Cost-of-Illness of patient-reported Adverse Drug Events – A population-based cross-sectional survey

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-002574
Article Type:	Research
Date Submitted by the Author:	08-Jan-2013
Complete List of Authors:	Gyllensten, Hanna; Nordic school of public health NHV, Rehnberg, Clas; Karolinska Institutet, Department of Learning, Informatics, Management and Ethics – LIME Jönsson, Anna; Faculty of Health Sciences, Linköping University, Department of Drug Research/Clinical Pharmacology; County Council of Östergötland, Department of Clinical Pharmacology Petzold, Max; Sahlgrenska academy, University of Gothenburg, Department of Public Health and Community Medicine Carlsten, Anders; Nordic school of public health NHV, Andersson Sundell, Karolina; Nordic school of public health NHV, ; Sahlgrenska Academy, University of Gothenburg, Department of Public Health and Community Medicine
Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology, Health economics, Health services research, Pharmacology and therapeutics
Keywords:	EPIDEMIOLOGY, HEALTH ECONOMICS, Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PUBLIC HEALTH, Adverse events < THERAPEUTICS

TITLE

Cost-of-Illness of patient-reported Adverse Drug Events – A population-based cross-sectional survey

Authors

Hanna Gyllensten, DrPH-student (**corresponding author**)
Nordic School of Public Health NHV, Box 121 33, SE-402 42 Gothenburg, Sweden
Phone: +46-31-693925
Fax: +46-31-691777

Clas Rehnberg, Professor
Department of Learning, Informatics, Management and Ethics – LIME, Karolinska Institutet, Stockholm, Sweden

Anna K. Jönsson, PhD
Department of Drug Research/Clinical Pharmacology, Faculty of Health Sciences, Linköping University, Linköping, Sweden, and Department of Clinical Pharmacology, County Council of Östergötland, Linköping, Sweden

Max Petzold, Professor
Akademistatistik – Centre for applied biostatistics, Sahlgrenska academy, University of Gothenburg, Department of Public Health and Community Medicine, Gothenburg, Sweden

Anders Carlsten, Associate professor
Nordic School of Public Health NHV, Gothenburg, Sweden, and
Medical Products Agency, Uppsala, Sweden

Karolina Andersson Sundell, Associate professor
Nordic School of Public Health NHV, Gothenburg, Sweden, and
Unit of Social Medicine, Department of Public Health and Community Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Keywords

adverse drug event
drug therapy
cost of illness
quality of life
survey

Word count: 3702

ABSTRACT

Objectives
To estimate the cost-of-illness (COI) of individuals with self-reported adverse drug events (ADE) 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 (ADR) and sub-therapeutic 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 7,099 responded, 1,377 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% confidence interval) 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 to other respondents (COI: 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 have been reported not only to cause harm but also cause resource use from patients attending hospitals.
- Even though adverse drug events have been identified also 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 adverse drug events and compare to those without adverse drug events.

Key messages

- Our study suggests high overall costs of illness for individuals with self-reported adverse drug events, estimated to 8,871 million international dollars annually in Sweden when including those with adverse drug reactions, drug dependence, drug intoxications, sub-therapeutic effects of medication therapy and untreated indications.
- The estimated annual direct costs for prescribed drugs and healthcare use resulting from treatment of two of the adverse drug event categories, i.e. adverse drug reactions and sub-therapeutic effects of medication therapy, were 370 million international dollars.
- A large proportion (56%) of the healthcare resource use in respondents with adverse drug events 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 underrepresented in the analysis.

INTRODUCTION

Adverse drug events (ADEs), "an injury resulting from medical intervention related to a drug", [1] have been identified as a public health problem that causes harm to patients and considerable resource use. According to previous research, 5-6 % of hospitalizations are drug-related, [2,3] and hospitalized patients experiencing adverse drug effects cause additional hospital costs of USD 2284-5640 per patient (in 2000 values). [4] Little is known about the corresponding costs outside hospitals, [4] 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. [5]

The cost-of-illness (COI) is the economic burden of disease or diseases to the society. The distribution of the cost items in the COI could be used to judge the financial relevance in relation to other public health problems, and for different actors in the healthcare system study the development of the associated resource use over time. [6] Information about COI could also be useful for developing future intervention studies to address ADEs and to retrieve the costs for modelling e.g. 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, sub-therapeutic effects of medication therapy (STE), drug dependence, drug intoxications and untreated indications. 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. [7]

METHODS

Study design

We conducted a population-based observational retrospective COI study of self-reported ADEs. The COI was prevalence-based and measured from a societal perspective, including direct and indirect costs during the 30 days study period. Costs were measured using a bottom-up approach using unit costs for resource use. Intangibles were approximated using health-related quality of life.

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 January 1st 2010. The sample size was calculated by assuming a one-month prevalence of 6.4% for ADRs in Sweden based on a previous study, [5] a preventable proportion of approximately 10%, [8,9] a 60% response rate, [5] and a maximum width of ± 0.3% for the 95% confidence interval of the preventable proportion. The estimated sample size (7,013) 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 February 1st 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 (OTC) as well as herbal remedies; experienced ADEs; and perceived preventability, consequences and use of healthcare due to ADRs and STEs. The questionnaire also included demographic and socioeconomic characteristics, and the EQ-5D questionnaire for health-related quality of life [10]. The questionnaire was piloted with

healthcare professionals, individuals from the general public and specific patient groups. All reported ADEs were carefully examined and cross-examined to exclude responses not indicating a suspected symptom or drug.

Data from the questionnaire was 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: i.e. 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.

Dispensed prescription medicines and associated costs were retrieved from the Swedish Prescribed Drug Register, National Board of Health and Welfare. Costs included both patient co-payments 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 in the survey for treating an ADR or STE and dispensed during the study period according to the register.

Healthcare use, both overall healthcare use and encounters resulting from ADRs or STEs, were

retrieved from the questionnaire. Results from pre-specified questions and from free text were categorized 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 hospitalizations. 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. [11] A visit to other healthcare personnel than physicians was weighted as 40% of the cost of a physician visit. Phone calls were weighted as 1/3 of the cost of visiting a nurse, and home healthcare as 2 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 [11]).

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. [12-14]

Indirect costs

Indirect costs included costs resulting from lost productivity for the respondent due to short-term morbidity (sick-leave) and of relatives to the respondents' due to informal care. [6] Because of 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. [15] In addition, productivity loss due to reported long-term sick-leave (among those <70 years) and disability pension (among those <65 years) was calculated. Lost productivity was identified from the questionnaire. Costs for lost productivity were measured with the human capital approach, [6] using national wages statistics and social security contributions. [16,17]

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 was approximated by the respondents' health-related quality of life using EQ-5D-5L and the UK value sets. [18,19]

Analyses

Respondents' characteristics were compared to the non-respondents, and compared based on ADE status (table 1), using register data for: age (young adults age 18-34, middle aged 35-64 years old, or individuals above the Swedish retirement age ≥65 years old), country of birth (Sweden or other than Sweden), educational level (mandatory education, intermediate education, i.e. high school and up to two years of university education, or high education, i.e. more than two 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 chi square tests.

