2617–€7931).

Figure 2 shows the prevalence of PIP, ADRs and ADR+ in the total population and the associated distribution of total direct costs for the individuals with PIP, ADRs and ADR+. There was a disproportion between the prevalence and costs for all the subgroups. PIP occurred in 46% of

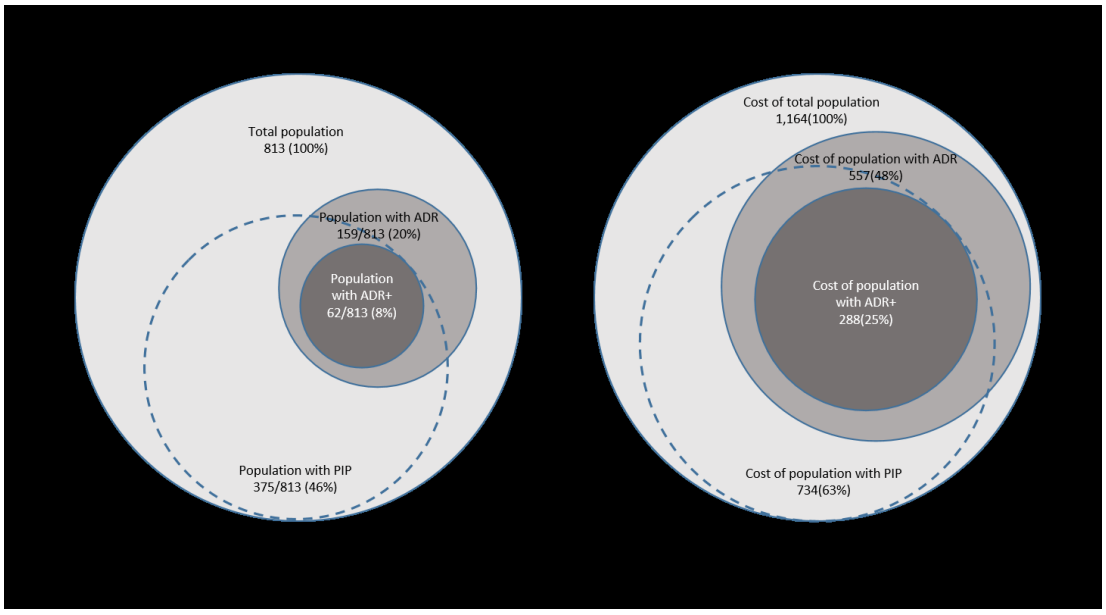

Figure 2 Prevalence of PIP, ADRs and ADR+ and the associated distribution of total direct costs for individuals with PIP, ADRs and ADR+. Costs in €1000. ADR, adverse drug reaction; ADR+, ADRs caused by PIP; PIP, potentially inappropriate prescribing.

the population who used 63% of the total healthcare costs. Furthermore, the 20% with ADRs used 48% of the total healthcare costs. The subgroup who experienced ADR+ represented 8% of the study population and used 25% of the healthcare costs.

Table 4 details the costs caused by ADRs into drug costs and costs of healthcare encounters for the subgroup with ADRs and the subgroup with ADR+. Healthcare costs were clearly the largest contributor to patient costs, whereas drug costs represented a small fraction of the total cost, both for the subgroup with ADRs and the subgroup with ADR+ (table 4). Among those with ADR+, the ADR+ caused approximately half of the costs of healthcare encounters caused by ADRs (mean €448 of €912). Moreover, their ADRs were the main contributor to healthcare encounters (mean €912 of €925). For the group with any ADRs, costs of healthcare encounters caused by ADRs were €705, and ADRs contributed to some extent to other encounters costing €1750.

Sensitivity analysis

In the sensitivity analysis without the 12 criteria that had been excluded in the newer version of the STOPP criteria, 271 persons (33%) had PIP (table 5). Total direct cost for persons with PIP was twice the total cost, compared

Table 4 Costs resulting from ADRs among older adults

	Costs for healthcare encounters	Drug costs	Total healthcare costs
	Cost per patient mean (95% CI), €	Cost per patient mean (95% CI). €	Cost per patient mean (95% CI), €
Persons with ADRs (n=159)			
Cost caused at least partially by ADRs	1750 (344 to 5305)	10 (5 to 17)	1760 (352 to 5321)
Cost caused by ADRs*	705 (271 to 1332)	7 (3 to 13)	711 (274 to 1338)
Persons with ADR+ (n=62)			
Cost caused at least partially by ADRs	925 (135 to 2432)	9 (3 to 20)	934 (143 to 2447)
Cost caused by ADRs*	912 (122 to 2474)	7 (2 to 18)	919 (129 to 2431)
Cost caused at least partially by ADR+	915 (126 to 2428)	8 (3 to 19)	924 (133 to 2443)
Cost caused by ADR+*	448 (94 to 1356)	3 (1 to 6)	451 (97 to 1362)

CIs were bias corrected using bootstrap.
*Costs where the main condition among identified ADEs were an ADR or an ADR+, respectively. Costs were calculated as described previously, including the full cost if dominantly caused by the considered ADR, or including only costs for specific resources used in diagnosing, treating or monitoring the considered ADR.
ADE, adverse drug event; ADR+, ADR caused by PIP; ADR, adverse drug reaction; PIP, potentially inappropriate prescribing.

