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Cost of illness of patient-reported adverse drug events: a population-based cross-sectional survey

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ABSTRACT

Objectives: To estimate the cost of illness (COI) of individuals with self-reported adverse drug events (ADEs) from a societal perspective and to compare these estimates with the COI for individuals without ADE. Furthermore, to estimate the direct costs resulting from two ADE categories, adverse drug reactions (ADRs) and subtherapeutic effects of medication therapy (STE).

Design: Cross-sectional study.

Setting: The adult Swedish general population.

Participants: The survey was distributed to a random sample of 14 000 Swedish residents aged 18 years and older, of which 7099 responded, 1377 reported at least one ADE and 943 reported an ADR or STE.

Main outcome measures: Societal COI, including direct and indirect costs, for individuals with at least one self-reported ADE, and the direct costs for prescription drugs and healthcare use resulting from self-reported ADRs and STEs were estimated during 30 days using a bottom-up approach.

Results: The economic burden for individuals with ADEs were (95% CI) 442.7 to 599.8 international dollars (Int$), of which direct costs were Int$ 279.6 to 420.0 (67.1%) and indirect costs were Int$ 143.0 to 199.8 (32.9%). The average COI was higher among those reporting ADEs compared with other respondents (COI: Int$ 442.7 to 599.8 versus Int$ 185.8 to 231.2). The COI of respondents reporting at least one ADR or STE was Int$ 468.9 to 652.9. Direct costs resulting from ADRs or STEs were Int$ 15.0 to 48.4. The reported resource use occurred both in hospitals and outside in primary care.

Conclusions: Self-reported ADRs and STEs cause resource use both in hospitals and in primary care. Moreover, ADEs seem to be associated with high overall COI from a societal perspective when comparing respondents with and without ADEs. There is a need to further examine this relationship and to study the indirect costs resulting from ADEs.

ARTICLE SUMMARY

Article focus

- Adverse drug events (ADEs) have been reported not only to cause harm but also resource use from patients attending hospitals.
- Even though ADEs have also been identified outside hospitals, little is known about the associated resource use.
- Thus, we conducted a population-based survey to identify the economic burden of diseases in individuals with ADEs and compare it with those without ADEs.

Key messages

- Our study suggests high overall costs-of-illness for individuals with self-reported ADEs, which are estimated to be more than 500 international dollars (Int$) per person per month in Sweden when including those with adverse drug reactions (ADRs), drug dependence, drug intoxications, subtherapeutic effects of medication therapy (STE) and untreated indications.
- The estimated direct costs for prescribed drugs and healthcare use resulting from treatment of two of the ADE categories, that is, ADRs and STE, were 30 Int$ per person per month. This corresponds to more than 10% of all costs for prescribed drugs and healthcare use among these individuals.
- A large proportion (56%) of the healthcare resource use in respondents with ADEs occurred in the outpatient setting.

Strengths and limitations of this study

- The main strength is the population-based design, including outpatient and inpatient healthcare, drug use, social services and transportation, lost productivity from both respondents and relatives and health-related quality of life.
- The main limitation of the study is the response rate (50%), where some groups were somewhat under-represented in the analysis.

INTRODUCTION

Adverse drug event (ADE), "an injury resulting from medical intervention related to a drug,"[1] has been identified as a public-health problem that causes harm to patients and considerable resource use. According to

previous research, 5–6% of hospitalisations are drug-related,[2] [3] and hospitalised patients experiencing adverse drug effects cause additional hospital costs of USD 2284–5640/patient (in 2000 values).[4] Little is known about the corresponding costs outside hospitals,[4] [5] or the magnitude of the problem in the general public, although patient-reported adverse drug reactions (ADR) have been reported to affect 6% of the Swedish population.[6]

The cost of illness (COI) is the economic burden of disease or diseases to the society. The distribution of cost items in the COI can be used to judge the financial relevance of a specific health issue in relation to other public-health problems, and to study the development of the associated resource use over time for different actors in the healthcare system.[7] Information about COI could also be useful for developing future intervention studies to address ADEs and to retrieve the costs for modelling, for example, cost-effectiveness of drug use in the general public.

Thus, we conducted a population-based survey to study self-reported ADEs. In ADEs, we included ADRs, subtherapeutic effects of medication therapy (STE), drug dependence, drug intoxications and untreated indications. This deviates from the common ADE inclusions used in many previous studies, focusing on ADRs and medication errors,[3] but were developed from exploring also, for example, drug-related problems that may cause drug-related morbidity. The aim of the current study was to estimate and compare the COI of individuals with and without self-reported ADEs, from a societal perspective. A secondary aim was to estimate the direct costs resulting from two ADE categories, ADRs and STEs. Additional results for prevalence and preventability of self-reported ADEs are reported elsewhere.[8]

METHODS
Study design
We conducted a population-based observational retrospective COI study of self-reported ADEs from a cross-sectional survey. The COI was prevalence-based and measured from a societal perspective, including direct and indirect costs during the 30 day study period. Costs were measured using a bottom-up approach using unit costs for self-reported resource use and productivity loss from short-term sick leave and informal care. Intangibles were approximated using health-related quality of life.