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

	Respondents reporting ADE Total = 1,377 N (%)	Respondents not reporting ADE Total = 5,722 N (%)	All respondents Total = 7,099 N (%)	Non-respondents Total = 6,832 N (%)
Age[#]				
18 – 34 years	294(21.4)	1036(18.1)	1330(18.7)	2328(34.1)
35 – 64 years	675(49.0)	2935(51.3)	3610(50.9)	3357(49.1)
65 – years	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$ ≤ 13,848	322(23.4)	1046(18.3)	1368(19.3)	2248(32.9)
Int$ 13,848-22,490	299(21.7)	1162(20.3)	1461(20.6)	1267(18.5)
Int$ 22,490-30,245	290(21.1)	1192(20.8)	1482(20.9)	1279(18.7)
Int$ 30,245-39,661	259(18.8)	1235(21.6)	1494(21.0)	1109(16.2)
Int$ 39,662 ≥	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 which 11 were ADE cases, and 203 of the non-respondents (3.0%).
[†] Occupation was missing for 60 respondents, of which 20 were ADE cases.

Abbreviations: ADE = adverse drug events; Int$ = international dollars; NA = not applicable.

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). [20] The Int$ is a hypothetical currency with the same purchasing power as the United States dollar (US$) in the Unites States of America, allowing for differences in price levels between countries. [21] Means and standard deviations 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 ADRs or STEs, 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 ADRs or STEs, using one-way anova (for age categories) and a two-tailed t-test with unequal variances (for sex). Extrapolated annual direct costs, indirect costs and COI were calculated for the adult Swedish population (N = 7,382,226) during 2010. All statistical analyses were made using the STATA 10.1 software.

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)	26,436	-
Healthcare use:			
Phone calls	106 (7.7)	267	18.5
Nurse visits	93 (6.8)	182	55.4
Physicians 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
Hospitalizations	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 disabled	38 (2.8)	420	29.8
Other transportation	240 (17.4)	2793	2.5
INDIRECT COSTS:			
Sick-leave (by age):			
18-24 years	24 (23.1)	1000	12.1[*]
25-34 years	35 (18.4)	1690	15.7[*]
35-44 years	36 (19.1)	1852	18.2[*]
45-54 years	29 (13.0)	1186	18.5[*]
55+ years	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.

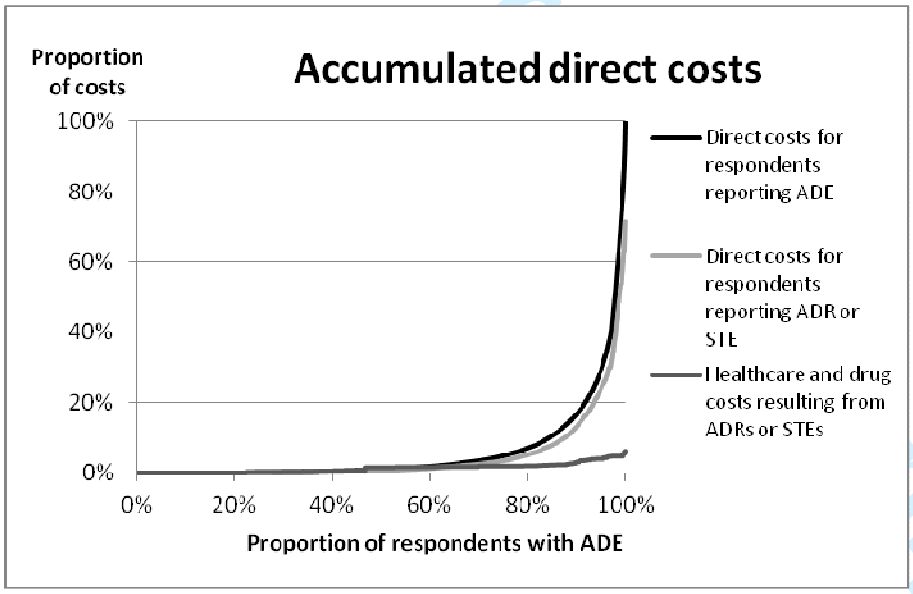
[*] The unit cost indicated was the average wage per hour in each age group [16], which was then multiplied by the general payroll tax. For citizens <26 years of age the general payroll tax was 15.49% and for citizens ≥26 years of age it was 31.42%. [17] For the informal care, the indicated unit cost was the average wage per hour, which was then multiplied by the general payroll tax for citizen's ≥26 years of age.

Abbreviations: ADE = adverse drug events; ED = emergency department; Int$ = international dollars; N = number; NA = not applicable; Q = quartile.

Sensitivity analyses

Sensitivity analyses were made based on available register data for hospitalizations and respondents' lost productivity from sick-leave. Moreover, an additional extrapolation to the annual COI in the Swedish population was made, under the assumption that all ADEs and resource use in the study population was reported by the respondents, thus assuming that non-respondents had no ADEs or resource use. Because of the skewed data, with resources corresponding to 80% of the direct costs for respondents with ADEs reported by 10% of these respondents (figure 1), a proposed sensitivity analysis based on interquartile range, in the research plan, was unachievable. Additional changes from the research plan were limited to how results were reported.

Figure 1: Accumulated direct costs of individuals with self-reported ADEs, including the subgroup reporting ADRs or STEs.



Abbreviations: ADE = adverse drug events; ADR = adverse drug reaction; STE = sub-therapeutic effect of medication therapy.

RESULTS

A total of 7,099 questionnaires were collected (response rate 51 %). At least one ADE was reported by 1,377 (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 to other respondents (table 1). Resource use for respondents with ADE is presented in table 2. Healthcare was attended by 239 (17.4%) of respondents reporting ADEs, of which 96 (40.2%) were hospitalized or visited a specialist physician (including psychiatrist visits). Among all respondents, 717 (10.1%) attended healthcare. Resource use among respondents with ADE included also outpatient care in hospitals with other healthcare personnel and primary care visits (e.g. nurse visits and physician visits). In addition, home-help services or a nursing home was attended by 51 (4.5%), of the 1,138 respondents with ADE that did not attend healthcare, while 164 (14.4%) reported informal care and 131 (11.5%) had stayed home from work.

The economic burden for individuals with ADEs were (mean ± standard deviation, 95% confidence interval) Int$ 521.2 ± 1,485.7, Int$ 442.7 to 599.8, of which direct costs were measured at Int$ 349.8 ± 1,328.7, 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 to 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 ± 1,149.6 for those with ADEs and Int$ 133.0 ± 728.5 for other respondents ($p < 0.001$). The COI of respondents with ADR or STE was Int$ 560.9 ± 1,439.8, Int$ 468.9 to 652.9. Extrapolated to the Swedish population, the annual direct costs, indirect costs and COI of individuals with ADE were: Int$ 5,953.4 million, Int$ 2,917.5 million, and Int$ 8,870.9 million, respectively (figure 3). Resource use among respondents with 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.

Table 3. Average cost-of-illness for patients with and without self-reported ADEs.