Table 5 Sensitivity analysis of direct costs over a 3-month period among older adults with and without PIP according to the STOPP criteria version 2

	Population with PIP (N=271)	Population without PIP (N=542)	Cost difference	
	Cost per patient mean (95% CI), €	Cost per patient mean (95% CI), €	Cost per patient mean (95% CI), €	
Direct cost, total	2131 (1475 to 3005)	1083 (890 to 1331)	1048 (274 to 1823)	**
Cost caused by ADRs	263 (71 to 609)	77 (15 to 240)	186 (–55 to 556)	NS
Persons with ADRs (n=159)	(n=91)	(n=68)		
Direct cost, total	3952 (2440 to 6259)	2897 (1930 to 4448)	1055 (–983–3873)	NS
Cost caused by ADRs	784 (225 to 1787)	614 (132 to 1857)	171 (–1085–1212)	NS

CIs were bias corrected using bootstrap.
P values for the cost difference between groups.
***p<0.01
ADR, adverse drug reaction; NS, not significant; PIP, potentially inappropriate prescribing; STOPP, Screening Tool of Older Persons' Prescriptions.

with those without PIP (€2131 (€1475–€3005) vs €1083 (€890–€1331), p=0.0089). Costs in SEK 2008 value are provided in online supplemental table S5. Online supplemental tables S2–S5 provide all the corresponding costs in SEK 2008 value.

DISCUSSION

Principal findings

This population-based study of adults ≥65 years from both primary and specialised healthcare settings adds to the previous knowledge that healthcare costs of individuals who experienced ADR+ were disproportionally high (25% of total costs) compared with the prevalence of such ADRs in the study population (8% of the 813). Individuals with PIP had higher healthcare costs than those without PIP (€1958 (€1428–€2616) vs €881 (€817–€1167), p=0.002), and the costs were mainly driven by the cost of healthcare encounters and not by the cost of drugs.

Strengths and limitations of this study

This study is the first to estimate costs caused by ADRs based on PIP status and PIP causation in the older adults of a random sample of the general population of the county Östergötland, recognised as representative of the general Swedish population.[21] The main strength of this study is the combination of medical records with data from four administrative registers, and the application of three sets of validated evaluation clinical criteria (STOPP, Howard's and Hallas' criteria). We have, therefore, been able to explore each patient's health and costs outcomes closely. Nevertheless, the findings should be interpreted with some limitations in mind. The evaluation of ADRs and costs was based on a dataset generated in 2008, and the first version of the STOPP criteria were used to identify PIP. The STOPP criteria have since been updated, including more criteria than the first version, and new drugs have been introduced to the market. The current study finds a PIP prevalence of 46%, which is in line with other studies using the STOPP criteria.[36 37] It is unlikely that the ADR prevalence has improved, as a recent Swedish report found the ADR prevalence of 10% for the full Swedish population in the period 2013–2018,[38] while the ADR prevalence in our full dataset and in this subset were 7%[21] and 20%, respectively, although the difference in time frames calls for a cautious comparison. The sensitivity analysis, employing only 53 of the criteria in STOPP V.2 yielded very similar results as the main analysis in terms of total direct costs. As the costs in this study were register based, reflecting the actual costs for healthcare use translated to 2020 values, and since the main point of this analysis was to compare costs between subgroups, it is unlikely that our findings would have changed significantly in the recent years.

The ADR costs were derived from a study evaluating costs of different types of ADEs and their contribution to healthcare encounters.[10] The cost evaluation method employed was the resource use method.[29] The reviewers were instructed that the ADE contributing the most to costs should be listed first. If the first ADE listed by a reviewer was an ADR, any additional ADEs contributing to the resource use during that same healthcare encounter could potentially contribute to an overestimation of cost. The method used to evaluate costs caused by ADRs may result in an underestimation in the encounters where ADRs only contributed to a small extent, or were not listed as the first ADE. Moreover, several resources used for diagnosing, treating or monitoring ADEs were not possible to single out as costs in the healthcare register.[29] Thus, although the total cost reported is the cost used by the Region in their administrative system and should

be well representing the healthcare costs in this patient group, the reported cost resulting from specific ADRs is likely underestimated, and should be viewed as more of an indication of its distribution.[29] Costs assessed as dominantly caused by an ADR can be expected to better represent the actual costs to the health system.[29] The analyses in this article are descriptive in nature, and the results were not adjusted for other factors, such as comorbidities. Thus, methods for estimating the attributable costs of ADRs were not used, such as adjusted regression analyses or propensity score matching, due to residual confounding limiting the comparability of groups.