ADE definitions
The terminology within patient safety related to drug therapy varies.[9] [10] ADEs have, for example, been defined as events that occur during drug treatment without a causal relationship to the drug[11] or, according to the definition used in this study,[1] that indicate a relationship between the treatment and the negative outcome. From a public-health perspective, there is a need to describe the epidemiology and negative

consequences of drug therapy, as a complement to measures of its beneficial effects. ADR reporting has recently been expanded to include all *suspected* ADRs, including overdose, misuse, abuse, medication errors and reactions associated with occupational exposure.[12] Thus, the reporting now includes both adverse effects occurring at normal doses and the consequences of errors. Still, there are other pathways for which drug treatment may cause harm. Examples are drug dependence,[13] and insufficient effect of medicines that may also occur at normal doses (often referred to as non-responders to the medication).[14] Moreover, untreated indication has been suggested to cause, for example, drug-related hospitalisations.[15] Part of these events will be weighed into the decision to initiate drug treatment.

All ADEs included in this study were self-reported; thus, we included preventable and non-preventable ADRs, STE, drug dependence, drug intoxications and untreated indications, as reported by the drug users. Owing to data constraints, it was unfeasible to perform a formal causality assessment for the cases, although reported ADEs were examined to exclude obvious deviations from our aim (eg, drug dependence reported for hypertension treatments). The categories were selected to be mutually exclusive and clarified in the questionnaire: ADRs were described as side effects, STEs were less effective than expected, drug dependence was explained by the inability to stop using the medication, drug intoxications were associated with using too much of the medication, and untreated indications were symptoms for which the respondent considered that he or she would have needed drug treatment. Only reported drug dependence associated with addictive medications were included in the final analyses.

Participants and data collection
A random sample of 14 000 Swedish residents aged 18 years or older was identified by Statistics Sweden from the Swedish adult population (7 382 226 individuals) on 1 January 2010. The sample size was calculated by assuming a 1-month prevalence of 6.4% for ADRs in Sweden based on a previous study,[6] a preventable proportion of approximately 10%,[16] [17] a 60% response rate[6] and a maximum width of ±0.3% for the 95% CI of the preventable proportion. The estimated sample size (7013) was doubled to enable analyses of predictors and costs. The cross-sectional postal survey was sent in the first week of October 2010. Statistics Sweden distributed the surveys and collected the responses. The envelope contained a letter with information relevant for the informed consent, the questionnaire and a prepaid envelope for returning the questionnaire. Three reminders were sent, one postcard and two with questionnaires. Data collection was closed on 1 February 2011.

The questionnaire encompassed, for the past 30 days, questions on use of healthcare and social services; use of prescribed and over-the-counter medicines as well as herbal remedies; experienced ADEs and perceived

preventability, consequences and use of healthcare due to ADRs and STEs. The questions of resource use after ADRs or STEs were: Overall, how were you affected by (ADR/STE) during the last 30 days: (seven check boxes for alternative effects)? If you indicated any of (three selected check boxes): how many days (were you unable to conduct your leisure activities/did you stay home from work or equivalent/did you have help from relatives to conduct everyday activities)? How many times during the last 30 days did you have any of the following (healthcare) contacts due to (ADR/STE): (10 types of healthcare encounters indicated, free text space and a check box for those not having had healthcare contacts)? Have your treatment/s been adjusted due to (ADR/STE) during the last 30 days: Yes, a new drug treatment was initiated, with (free text box to indicate drug); Yes, existing drug treatment was changed, for example, stopped or dose adjustment; Yes, a new other treatment was initiated (eg, lifestyle change, surgery/orthopaedic treatment), namely (free text box to indicate treatment); No, the treatment was not changed? The questionnaire also included demographic and socioeconomic characteristics, and the EQ-5D questionnaire for health-related quality of life.[18] The questionnaire was piloted with healthcare professionals, individuals from the general public and specific patient groups. All reported ADEs were carefully examined by one of the researchers, a pharmacist (Katja M Hakkarainen), to exclude responses not indicating a suspected symptom or drug. The first author, HG, also a pharmacist with clinical experience, did an independent examination of 10% of reported ADEs. Differences in opinion were discussed in the research group to reach consensus.

Data from the questionnaire were combined with register data by record linkage, using each respondent's unique personal identification number, by Statistics Sweden. The register data included demographic and socioeconomic variables from the Longitudinal Integration Database for Health Insurance and Labour Market Studies from Statistics Sweden; sick leave and disability pension from the Swedish Social Insurance Agency; as well as filled prescriptions from the Swedish Prescribed Drug Register and hospitalisations from the Swedish Patient Register; the last two are held by the National Board of Health and Welfare.

Direct costs

Direct costs included used resources, that is, costs resulting from prescription drugs, healthcare, social services and transportation. Direct costs resulting from ADRs or STEs included the costs for prescription drugs and healthcare use caused by either ADRs or STEs reported by the respondents.

Dispensed prescription medicines and associated costs were retrieved from the Swedish Prescribed Drug Register, National Board of Health and Welfare. Costs included both patient copayments and expenses for medicines, and costs paid by the reimbursement scheme.

The prescription drug cost during the study period was the average cost per month calculated from the 2010 annual prescription medicine cost per respondent. Costs of medicine use resulting from ADRs or STEs were the cost of any medicine, reported by the survey respondents to be initiated for treating an ADR or STE, which was dispensed during the study period according to data from the Swedish Prescribed Drug Register. Costs for adjustments to the drug treatment related to, for example, drugs administered from healthcare units, initiation of drug treatment for which the individual already had the medication, initiation of a prescription that was not filled during the period for which we had register data, initiation of over-the-counter drugs or herbal remedies that are not registered, dose adjustments and termination of drug treatment were excluded.