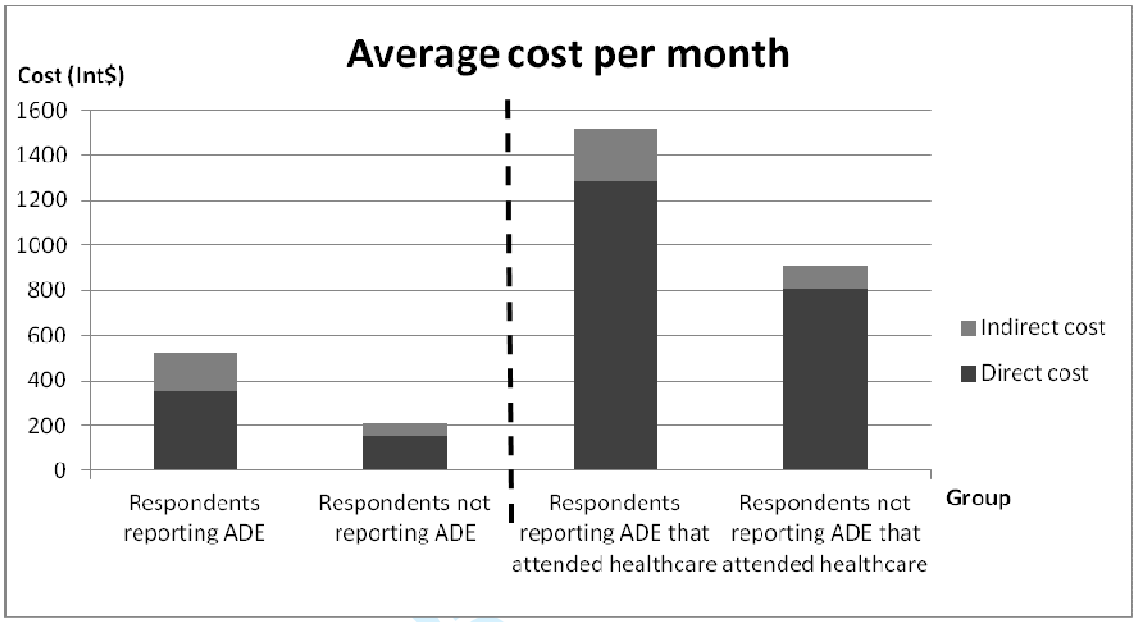
	COI with ADE N = 1377 average ± SD	**COI without ADE** N = 5722 average ± SD
Dispensed prescription medicines (Int$)[#]	48.6 ± 119.0	24.7 ± 103.3
Healthcare use (Int$)[#]	164.9 ± 935.3	40.1 ± 360.7
Social services (Int$)	122.1 ± 778.8	83.6 ± 673.5
Transportation (Int$)[#]	14.3 ± 84.8	6.9 ± 67.2
Total direct cost (Int$)[#]	**349.8 ± 1,328.7**	**155.2 ± 805.3**
Productivity loss, sick-leave (Int$)[#]	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 ± 1,485.7***	***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.

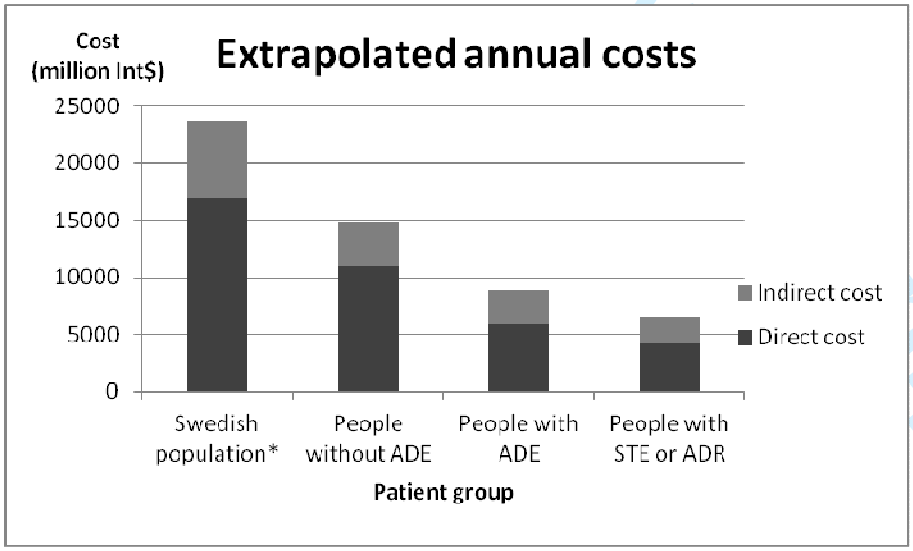
Abbreviations: ADE = adverse drug events; EQ-5D™ = The EuroQol Group's five dimension health state questionnaire with five levels of severity; EQ-VAS = The EuroQol Group's visual analogue scale; Int$ = international dollars; N = population size; SD = standard deviation.

Figure 2: The average monthly cost-of-illness of respondents based on reported ADE-status and healthcare attendance, divided into direct and indirect costs.



Abbreviations: ADE = adverse drug events; Int$ = international dollars.

Figure 3: The annual cost-of-illness during 2010, extrapolated to the Swedish adult population, divided into direct and indirect costs.



* Summary measure for all individuals with and without ADEs.

Abbreviations: ADE = adverse drug events; Int$ = international dollars.

Among all respondents with at least one 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 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).

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 the ADRs or STEs*** average ± SD, Int$
Total resource use among the respondents with ADRs or STEs (N = 943)			
Cost-of-illness	-	560.9 ± 1,439.8	NA
Direct costs	-	*(365.6 ± 1,279.4)*	NA
Indirect costs	-	*(195.3 ± 564.7)*	NA
Age			
18 – 34 years	209 (22.2)	556.5 ± 1,580.8	31.4 ± 241.7
35 – 64 years	473 (50.2)	511.5 ± 1,154.4	41.5 ± 326.9
65 – years	261 (27.7)	653.9 ± 1,754.8	14.3 ± 77.3
Sex			
Men	346 (36.7)	486.4 ± 1,182.8	32.1 ± 232.4
Women	597 (63.3)	604.0 ± 1,568.9	31.5 ± 276.7
Type of ADE†			
ADR	554 (58.7)	659.0 ± 1,613.6	36.6 ± 290.8
STE	539 (57.2)	566.0 ± 1,446.1	47.5 ± 335.5
Self-reported preventability			
Preventable¥	207 (22.0)	720.9 ± 1,901.3	57.1 ± 343.7
Non-preventable	736 (78.0)	515.9 ± 1,278.4	24.6 ± 232.6