Interpretation of results

Comparing healthcare costs: different methods

Comparing healthcare costs between studies is difficult, due to varying use of methods and definitions of outcomes. Some studies only included drug costs,[13 14 39] or used other PIP criteria, like the European PIM-list[13 14] or Beers criteria.[39] Among studies including full healthcare costs, comparison is complicated by the use of different PIP criteria. A German study found a difference in healthcare costs of €1237 the first 3 months after being prescribed a PIM, compared with those not receiving a PIM, defined by the German PRISCUS list.[17] Although that study used a different PIM-list and estimated the incidence and not prevalence, its finding corresponds to our result of €1933 mean cost per patient with PIP (table 3). A recent population-based study from Canada found a healthcare cost of €528 ($C773, 2017 value[32]) attributable to PIP per individual with STOPP/START criteria for a 90-day follow-up.[19] This may to a certain degree correspond to our results in persons with ADR+ of €451 per patient caused by ADR+. They also found that 39% of total costs of hospitalisations, emergency department visits and drugs were attributable to PIP, which was similar to our findings, in spite of the difference in methodology. The Canadian study estimated costs attributable to PIP by multiplying the total cost with a population attributable fraction, while our study reported cost data from the cost per patient register for each patient with PIP. Furthermore, they did not associate the cost to ADRs, although the resulting healthcare costs attributable to PIPs are likely to partly reflect ADR costs.

We can draw other knowledge from relating our results to other studies. Patients who experienced ADR+ had relatively high total direct costs compared with other patients with ADRs not caused by PIP or to the total patients with PIP. Several studies have found similar increase in costs due to PIP.[20] However, patients with ADR+ can be expected to differ from other patients with either ADRs alone or PIP alone. They are presumably susceptible to developing an ADR due to their PIP, making it likely that there are unmeasured confounding factors influencing the comparisons. This was also deduced from a study where numerous matching criteria were used, and where PIM exposure was associated with polypharmacy and higher healthcare costs,[17] which are both associated with ADRs.

Healthcare costs versus drug costs or PIM costs

Previous studies have suggested there is a potential to reduce costs by exchanging PIMs with recommended alternatives,[14] or that PIMs have a higher cost than non-PIMs, so that costs can be reduced by exchanging the treatment itself,[13] and that in particular drug costs are reduced after multidisciplinary medication reviews to reduce PIMs among patients in nursing homes.[40] However, there is a potential to save drug costs by simply removing a drug without replacing it (deprescribing), and removing a PIM may reduce the need to treat ADRs with further medications, hence reducing costs. In our study, drug costs had only a marginal contribution to the total costs of the healthcare encounters mainly caused by ADRs. Only assessing drug costs does not give the full picture on preventable costs of negative health outcomes. Thus, we believe our results presenting the healthcare costs specifically caused by the ADRs associated with PIP use contributes with a new and important perspective.

Distribution and preventability of costs

The distribution of costs compared with the prevalence of PIP, ADRs and ADR+, shows that in particular ADR+represent a considerable burden of cost. Only 8% of the population had ADR+, but the costs for this subgroup is more than triple that level, at 25% of the cost of the total population. 5.7% of the study population ≥65 years had ADRs deemed to be preventable[21] and by using STOPP criteria, it may be possible to prevent ADR+.[2] However, a cost that has already incurred cannot be reversed. Hence, it is necessary to prevent the occurrence of ADR+ before the ADR occurs in order to save healthcare costs, although primary prevention as well as secondary prevention strategies would also incur a cost. The subgroup with PIP also represents a burden of cost higher than the corresponding prevalence, and so does the subgroup with ADRs. It is possible that other factors like age, polypharmacy and multidose use influences the costs of the subgroup with PIP. As this study is a snapshot of the development in the subgroups, it is also possible that some of the persons with PIP are in the process of developing ADR+, and hence may have increased healthcare costs.

Implications

This study indicates that ADRs caused by PIP generate disproportionally high healthcare costs. However, there is a need to further study which PIPs are more likely to cause ADRs and reduce or prevent their use at an early stage, before the patient develops an ADR, thus preventing negative health outcomes and associated healthcare costs. Targeting PIPs likely to cause ADRs should have implications for future prescribing practice among older adults, and should also be reflected in future prescribing guidelines. These findings warrant further study of the costs associated with PIP, ADR and ADRs causally linked to PIP.

CONCLUSION

The occurrence of PIPs and ADRs resulted in high healthcare costs among older adults, especially when the ADRs were caused by PIP. Healthcare use and especially hospitalisations were the main cost drivers. Since costs caused by ADRs associated with PIP appear to be substantial, the potential savings by preventing their occurrence and mitigating them may, to a certain degree, cover the added cost of such activities. Further studies on the relationship between PIP, ADRs and healthcare costs should be undertaken to provide updated evidence on the costs of PIP, ADRs and ADRs causally linked to PIP.

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