Healthcare use, both overall healthcare use and encounters resulting from ADRs or STEs, were retrieved from the questionnaire, that is, self-reported by the respondents. Results from prespecified questions and from free text were categorised into: phone calls, nurse visits, outpatient physician visits, home healthcare, specialist physician and emergency department visits, visits to other healthcare personnel in somatic care, psychiatrist visits, visits to other healthcare personnel in psychiatric care and hospitalisations. Encounters for healthcare use of relatives, and respondent's donations of blood or tissues, were not included in respondents' healthcare use. Unit costs of healthcare services were based on national statistics on healthcare use and costs.[19] A visit to other healthcare personnel than physicians was weighted as 40% of the cost of a physician visit. Phone calls were weighted as one-third of the cost of visiting a nurse, and home healthcare as two times the cost of a nurse visit. Costs paid by the patient were not included in the healthcare costs (2.3% of the proceeds to the healthcare producers[19]).

Costs for social services included nursing home stay and home-help services reported in the questionnaire. Transportation costs included reported transportation for the disabled and other transportation for healthcare encounters, identified from the questionnaire. Costs for overall use of social services and transportation were based on national statistics.[20–22]

Indirect costs

Indirect costs included costs resulting from lost productivity for the respondent due to self-reported short-term morbidity (sick leave) and of relatives to the respondents due to informal care.[7] Sick leave below 2 weeks is not reported in the Social Insurance Agency's register. Owing to the study design, it was not possible to identify deaths during the study period, and there were no respondents initiating disability pension during the study period; therefore, no future indirect costs were estimated.[23] In addition, productivity loss due to reported long-term sick leave (among those <70 years) and disability pension (among those <65 years) was

calculated. Sick leave and disability pension during the study period were identified from the questionnaire, and the costs for lost productivity were measured by the human capital approach,[7] using national wages statistics and social security contributions.[24 25]

Additional resource use and intangibles

Visits to dental care and pharmacies, and lost leisure time, were reported descriptively. In addition to the estimated costs for healthcare and drug use, resource use resulting from ADRs and STEs was reported descriptively, including changes to drug therapy not identified as a dispensed medicine in the register during the study period, days of lost leisure time, patients' sick leave and relatives' informal care. Intangible costs were omitted in the cost analysis, but pain and suffering were approximated by the respondents' health-related quality of life using EQ-5D-5L (the EuroQol Group's five-dimension health state questionnaire with five levels of severity) and the UK value sets.[26 27] The EQ-5D-5L is a generic health-related quality of life instrument with five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has five levels of severity: no problems/slight problems/moderate problems/severe problems/extreme problems. The responses for each dimension created a health profile for each respondent, which was transferred using the stated value set to the respondents' EQ-5D index value: ranging from dead (=0) to full health (=1). The EQ-5D-5L responses were complemented with results from the EQ-VAS scale (the EuroQol Group's visual analogue scale): from 'Worst imaginable health state' (=0) to 'best imaginable health state' (=100).

Analyses

Respondents' characteristics were compared with those for non-respondents based on ADE status (table 1), using register data for: age (young adults' age 18–34 years, middle-aged 35–64 years, or individuals above the Swedish retirement age ≥65 years of age), country of birth (Sweden or other than Sweden), educational level (mandatory education, intermediate education, ie, high school and up to 2 years of university education, or high education, ie, more than 2 years of university education), income during 2009, marital status and sex. Main occupation was interpreted from survey responses for occupations, age and income data during 2009. Differences in characteristics were tested for statistical significance (at p<0.05), for respondents with or without ADEs, using χ^2 tests.

All unit costs (table 2) were translated to international dollars (Int$) using the 2010 purchasing power parity for gross domestic product (1 Int$=9.026383 Swedish krona).[28] The Int$ is a hypothetical currency with the same purchasing power as the US dollar (US$) in the USA, allowing for differences in price levels between countries.[29] Means and SDs for direct costs, indirect costs and COI were calculated for the 30-day period.

Cost differences were tested for statistical significance (at p<0.05), for respondents with or without ADEs, and for ADE respondents with or without at least one ADR or STE, using a two-tailed t test with unequal variances. Cost differences and respondents' characteristics were tested for statistical significance (at p<0.05), for respondents with at least one ADR or STE, using one-way analysis of variance (for age categories) and a two-tailed t test with unequal variances (for sex). All statistical analyses were made using the STATA V.10.1 software.

Sensitivity analyses

Sensitivity analyses were made based on the available register data for hospitalisations and respondents' lost productivity from sick leave. Owing to the skewed data, 80% of the direct costs for respondents with ADEs were reported by 10% of these respondents (figure 1); a sensitivity analysis proposed in the research plan, based on the IQR of responses, was unachievable. Propensity score matching and analyses were conducted to estimate the direct healthcare costs and indirect costs (excluding informal care), respectively, attributable to ADEs. Propensity scores were calculated by logistic regression from the respondent ADE status and characteristics (age, sex country of birth, educational level, main occupation, income category and self-reported prescription drug use). Single nearest neighbour matching with callipers (0.01) and without replacement was made using the Psmatch2 module for STATA.[30] The matching resulted in 1362 pairs of respondents (excluding 15 respondents reporting ADE), each respondent with self-reported ADEs matched by the estimated propensity scores to a respondent without ADE, for whom costs were compared. Additional changes from the research plan were limited to how results were reported.