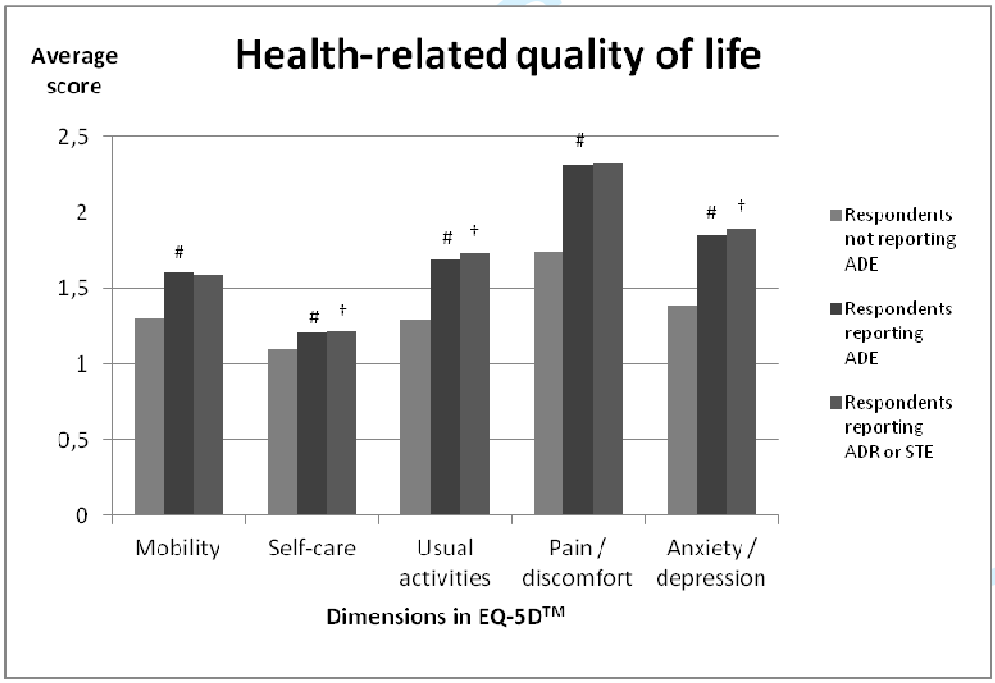
Percentages and costs are rounded.

Include persons with at least one self-reported ADR or STE.
* Include resource use reported for both ADRs and STEs.
† Categories overlap, both includes persons with at least one self-reported ADR or STE respectively.
¥ Includes persons with at least one preventable self-reported ADR or STE.

Abbreviations: ADR = adverse drug reaction; Int$ = international dollars; N = subgroup sample size; NA = not applicable; STE = sub-therapeutic effect of medication therapy.

Additional resource use attributed to ADRs by 554 respondents, reported during the 30 days study period, included: 90 medication changes not identified in the register, 1,448 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, 2,510 days of lost leisure time (n = 187), 857 days of sick-leave (n = 88), and 1,171 days with informal care (n = 92). The health-related quality of life scores were significantly lower for respondents with ADEs compared to other respondents (figure 4): the EQ-5D™ summary estimates were 0.84 ± 0.18 vs. 0.71 ± 0.22 ($p < 0.001$), and results from the visual analogue scale were 69.79 ± 20.69 vs. 81.17 ± 16.94 ($p < 0.001$).

Figure 4: Dimensions of health-related quality of life, health profile results from the EQ-5D™ instrument, categorized based on reported ADE-status.



[#] Statistically significant difference between respondents with/withoutADEs ($p<0.05$).
[†] Statistically significant difference between respondents with at least one ADR or STE compared to other respondents with ADEs ($p<0.05$).

Abbreviations: ADE = adverse drug events; ADR = adverse drug reaction; EQ-5D™ = The EuroQol Group's five dimension health state questionnaire with five levels of severity; STE = sub-therapeutic effect of medication therapy.

Sensitivity analyses

The hospitalization rate reported in the survey (19 respondents reported 24 hospitalizations during the study period) was compared to the hospitalization rate identified from register data: 85 respondents had 101 hospitalizations covering a total of 365 days during the 5 weeks before answering the survey. Thus the sensitivity of the reporting of hospitalizations in the questionnaire was 59% and the specificity was 99% compared to register data. Among the 85 respondents, 24 hospitalisations lasted only one day or night, 10 hospitalisations occurred less than one 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 the specificity was 99%, compared to 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 reported to be on long-term sickness absence, seeking a job or on parental leave, 45 persons had not reported the sick-leave identified in the register. Of those 390 persons reporting sick-leave that were 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 persons did not receive sickness benefit for their absence. Additional deviations were not possible to explain using available data.

Assuming that all ADEs and resource use in the study population was reported by our respondents, resulted in an annual COI of individuals with ADEs in the Swedish population Int$ 746 million (direct costs: Int$ 501 million).

DISCUSSION

In this study, the societal COI of 1,377 individuals with self-reported ADEs was Int$ 717,750.4 and the direct costs resulting from self-reported ADRs and STEs in 943 individuals was Int$ 29,935.9. Thus, the extrapolated annual direct costs in Sweden resulting from ADRs and STEs, was Int$ 370 million in 2010. Our results suggest that ADEs cause costs also outside hospitals, and 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 further analyzing in future studies.

The strengths of this study include a large number of respondents. However, certain groups were underrepresented among respondents, e.g. 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 citizens being less prone to respond. Therefore we report a minimum estimation of the extrapolated annual COI for individuals with ADEs in the Swedish general public, assuming the non-respondents had no ADEs or resource use; thus were healthier than the respondents. This resulted in healthcare costs far below what was expected if compared to the annual healthcare expenditure in Sweden, [22] and even comparing our main analysis of extrapolated direct costs for the population, suggest that much resource use was unaccounted for in our analyses, thus we underestimate rather than overestimate the economic impact of ADEs. Moreover, previous research suggests the bias is mainly towards survey respondents being healthier than those not responding. [23] 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 e.g. resulting from the underlying disease rather than the drug use, and other relevant symptoms may not have been perceived related to the drug use by the respondent or

not being included in the five ADE categories included in the questionnaire. Still, previous research has shown that there is little overlap between ADEs reported by patients and by physicians, [24] thus we may underestimate the prevalence and resulting resource use of ADEs. The sensitivity analyses included comparing the resource use to what was reported in registers, only data for hospitalizations and sick-leave were available in national registers, which also indicated an underreporting rather than overestimating the resource use. Yet our main cause for underestimating the COI should 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. [25] Lost wages and household production has 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). [26] Our design (time frame and data collection method) did not allow estimation of indirect costs from disability pension and mortality, thus underestimating the economic impact of ADEs.

Our estimated one-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. [5] In our study, less than one fifth of respondents with ADEs attended healthcare during the study period, and on 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 hospitalized due to the ADR during a one year study period, [27] but the disparity may depend on the length of the study period and the age of respondents. Our average direct costs resulting from ADRs (Int$ 37) were, as expected, low compared to previous estimates of approximately Euro 2,800 for ADRs in patients attending hospitals. [28] Though, the small proportion of respondents reporting healthcare contacts due to their ADR or STE (with no respondent reporting hospitalization 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$

1,283) was similar to the attributable charges previously reported for ADEs identified after a visit to ambulatory care: US$ 926 (2006 value). [29] Our extrapolated annual direct costs for individuals with ADEs (Int$ 5,953.4 million) equals 17% of the total healthcare expenditures in Sweden during 2010 (Int$ 35,257.8 million). [22] The extrapolated direct costs resulting from ADRs and STEs (Int$ 370 million) represented a small part of the total healthcare costs, but was comparable to the excess hospital costs estimated for obesity in Sweden (US$ 269 million in 2003). [30]

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. Moreover, additional efforts are needed to handle STE, which seem to be just as common and costly as ADRs. Since ADE status seems to be associated with high overall COI and incur healthcare resource use, many of these patients should be possible to identify in the healthcare system, even when the ADE in itself may not be the main cause of resource use.