RESULTS

A total of 7099 questionnaires were collected (response rate 51%). At least one ADE was reported by 1377 (19.4%) respondents. Of these, 68.5% (943 respondents) reported at least one ADR or STE. There were statistically significant differences in age (p<0.05), sex (p<0.001), education (p<0.01), main occupation (p<0.001) and income (p<0.001), comparing respondents reporting at least one ADE compared with other respondents (table 1). Resource use for respondents with self-reported ADE is presented in table 2. Healthcare was attended by 239 (17.4%) respondents reporting ADEs, of which 96 (40.2%) were hospitalised or visited a specialist physician (including psychiatrist visits). Among all respondents, 717 (10.1%) attended healthcare. Resource use among respondents with ADE also included outpatient care in hospitals with other healthcare personnel and primary care visits (eg, nurse visits and physician visits). In addition, home-help services or a nursing home was attended by 51 (4.5%), of the 1138 respondents with ADE that did not attend

Table 1 Description of the study population and comparison with non-respondents

	Respondents reporting ADE Total=1377 N (%)	Respondents not reporting ADE Total=5722 N (%)	All respondents Total=7099 N (%)	Non-respondents Total=6832 N (%)
Age (years)*				
18–34	294 (21.4)	1036 (18.1)	1330 (18.7)	2328 (34.1)
35–64	675 (49.0)	2935 (51.3)	3610 (50.9)	3357 (49.1)
65	408 (29.6)	1751 (30.6)	2159 (30.4)	1147 (16.8)
Sex*				
Men	528 (38.3)	2732 (47.7)	3260 (45.9)	3715 (54.4)
Women	849 (61.7)	2990 (52.3)	3839 (54.1)	3117 (45.6)
Country of birth				
Sweden	1218 (88.5)	1276 (92.7)	6280 (88.5)	5328 (78.0)
Other than Sweden	159 (11.5)	101 (7.3)	819 (11.5)	1504 (22.0)
Marital status				
Single	457 (33.2)	1774 (31.0)	2231 (31.4)	3226 (47.2)
Married or registered partnership	633 (46.0)	2872 (50.2)	3505 (49.4)	2424 (35.5)
Divorced	188 (13.7)	681 (11.9)	869 (12.2)	802 (11.7)
Widowed	99 (7.2)	395 (6.9)	494 (7.0)	380 (5.6)
Education*†				
Mandatory education	240 (17.6)	1144 (20.1)	1499 (21.1)	1804 (26.4)
Intermediate education	655 (48.0)	2840 (49.9)	3438 (48.4)	3483 (51.0)
High education	471 (34.5)	1706 (30.0)	2115 (29.8)	1342 (19.6)
Main occupation*‡				
Employee	584 (43.0)	2783 (49.0)	3367 (47.8)	NA
Company owner	58 (4.3)	351 (6.2)	409 (5.8)	NA
Student	81 (6.0)	290 (5.1)	371 (5.3)	NA
Retired	391 (28.8)	1697 (29.9)	2088 (29.7)	NA
On long-term sickness absence or disability pensioner	131 (9.7)	202 (3.6)	333 (4.7)	NA
Other	112 (8.3)	359 (6.3)	471 (6.7)	NA
Income in 2009*				
Int$ ≤13848	322 (23.4)	1046 (18.3)	1368 (19.3)	2248 (32.9)
Int$ 13848–22490	299 (21.7)	1162 (20.3)	1461 (20.6)	1267 (18.5)
Int$ 22490–30245	290 (21.1)	1192 (20.8)	1482 (20.9)	1279 (18.7)
Int$ 30245–39661	259 (18.8)	1235 (21.6)	1494 (21.0)	1109 (16.2)
Int$ 39662≥	207 (15.0)	1087 (19.0)	1294 (18.2)	929 (13.6)

Resource use quantities, percentages and costs are rounded.
*Statistically significant difference between respondents with/without ADEs (p<0.05).
†Educational level was missing for 47 of the respondents (0.7%), of whom 11 were ADE cases, and for 203 of the non-respondents (3%).
‡Occupation was missing for 60 respondents, of whom 20 were ADE cases.
ADE, adverse drug events; Int$, international dollars; NA, not applicable.

healthcare, while 164 (14.4%) reported informal care and 131 (11.5%) had stayed home from work.

The economic burden for individuals with self-reported ADEs were (mean±SD, 95% CI) Int$ 521.2 ±1485.7, Int$ 442.7 to 599.8, of which direct costs were measured at Int$ 349.8±1328.7, Int$ 279.6 to 420.0 (67.1%) and indirect costs were Int$ 171.4±537.1, Int$ 143.0 to 199.8 (32.9%; table 3 and figure 2). The average COI was higher among those reporting ADEs compared with respondents without ADEs (COI: Int$ 208.5±876.3, Int$ 185.8 to 231.2; p<0.001). Productivity loss due to long-term sick leave and disability pension increased the indirect costs by Int$ 353.5±1149.6 for those with self-reported ADEs and by Int$ 133.0±728.5 for other respondents (p<0.001). The COI of

respondents with ADR or STE was Int$ 560.9±1439.8, Int$ 468.9 to 652.9. Resource use among respondents with self-reported ADEs, or resulting from ADRs or STEs, occurred both in hospitals and outside of hospital in primary care. For respondents with ADEs, 12% of the healthcare costs originated from primary care nurse or general practitioner visits, while the remaining costs were equally distributed to other outpatient care (44%) and hospitalisations (44%), while the proportions were: 15%, 44% and 41% among all respondents.