Future research is needed to further analyze the relationship between ADEs and the associated resource use, to identify when and how the resource use occurs, and 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 estimating the 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 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.

ACKNOWLEDGEMENT

We wish to thank the survey respondents for taking the time to share their experience with us.

ETHICS APPROVAL

The study received ethical approval from the Regional Ethical Review Board in Gothenburg (approval reference number: 238-10), in 2010.

The questionnaire cover letter included information about how and why the research was conducted, contact information, and how to withdraw. Informed consent was implied by returning the questionnaire. The questionnaire and the cover letter were developed in accordance with the declaration of Helsinki.

The ethical approval did not include an approval to share individual responses or register data publicly.

COMPETING INTEREST DECLARATION

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: all authors had financial support from National Corporation of Swedish Pharmacies (Apoteket AB) for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

The opinions or assertions contained herein are the private views of the authors, and are not to be construed as official or as reflecting the views of the Medical Products Agency.

FUNDING

The research is part of the DRUMS project (Drug-related morbidity and mortality in Sweden: prevalence, preventability and costs) funded by an unrestricted grant from the National Corporation of Swedish Pharmacies (Apoteket AB). The study sponsor had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the article; and in the decision to submit it for publication. The researchers work was independent from the sponsor. All authors, external and internal, had full access to all of 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.

DETAILS OF CONTRIBUTORS

KAS was the principal investigator. HG did the analyses and drafted the manuscript. AC, AKJ, CR, HG, KAS and MP contributed to the study design and development of the questionnaire, data

analysis, and interpretation of the results and commented on the draft. Also, Katja M Hakkarainen, Staffan Hägg, Johnny Pettersson and Annika Yeiter contributed to the study design, and the development and piloting of the questionnaire. Tatiana Zverkova Sandström contributed to the data analysis. All authors had full access to all data. HG is the guarantor of the study.

LICENCE FOR PUBLICATION

REFERENCES

1. Bates DW, Boyle DL, Vander Vliet MB, et al. Relationship between medication errors and adverse drug events. J Gen Intern Med 1995**;10**:199-205. doi:10.1007/BF02600255.

2. Einarson TR. Drug-related hospital admissions. Ann Pharmacother 1993**;27**:832-840.

3. Krähenbühl-Melcher A, Schlienger R, Lampert M, et al. Drug-related problems in hospitals: a review of the recent literature. Drug Saf 2007**;30**:379-407.

4. Rodríguez-Monguió R, Otero MJ, Rovira J. Assessing the economic impact of adverse drug effects. Pharmacoeconomics 2003**;21**:623-650.

5. Isacson D, Johansson L, Bingefors K. Nationwide survey of subjectively reported adverse drug reactions in Sweden. Ann Pharmacother 2008**;42**:347-353. doi:10.1345/aph.1K488.

6. Segel JE editor. Cost-of-Illness Studies - A Primer. RTI-UNC Center of Excellence in Health Promotion Economics, 2006:1-39.

7. Hakkarainen KM, Andersson Sundell K, Petzold M, et al. Self-reported adverse drug events equally prevalent across age groups - a population-based survey in Sweden. Manuscript submitted for publication. .

8. Gandhi TK, Seger DL, Bates DW. Identifying drug safety issues: from research to practice. Int J Qual Health Care 2000**;12**:69-76. doi:10.1093/intqhc/12.1.69.

9. Gandhi TK, Weingart SN, Borus J, et al. Adverse drug events in ambulatory care. N Engl J Med 2003**;348**:1556-1564. doi:10.1056/NEJMsa020703.

10. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. The EuroQol Group. Health Policy 1990**;16**:199-208.

11. Swedish Association of Local Authorities and Regions editor. Statistik om hälso- och sjukvård samt regional utveckling 2010. Sveriges kommuner och landsting, Stockholm, 2011:1-216. ISBN: 978-91-7164-683-5. Swedish.

12. Swedish Association of Local Authorities and Regions editor. Kostnad per brukare: jämförelser mellan kommuner inom omsorg om äldre och personer med funktionsnedsättning : utfall 2010. Sveriges kommuner och landsting, Stockholm, 2011:39. ISBN: 978-91-7164-722-1. Swedish.

13. Transport Analysis editor. Special transport service and inter-municipal transport service 2010. Trafikanalys, Stockholm, 2011. Report: 2011:16. Swedish.

14. Transport Analysis editor. Local and regional public transport 2010. Trafikanalys, Stockholm, 2011. Report: 2011:19. Swedish.

15. Lindgren B. Costs of illness in Sweden 1964-1975. Lund, Sweden: Lund University; 1981.

16. Statistics Sweden. Genomsnittlig grund- och månadslön samt kvinnors lön i procent av mäns lön efter sektor, yrke (SSYK), kön och ålder. År 2005-2010. Available at: http://www.ssd.scb.se/databaser/makro/Visavar.asp?yp=tansss&xu=C9233001&omradekod=AM&huvudtabell=LonYrkeAlder4&omradetext=Arbetsmarknad&tabelltext=Genomsnittlig+grund%2D+och+m%E5nadsl%F6n+samt+kvinnors+l%F6n+i+procent+av+m%E4ns+l%F6n+efter+sektor%2C+yrke+%28SSYK%29%2C+k%F6n+och+%E5lder%2E+%C5r&preskat=O&prodid=AM0110&deltabell=&deltabellnamn=Genomsnittlig+grund%2D+och+m%E5nadsl%F6n+samt+kvinnors+l%F6n+i+procent+av+m%E4ns+l%F6n+efter+sektor%2C+yrke+%28SSYK%29%2C+k%F6n+och+%E5lder%2E+%C5r&innehall=Antal&starttid=2005&stopptid=2010&Fromwhere=M&lang=1&langdb=1. Accessed 03/06, 2012. Swedish.

17. Statistics Sweden. Mer om Arbetskostnadsindex (AKI). Available at: http://www.scb.se/Pages/Standard____23066.aspx. Accessed 11/26, 2012. Swedish.

18. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011**;20**:1727-1736. doi:10.1007/s11136-011-9903-x.

19. EuroQol Group. EQ-5D-5L Crosswalk Value Sets. 2012; Available at: http://www.euroqol.org/about-eq-5d/valuation-of-eq-5d/eq-5d-5l-value-sets.html. Accessed 11/26, 2012.

20. Organisation for economic co-operation and development. PPPs and exchange rates. Available at: http://stats.oecd.org/Index.aspx?DataSetCode=CPL#. Accessed 09/24, 2012.

21. Evans DB, Edejer TT, Adam T, et al. Methods to assess the costs and health effects of interventions for improving health in developing countries. BMJ 2005**;331**:1137-1140. doi:10.1136/bmj.331.7525.1137.

22. Statistics Sweden. Svenska hälsoräkenskaper 2001-2010. Available at: http://www.scb.se/Pages/ProductTables____231546.aspx. Accessed 06/28, 2012. Swedish.

23. Suominen S, Koskenvuo K, Sillanmaki L, et al. Non-response in a nationwide follow-up postal survey in Finland: a register-based mortality analysis of respondents and non-respondents of the Health and Social Support (HeSSup) Study. BMJ Open 2012**;2**:e000657. doi:10.1136/bmjopen-2011-000657.

24. Morimoto T, Gandhi TK, Seger AC, et al. Adverse drug events and medication errors: detection and classification methods. Qual Saf Health Care 2004**;13**:306-314. doi:10.1136/qhc.13.4.306.

25. Ramsberg J, Ekelund M. Stuprörstänkande gör samhällets kostnader för ohälsa onödigt höga. Ekonomisk debatt 2011**;39**:41-53. Swedish.

26. Thomas EJ, Studdert DM, Newhouse JP, et al. Costs of medical injuries in Utah and Colorado. Inquiry 1999**;36**:255-264.

27. Chrischilles EA, Segar ET, Wallace RB. Self-reported adverse drug reactions and related resource use. A study of community-dwelling persons 65 years of age and older. Ann Intern Med 1992**;117**:634-640.

28. Gautier S, Bachelet H, Bordet R, et al. The cost of adverse drug reactions. Expert Opin Pharmacother 2003**;4**:319-326. doi:10.1517/14656566.4.3.319.

29. Burton MM, Hope C, Murray MD, et al. The cost of adverse drug events in ambulatory care. AMIA Annu Symp Proc 2007:90-93.

30. Borg S, Persson U, Odegaard K, et al. Obesity, survival, and hospital costs-findings from a screening project in Sweden. Value Health 2005**;8**:562-571. doi:10.1111/j.1524-4733.2005.00048.x.

Population-based survey, research plan 2011-06-08
Hanna Gyllensten

Cost-of-Illness of patient-reported Adverse Drug Events – A population-based survey

Hanna Gyllensten, Clas Rehnberg, Anna K Jönsson, Max Petzold, Anders Carlsten, Karolina Andersson Sundell

BACKGROUND

Patient-reported adverse drug reactions have been reported to affect 6% of the Swedish population (**Isacson**). According to previous research 5-6 % of hospitalizations are caused by adverse drug events (ADE) or reactions (ADR) (Einarson, 1993; Krähenbühl-Melcher, 2007). Hospitalized patients experiencing drug-related morbidity, has been suggested to cause additional hospital costs of USD 2284-5640 per patient (2000 values), but few studies have included indirect costs in the analysis or estimated the costs of drug-related morbidity outside of the hospital setting (Rodríguez-Monguió, 2003).

Cost-of-illness (COI) studies measure the economic burden of disease or diseases. An analysis of the societal COI includes direct and indirect costs. Direct costs generally includes resources used for treating the disease: e.g. costs resulting from hospitalizations, visits to health care professionals, prescription drug use, laboratory tests, nursing home care, rehabilitation. Indirect costs include costs resulting from lost productivity due to morbidity and mortality, as well as the lost productivity due to informal care. The cost of lost production can be measured using the human capital approach (Segel, 2005). Prevalence-based COI analyses include direct and indirect costs during the study period, and the discounted future costs resulting from permanent disability and mortality which occurs during the study period (Lindgren, 1981). The recommended annual discount rate varies between countries, but 3-3,5 % has been recommended, with a sensitivity analysis with discount rates of 0% to 5-6% (LFNAR 2003; NICE, 2008).

AIMS AND OBJECTIVES

Primary objectives:
1. To estimate the COI of people with self-reported ADE, from the societal perspective.
2. To estimate the societal COI resulting from self-reported ADR and sub-therapeutic effects of medication therapy (ST) , from the societal perspective.

Secondary objectives:
1.1. To compare the COI of people with and without self-reported ADE, from the societal perspective.
2.1. To analyze differences in COI of self-reported ADR and STs according to type of drug-related morbidity and patient characteristics, from the societal perspective.

METHODS / DESCRIPTION OF THE STUDY

Terminology within the study

1. The questionnaire includes questions about five types of drug-related morbidity: ADRs, STs, untreated indications, dependency and intoxication. In analyses comparing COI of patients with and without drug-related morbidity, respondents with any of the five types of drug-related morbidity will be included, which in the study will be named ADE.

2. Questions about health-care use resulting from drug-related morbidity include usage resulting from ADRs and STs. COI of patients with ADRs and STs will be used for comparisons with the COI resulting from ADRs and STs, and when analyzing differences in COI of self-reported ADRs and STs according to type of drug-related morbidity and patient characteristics.

Study population
A cross sectional study of a random sample of 14 000 adults aged 18 years and over resident in Sweden on January 1st 2010.

Definition of the primary outcomes
1. The primary outcome measure is the COI of respondents with at least one self-reported ADE, from the societal perspective.
2. The primary outcome measure is the COI resulting from self-reported ADR or ST, from the societal perspective.

Data sources and measurement
A cross-sectional population-based postal questionnaire was sent to a random sample of 14 000 Swedish residents aged 18 years or older in the first week of October 2010. The questionnaire encompassed questions on demographic and socioeconomic characteristics, health-related quality of life, utilisation of health and social services, beliefs about medicines and perceived sensitivity to medicines, use of prescribed and over-the-counter medicines (OTCs) as well as herbal remedies, experienced ADEs, perceived preventability of ADRs and ST as well as consequences and utilisation of health care due to ADRs and ST. Utilisation of health care and social services, medicines and remedies and experienced ADEs and ADRs were all assessed during the past month.

Previously introduced and validated questionnaires on health-related quality of life (EQ-5D) (Burström, 2001; EuroQol, 1990) and beliefs about medicines (BMQ General including Sensitive Soma) (Horne, 1999) were used. For questions on demographic and socioeconomic characteristics, existing standardised questions developed by SCB are used. As no validated Swedish instruments on the use of medicines, experienced ADEs, perceived preventability of ADRs and STs or the utilisation of health services in Sweden exist, these questions were developed by the research group based on earlier studies (Isacson, 2008; Gandhi, 2003; Borgström, 2006).

Data from the questionnaire was complemented with register data by record linkage. Register data collected encompassed information on demographic and socioeconomic variables (such as income, education, country of birth, marital status and number of persons in the family), information on sick-leave and disability pension and information on filled prescriptions and hospitalisations in the preceding year.

Costs
Unit costs of health-care services will be based on national statistics on health-care utilization and costs (SKL). The cost of home-help services and nursing homes will be identified from national statistics on community care (SKL). The unit cost of granted mobility services will be the average travel cost of transportation costs for the disabled (SIKA) and all other traveling related to health-care use will be applied the average cost of a bus trip (Trafa). Average income data for 2010, including social insurance contribution, will be used for

measuring the cost of productivity loss due to sick leave, and informal care (i.e. help with personal care and household from unpaid caregivers), during the study period (SCB).

The cost of dispensed prescription medicines will be retrieved from the Swedish Prescribed Drug Register, including both costs paid by the patient and reimbursement costs (Wettermark, 2007). Drug-utilization resulting from drug-related morbidity is the cost of the dispensed medicine (patient cost and reimbursement) while the total prescription drug costs during the study period will be estimated from the annual prescription drug cost per patient.