Among all respondents with at least one self-reported ADR or STE, the average direct costs resulting from ADRs and STEs were Int$ 31.7±8.5, Int$ 15.0 to 48.4. The resulting costs correspond to 8.7% of the direct costs and 12.5% of the costs of prescription drugs and

Table 2 Resource use in respondents with ADEs, and unit costs for the resources

	Respondents reporting ADE and resource use Total=1377 N (% of total)	Quantity of resources used N or hours	Unit cost (Int$)
Direct costs			
Dispensed medicines*	1218 (88.5)	26436	–
Healthcare use:			
Phone calls	106 (7.7)	267	18.5
Nurse visits	93 (6.8)	182	55.4
Physician visits	92 (6.7)	124	138.6
Specialist physician and ED visits	91 (6.6)	191	313.0
Home healthcare	6 (0.4)	39	110.9
Other somatic visits	52 (3.8)	159	55.4
Psychiatrist visits	4 (0.3)	4	407.5
Other psychiatric visits	49 (3.6)	120	163.0
Hospitalisations	16 (1.2)	20	5036.7
Social services:			
Home-help services	52 (3.8)	1851	45.7
Nursing homes	19 (1.4)	480	173.9
Transportation:			
Services for the disabled	38 (2.8)	420	29.8
Other transportation	240 (17.4)	2793	2.5
Indirect costs			
Sick leave (by age) (years)			
18–24	24 (23.1)	1000	12.1†
25–34	35 (18.4)	1690	15.7†
35–44	36 (19.1)	1852	18.2†
45–54	29 (13.0)	1186	18.5†
55+	39 (5.8)	2062	18.2†
Informal care	228 (16.6)	2871	17.2†

Resource use quantities, percentages and costs are rounded.
*Based on register data.
†The unit cost indicated was the average wage per hour in each age group,[24] which was then multiplied by the general payroll tax. For residents <26 years of age, the general payroll tax was 15.49% and for residents ≥26 years of age it was 31.42%.[25] For informal care, the indicated unit cost was the average wage per hour, which was then multiplied by the general payroll tax for residents ≥26 years of age.
ADE, adverse drug events; ED, emergency department; Int$, international dollars; N, number; NA, not applicable; Q, quartile.

healthcare use for those with ADRs or STEs. The average direct costs resulting from ADRs were Int$ 0.5±4.1 for prescription drugs and Int$ 17.3±159.0 for healthcare use, for those with ADRs. For STEs, the average direct costs were Int$ 1.4±8.7 and Int$ 33.9 ±281.2, respectively. Extrapolated to the Swedish population, the annual direct costs resulting from ADRs or STEs were Int$ 370.1 million. There were no statistically significant differences in COI for respondents with ADRs or STEs, or direct costs resulting from the ADRs or STEs, by age or sex (table 4).

Additional resource use attributed to ADRs by 554 respondents, reported during the 30 days study period, included: 90 medication changes not registered in the Swedish Prescribed Drug Register, 1448 days of lost leisure time (n=117), 529 days of sick leave (n=61) and 600 days with informal care (n=49). For STEs, additional resource use among the 539 respondents included: 116 medication changes, 2510 days of lost leisure time (n=187), 857 days of sick leave (n=88) and 1171 days with informal care (n=92). The health-related quality-of-life scores were significantly lower for respondents with ADEs compared with other respondents (figure 3): the EQ-5D summary estimates were 0.84±0.18 versus 0.71±0.22 (p<0.001), and results from the visual analogue scale were 69.79±20.69 versus 81.17±16.94 (p<0.001).

Sensitivity analyses
The hospitalisation rate reported in the survey (19 respondents reported 24 hospitalisations during the study period) was compared with the hospitalisation rate identified from register data: 85 respondents had 101 hospitalisations covering a total of 365 days during the 5 weeks before answering the survey. Thus, the sensitivity of the reporting of hospitalisations in the questionnaire was 59% and the specificity was 99% compared with register data. Among the 85 respondents, 24 hospitalisations lasted only 1 day or night, 10 hospitalisations occurred less than 1 week before the respondent's questionnaire was registered at Statistics Sweden, and 7 hospitalisations identified from the register were duplicate registrations based on transfers between hospitals or departments. For sick leave, the sensitivity was 12% and
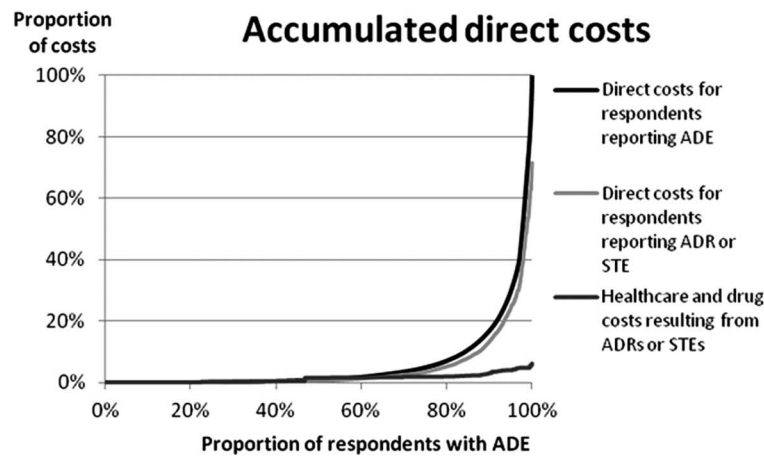
Abbreviations: ADE = adverse drug events; ADR = adverse drug reaction; STE = sub-therapeutic effect of medication therapy.