Analysis

An analysis of attrition will be made by characterizing respondents based on socio-demographic variables and compare to the study sample and the Swedish population, according to: age, sex, marital status, disposable income 2009, foreign background, level of education, and employment status (table 1).

Societal COI will include direct costs (medical and non-medical), and indirect costs (non-medical). For each respondent the direct costs will be estimated by adding the costs of health-care services, community care, transportation, and dispensed prescription medicines. Indirect costs will be the lost productivity of patients due to sick leave, and of relatives caused by informal care. Costs will be calculated for each patient by multiplying the resource use by a corresponding unit cost.

Use of OTCs and herbal remedies, patients reporting lost leisure time, incident and prevalent disability pension during the study period, and health-related quality of life (HRQoL) results are reported descriptively (figure 3). Average HRQoL in patients with and without drug-related morbidity will be compared using t-test. Lost leisure time will be reported separately for patients not working (due to retirement or other causes) and patients in working age.

Primary outcome No 1:

The societal COI of respondents (including also costs resulting from other diseases than drug-related morbidity) will be estimated, including all direct and indirect costs reported by the patient. The societal COI of patients experiencing drug-related morbidity (table 2), and of all respondents will be reported (table 3), to allow comparison of the costs resulting of drug-related morbidity to the COI.

Primary outcome No 2:

The societal COI resulting from ADE will be estimated, including all direct and indirect costs resulting from ADE. Societal COI resulting from self-reported ADRs and STs will be presented. Societal COI of patients with self-reported ADRs and STs and societal COI resulting from self-reported ADRs and STs will be reported based on patient characteristics and information about the reported drug-related morbidity (table 4). The proportion of the societal COI resulting from ADRs and STs of the societal COI of patients with ADRs and STs will be reported in text.

Average direct, indirect and societal COI will be presented together with standard deviations. Extrapolation of annual costs for the Swedish population will be made, from societal COI of patients with self-reported ADEs and of societal COI resulting from self-reported ADRs and STs.

Sensitivity analysis

A sensitivity analysis (table 2), of the societal COI of respondents reporting ADE, will be made varying the likelihood of separate cost items, using the interquartile range of survey results. Another analysis of the sensitivity of results will be made based on register data for: number and length of hospitalizations during the study period, days receiving sickness benefit, productivity loss estimated from income during 2009 (adjusted according to occupational status in 2010), using dispensed prescription medicines cost data from the month before questionnaire submission, and using the Washington panel approach (Tranmer, 2005) for estimating lost leisure time (including lost leisure time due to health care contacts only).

TABLES AND FIGURES

Table 1. Description of the study population and analysis of attrition:

	Respondents reporting ADE	Respondents without ADE	All respondents	Non-respondents
Age				
18 – 34 years				
35 – 64 years				
65 – years				
Sex				
Men				
Women				
Background				
Foreign				
Swedish				
Marital status				
Single				
Cohabiting, married or registered partnership				
Divorsed				
Widowed				
Education				
Low education				
Intermediate education				
High education				
Occupation				
Employee				NA
Company owner				
Student				NA
Retired				NA
On longterm sickness absence or disability pensioner				NA
Other				
Disposable income in 2009				
– 1 quartile				
1 – 2 quartile				
2 – 3 quartile				
4 – quartile				

Abbreviations: ADE = ADR, untreated indication, dependency, intoxications, or ST; NA = not applicable; ADR = adverse drug reaction; ST = sub-therapeutic effect of medication therapy.

Table 2. Societal COI in patients with ADR or ST, and sensitivity analysis of the estimate:

			Main results		Sensitivity analysis A*		Sensitivity analysis B**	
	Patients with self-reported ADEs*	Quantity of resources used, days /visits	Unit cost	Total cost	Quantity of resources used	Total cost	Q1	Q3
	N (%)	N(%)	(SEK)	(SEK)	Days	(SEK)	N (SEK)	N (SEK)
Dispensed prescription medicines			-		-			
Health-care use:								
Phone calls								
Nurse visits								
Physicians visits								
Emergency department visits								
Home-health care								
Physiotherapist visits								
Occupational therapist visits								
Specialist physician visits								
Hospitalizations								
Social services:					-	-		
Home-help services								
Nursing homes								
Transportation:					-	-		
Proportion by transportation services for the disabled								
Total direct cost					-	-		
Productivity loss, sick leave								
Informal care								
Total indirect cost					-	-		
Societal cost-of-illness					-	-		
Other resource use:								
Lost leisure time (days)					-	-		

* Sensitivity analysis based on register data.

** Sensitivity analysis based on the interquartile ranges (quartile 1 (Q1) and quartile 3 (Q3)) of answers in the questionnaire, with number of resources used (N) and the resulting cost (in SEK).

Abbreviations: ADE = ADR, untreated indication, dependency, intoxications, or ST; ADR = adverse drug reaction; ST = sub-therapeutic effect of medication therapy.

Table 3. Societal COI of patients with and without self-reported drug-related morbidity:

	COI without ADE (SEK)	COI with ADE (SEK)	COI with ADR or ST (SEK)	COI from ADR (SEK)	COI from ST (SEK)
Dispensed prescription medicines					
Health-care use					
Social services					
Transportation					
Total direct cost					
Productivity loss, sick leave					
Informal care					
Total indirect cost					
Societal cost-of-illness					
Other resource use:					
Over-the-counter drugs (N)				NA	NA
Natural remedies (N)				NA	NA
Lost leisure time (days)				NA	NA
Incident disability pension (N)				NA	NA
Prevalent disability pension (N)				NA	NA
Health-related quality of life (EQ-5D average +/- SD)				NA	NA
EQ VAS (average +/- SD)				NA	NA

Abbreviations: ADE = ADR, untreated indication, dependency, intoxications, or ST; ADR = adverse drug reaction; COI = cost-of-illness; SD = standard deviation; ST = sub-therapeutic effect of medication therapy.

Table 4. Societal COI of patients with self-reported ADRs or STs, description of patients and characteristics of drug-related morbidity:

	Patients with self-reported ADR or ST* N (%)	Societal COI (SEK)	Societal COI resulting from ADR and ST** (SEK)
Age			
18 – 34 years			
35 – 64 years			
65 - years			
Sex			
Men			
Women			
Type of drug-related morbidity			
Adverse drug reactions			
Therapeutic failures			
Self-reported preventability			
Preventable***			
Non-preventable			

* Includes persons with at least one self-reported ADR or ST.
** Includes either COI resulting from ADR or ST when describing the costs depending on type of drug-related morbidity.
*** Includes persons with at least one preventable self-reported ADR or ST.
Abbreviations: ADR = adverse drug reaction; COI = cost-of-illness; ST = sub-therapeutic effect of medication therapy.

Figure 1: The societal COI in Sweden during 2010, divided into direct and indirect costs: *societal COI in the population, societal COI in people with self-reported drug-related morbidity, and societal COI resulting from self-reported ADRs and STs.*
Description: Bar chart.

Figure 2: The average monthly societal COI of Swedish citizens, divided into direct and indirect costs: *average societal COI in the population, average societal COI of inhabitants with health care utilization, average societal COI in people with self-reported drug-related morbidity, and average societal COI resulting from self-reported ADRs and STs.*
Description: Bar chart.