Figure 1 Accumulated direct costs of individuals with self-reported adverse drug events, including the subgroup reporting adverse drug reactions or subtherapeutic effects of medication therapies.

the specificity was 99%, compared with register data, with 55 persons identified from both the register and the questionnaire. Of the 70 respondents identified from the register but not from the questionnaire, 25 were reported to be on long-term sickness absence, seeking a job or on parental leave, whereas 45 persons had not reported the sick leave identified in the register. Of those 390 respondents reporting sick leave that was not identified in the register, 306 reported sick leave of less than 2 weeks (which in Sweden is paid by the employer and is not registered), 7 had disability pension and the remaining 77 individuals did not receive

sickness benefit for their absence. Additional deviations were not possible to explain using the available data.

According to the propensity score analyses, the attributable costs for ADEs were Int\$ 99.4 for direct healthcare costs and Int\$ 221.5 for indirect costs (excluding informal care).

DISCUSSION

In this study, the societal COI of 1377 individuals with self-reported ADEs was Int\$ 717 750.4 and the direct costs resulting from self-reported ADRs and STEs in 943

**Table 3** Average cost of illness for respondents with and without self-reported ADEs

	COI with ADE N=1377 average±SD	COI without ADE N=5722 average±SD
Dispensed prescription medicines (Int\$)*	48.6±119.0	24.7±103.3
Healthcare use (Int\$)*	164.9±935.3	40.1±360.7
Social services (Int\$)	122.1±778.8	83.6±673.5
Transportation (Int\$)*	14.3±84.8	6.9±67.2
Total direct cost (Int\$)*	349.8±1328.7	155.2±805.3
Productivity loss, sick leave (Int\$)*	124.4±496.2	41.1±272.8
Informal care† (Int\$)*	47.1±187.0	12.1±89.3
Total indirect cost (Int\$)*	171.4±537.1	53.3±290.9
Cost of illness (Int\$)*	521.2±1485.7	208.5±876.3
Other resource use:		
Over-the-counter drugs, number	1.6±1.5	1.0±1.9
Natural remedies, number	0.5±1.0	0.3±1.2
Lost leisure time, days	3.7±7.8	1.0±4.2
Prevalent disability pension, n (%)	135 (9.8)	242 (4.2)
EQ-5D index value	0.71±0.22	0.84±0.18
Self-rated health by EQ-VAS	69.8±20.7	81.2±16.9

Resource use quantities, percentages and costs are rounded.
*Statistically significant cost difference between respondents with/without ADEs (p<0.05).
†Of the 546 respondents reporting informal care, 56 respondents were excluded from the analyses since the amount of care (days and hours) was not reported.
ADE, adverse drug events; EQ-5D, The EuroQol Group's five dimension health state questionnaire with five levels of severity; EQ-VAS, The EuroQol Group's visual analogue scale; Int\$, international dollars; N, population size.
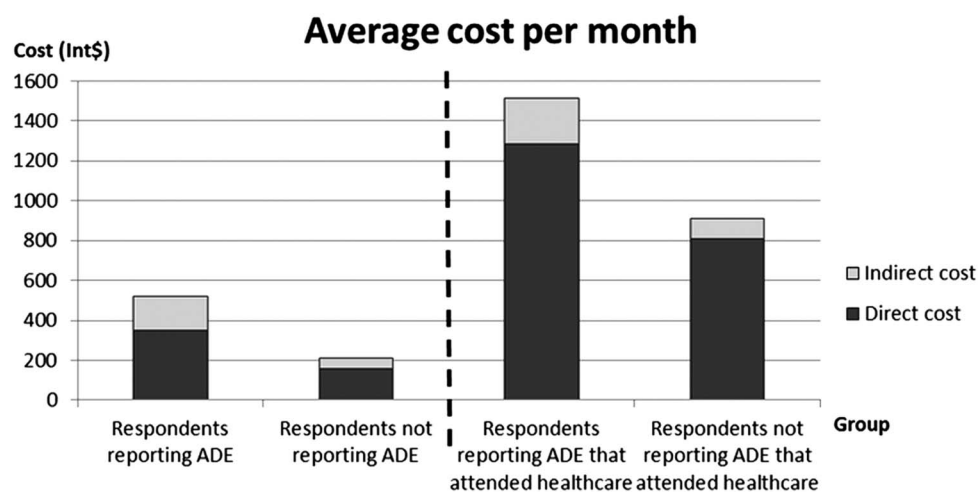
Figure 2 The average monthly cost of illness of respondents based on reported adverse drug event status and healthcare attendance, divided into direct and indirect costs.

individuals were Int\$ 29 935.9. Thus, the extrapolated annual direct costs in Sweden resulting from ADRs and STEs were Int\$ 370 million in 2010. Our results suggest that ADEs also cause costs outside hospitals, as well as for patients not attending hospitals. Thus, studies limited to drug-related admission will underestimate the economic impact in society. We have also found an association between the occurrence of ADEs and high overall COI that needs to be further analysed in future studies. Those reporting ADEs were more extensive users of prescription drugs, healthcare resource use, transportation services and informal care, compared with other respondents. Moreover, they had more short-term sick leave and disability pension than other

Table 4 Distribution of costs among respondents with self-reported ADRs or STEs*, including cost of illness (all-cause morbidity) and direct costs resulting from self-reported ADRs or STEs

|	Respondents with ADR or STE N (%)	Average cost of illness for respondents with ADR or STE Average±SD, Int\$	Direct cost resulting from ADRs or STEs† Average±SD, Int\$
Total resource use among respondents with ADRs or STEs (N=943)			
Cost of illness	–	560.9±1439.8	NA
Direct costs	–	(365.6±1279.4)	NA
Indirect costs	–	(195.3±564.7)	NA
Age (years)			
18–34	209 (22.2)	556.5±1580.8	31.4±241.7
35–64	473 (50.2)	511.5±1154.4	41.5±326.9
65+	261 (27.7)	653.9±1754.8	14.3±77.3
Sex			
Men	346 (36.7)	486.4±1182.8	32.1±232.4
Women	597 (63.3)	604.0±1568.9	31.5±276.7
Type of ADE‡			
ADR	554 (58.7)	659.0±1613.6	36.6±290.8
STE	539 (57.2)	566.0±1446.1	47.5±335.5
Self-reported preventability			
Preventable§	208 (22.1)	717.6±1897.3	56.8±342.9
Non-preventable	735 (77.9)	516.5±1279.2	24.7±232.7

Percentages and costs are rounded.
*Include respondents with at least one self-reported ADR or STE.
†Include resource use reported for both ADRs and STEs.
‡Categories overlap; both includes respondents with at least one self-reported ADR or STE, respectively.
§Includes respondents with at least one preventable self-reported ADR or STE.
ADR, adverse drug reaction; Int\$, international dollars; N, subgroup sample size; NA, not applicable; STE, subtherapeutic effect of medication therapy.
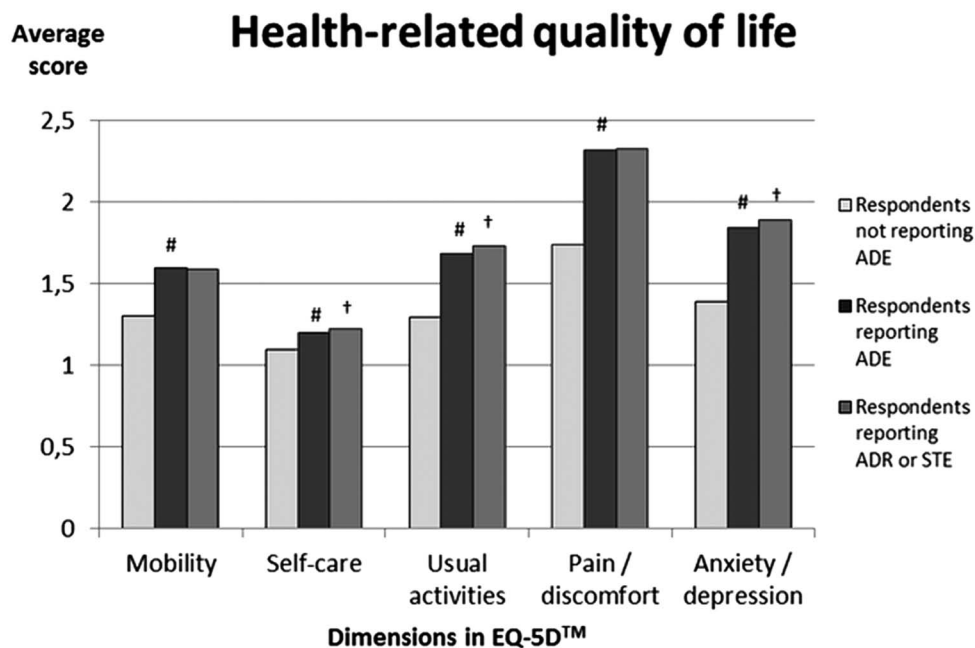
Abbreviations: ADE, adverse drug events; EQ-5D, The EuroQol Group's five dimension health state questionnaire with five levels of severity.

Figure 3 Dimensions of health-related quality of life, health profile results from the EQ-5D instrument, the severity reported for each domain using the 1–5-point Likert scale (from 'no problem' to 'extreme problem'), categorised based on the reported adverse drug event status.

respondents. Much of this increase in resource use will be due to comorbidities, and will be involved in causing ADEs, but although not quantified as costs caused by ADEs, some respondents also reported that they had experienced sick leave, informal care and lost leisure time resulting from ADRs and STEs.

The strengths of this study include a large number of respondents. However, certain groups were under-represented among respondents, for example, young adults, men and those born in another country than Sweden. It is possible that the decision to respond is associated with health status, with either severely ill patients or healthy residents being less prone to respond. Previous research suggests that the bias is mainly towards survey respondents being healthier than those not responding.[31] Other causes for incorrect estimation of the costs for ADEs in our study were the limitation to ADE status and used resources reported by the respondents. Responses were carefully examined to exclude responses not indicating a suspected symptom or drug; there may be symptoms reported that were, for example, resulting from the underlying disease rather than the drug use, and other relevant symptoms perceived by the respondent to be either not related to the drug use or not included in the five ADE categories included in the questionnaire. Previous research has shown that there is little overlap between ADEs reported by patients and by physicians[32]; thus, we may underestimate the prevalence and resulting resource use of ADEs by not including the physicians' experiences. However,

previous research has identified patients themselves as important actors in reporting adverse events, also due to drug use.[33] Moreover, the general public is today expected to monitor drug use and report suspected ADRs. Thus, we believe that the self-reported ADEs reported in our survey adds a relevant aspect to the knowledge of drug use outcomes, although it needs to be acknowledged that the events were self-reported and not assessed for causality by any experienced clinician. The sensitivity analyses included comparing resource use with what was reported in national registers, including data for hospitalisations and sick leave. The register analyses indicated an under-reporting rather than an overestimation of the resource use. Moreover, our main cause for underestimating COI may be the limitation of indirect costs to short-term sick leave and informal care. In a recent study of the total COI in Sweden, short-term sickness represented approximately 30% of the indirect costs and 17% of the COI.[34] Lost wages and household production have been reported to cause 47% of the total costs in patients discharged from hospital with adverse events (of which ADEs corresponded to 32% of all costs).[35] Our design (time frame and data collection method) did not allow the estimation of indirect costs from disability pension and mortality, thus underestimating the economic impact of ADEs.

Our ADE definition was more inclusive than those of some previous studies',[3] although the included categories' associations with drug treatment and drug-related problems have been acknowledged previously. On the

basis of the ADE definition applied, the prevalence and associated costs will differ. Limiting the inclusion to only, for example, ADRs and STEs resulted in a prevalence of 13% in the Swedish population, which is equal to the previously estimated ambulatory care prevalence of ADEs.[36] Our estimated 1-month prevalence of ADRs of 7.8% was similar to the 2-week prevalence (6.4%) identified in a previous survey in the Swedish general public.[6]

Our results suggest that the drug users experience ADEs and associated consequences that have not so far been included in studies of injuries resulting from medical intervention related to drugs. Thus there is a need to further explore and identify the causes, consequences and possibilities for prevention of experienced ADEs. In our study, less than one-fifth of respondents with ADEs attended healthcare during the study period, and one-fifth of those with ADRs or STEs reported drug-related healthcare contacts. A previous study has reported that three quarters of elderly participants experiencing ADRs contacted a physician and 5% were also hospitalised due to ADR during a 1-year study period,[37] but the disparity may depend on the length of the study period and the age of the respondents. Our average direct costs resulting from ADRs (Int$ 37) were, as expected, low compared with previous estimates of approximately Euro 2800 for ADRs in patients attending hospitals.[38] However, the small proportion of respondents reporting healthcare contacts due to their ADR or STE (with no respondent reporting hospitalisation due to an ADR or STE), and the short study period, makes direct comparisons impossible. Our estimated average direct cost for respondents with ADEs that attended healthcare during the study period (Int$ 1283) was similar to the attributable charges previously reported for ADEs identified after a visit to ambulatory care: US$ 926 (2006 value).[39]

According to our results, there is a need for increased awareness about the impact of ADEs which does not result in the patient attending hospital. Lundkvist and Jönsson[40] have previously remarked on the balance between the costs of ADRs and benefits of drug treatments, and the two costs of ADRs: costs resulting from treating ADRs and from avoiding ADRs. Moreover, additional efforts are needed to handle STE, which seem to be just as common and costly as ADRs. According to our results, the balancing of costs and benefits for drugs will also include the occurrence of and costs associated with insufficient effects of medicines, although not all these costs will be possible to prevent or avoid through improved drug treatments. Since ADE status seems to be associated with high overall COI and incurs healthcare resource use, many of these patients should be possible to identify in the healthcare system, even when ADE in itself may not be the main cause of resource use. On the basis of the perspective of a decision or analysis, our results indicate that such costs will also occur outside the healthcare system, for example, for sick leave, informal care and lost leisure time. The result was strengthened by the propensity score analyses indicating that there were both direct healthcare costs and indirect costs attributable to ADEs. Thus, the patient's views and experiences of drug treatments need to be further addressed in treatment decisions.

Future research is needed to further analyse the relationship between ADEs and the associated resource use, to identify when and how the resource use occurs, as well as the true relationship between ADEs and the overall COI. There is also a need to examine the indirect costs resulting from ADEs, since our study could only briefly describe sick leave and informal care resulting from ADRs and STEs. Moreover, the resource use identified from patients' self-reports should be contrasted by population-based estimates of ADEs and the associated resource use identified by healthcare professionals, to enable further analyses of the clinical and economic impact of ADEs, identify high-risk patients and study the causes and consequences of ADEs in the general public.

CONCLUSIONS

To our knowledge, this is the first study to estimate COI of ADEs in the general public. Our results show that self-reported ADRs and STEs cause resource use both in hospitals and primary care. Moreover, ADEs seem to be associated with a high overall COI from the societal perspective, when comparing respondents with and without ADEs. There is a need to further examine the relationships between ADEs and associated resource use and overall COI, respectively, and to study the indirect costs resulting from ADEs.

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in the decision to submit it for publication. The researcher's work was independent from that of the sponsor. All authors, external and internal, had full access to all the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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