Figure 3: Health-related quality of life, estimated using the EQ-5D™ instrument.
Description: Bar chart of averages (with t-tests of differences in averages between groups) in each dimension of the instrument, separated into three parallell bars: without drug-related morbidity, with ADEs, and with ADRs and STs.

REFERENCES

Borgström, F., Zethraeus, N., Johnell, O., Lidgren, L., Ponzer, S., Svensson, O., Abdon, P., Ornstein, E., Lunsjo, K., Thorngren, K.G., Sernbo, I., Rehnberg, C., Jonsson, B. Costs and quality of life associated with osteoporosis-related fractures in Sweden. Osteoporosis international 2006;17(5):637-650.

Burström, K., Johannesson, M., Diderichsen, F. Swedish population health-related quality of life results using the EQ-5D. Quality of Life Research 2001;10(7):621-635.

Einarson, TR. Drug-related hospital admissions. Annals of Pharmacotherapy 1993;27(7-8):832-40.

EuroQol Group. EuroQol - A new facility for the measurement of health-related quality of life. Health Policy 1990;16(3):199-208.

Gandhi, T.K., Weingart, S.N., Borus, J., Seger, A.C., Peterson, J., Burdick, E., Seger, D.L., Shu, K., Federico, F., Leape, L.L. & Bates, D.W. Adverse drug events in ambulatory care. New England Journal of Medicine 2003;348(16):1556-1564.

Horne, R., Weinman, J. & Hankins, M. The Beliefs about Medicines Questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. Psychology and Health 1999;14(1):1-24.

Isacson, D., Johansson, L., Bingefors, K. Nationwide survey of subjectively reported adverse drug reactions in Sweden. Annals of Pharmacotherapy 2008;42(3):347-353.

Krähenbühl-Melcher, A., Schlienger, R., Lampert, M., Haschke, M., Drewe, J., Krähenbühl, S. Drug-related problems in hospitals: a review of the recent literature. Drug Safety 2007;30(5):379-407.

Lindgren, B. Costs of illness in Sweden, 1964-1975. 1981 Liber, Lund, Sweden. ISBN 9140047911.

NICE, National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal. Issue date: June 2008. ISBN: 1-84629-741-9.

LFN, Pharmaceutical Benefits Board, Sweden. General guidelines for economic evaluations from the Pharmaceutical Benefits Board (LFNAR 2003:2). 2003.

Rodríguez-Monguió, R., Otero, M.J., Rovira, J. Assessing the economic impact of adverse drig effects. Pharmacoeconomics 2003;21(9):623-650.

Segel, J.E. Cost-of-Illness Studies-A Primer. Report of the RTI-UNC Center of Excellence in Health Promotion Economics. 2005.

Tranmer, J.E., Guerriere, D.N., Ungar, W.J., Coyte, P.C. Valuing patient and caregiver time: a review of the literature. Pharmacoeconomics. 2005;23(5):449-59.

Wettermark, B., Hammar, N., Fored, M., Leimanis, A., Otterblad Olausson, P., Bergman, U., Persson, I., Sundström, A., Westerholm, B., Rosén, M. The new Swedish Prescribed Drug Register—Opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiology and Drug Safety 2007;16(7):726-735.

Population-based survey, research plan 2011-06-08
Hanna Gyllensten

List of variables to be used in this study

Content	List of variables	To be used for:
Survey data		
Respondent ID	UENR	Identifying respondents.
Drug-related morbidity	$Case_{Adverse\ drug\ reaction}$ $Case_{Untreated\ indication}$ $Case_{Dependency}$ $Case_{Intoxication}$ $Case_{Sub\text{-}therapeutic\ effect}$	Identify respondents with drug-related morbidity, using variables from Katja.
Preventability	$Case_{Preventable\ ADR}$ $Case_{Preventable\ ST}$	Identify preventable drug-related morbidity, using variables from Katja.
Medicines	F24_ant F27_ant F29_ant F34_txt1 F40_txt1	Identify use of dispences prescription medicines, over-the counter drugs and herbal remedies.
Health-care use	F14_1-8 F14_txt F33_1-8 F33_txt F39_1-8 F39_txt	Identify health care use.
Social services	F19a F19b_tim F20a F20b_dgr	Identify use of home help services and nursing home care.
Transportation	F14_1-8 F14_10-11 F33_1-8 F33_10-11 F39_1-8 F39_10-11 F18a F18b_res	Identify use of health related traveling and mobility care.
Informal care	F21a F21b_tim F32a_5 F38a_5	Identify use of informal care.
Sick leave	F16a F16b_dgr F16c_tim F32a_4 F38a_4	Identify sick leave.
Leisure time	F17a F17b_dgr F32a_2 F38a_2	Identify lost leisure time.
HR-QoL	F12a-e	Health-related quality of life-

	F13_skala	measures.
Occupation	F09_1-11	Identify main occupation.
Results of drug-related morbidity	F34_2 F34_txt2 F40_2 F40_txt2	Descripion of drug-related morbidity results
LISA Database		
Demographic and socio-economic information	Alder Kon Civil FodlEgenEG15 FodlMorEG15 FodlFarEG15 Sun2000niva SyssStatJ DispInkPersF04	Description of respondents and analysis of attrition.
Income, 2009	LoneInk InkFNetto StudDelt and Stud Starting day of retirement and AldPens ForLed ArbLos, AlosDag, AdelDag, Ak14Dag, AstuDag, AsysDag and SocBidrPersF VPLErs	Sensitivity analysis of the productivity loss.
Income, 2009	ForvErsNetto CSFVI_08	Checking for missing income information.

Swedish Prescribed Drug Register		
Dispensed prescription medicines, autumn 2010 – questionnaire submission	ATC FDATUM EDATUM FORPSTL ANTAL DDDFORP	Identify dispensed prescription medicines resulting from ADE.
Cost of dispensed prescription medicines, 2010 – questionnaire submission	PATKOST MERKOST LANKOST MOMS	Estimate the average monthly cost of dispensed prescription medicines during 2010, and the cost during the month before questionnaire submission (part of the sensitivity analysis).
Patient register		
Hospitalizations, autumn 2010 – questionnaire submission	Inskrivningsdatum Utskrivningsdatum Vårdtid Klinik	Estimate the cost of hospitalizations during the month before questionnaire submission (part of the sensitivity analysis).
Social Insurance in Sweden		
Sickness benefit, autumn 2010 – questionnaire submission	Sjukpenning Rehabiliteringsersättning Sjukersättning Aktivitetsersättning - Start date - End date - Extent	Sensitivity analysis of the productivity loss.
Income, 2009	Vårdbidrag	Sensitivity analysis of the productivity loss.

STROBE statement checklist of items that should be included in the report:

	Item No	Recommendation	Comments about our paper
Title and abstract			
	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	√ Title: Population-based cross-sectional survey √ Abstract: cross-sectional study
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	√ What was done: Methods √ What was found: Results
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	√ Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	√ Aim in Introduction No prespecified hypotheses, descriptive analysis only
Methods			
Study design	4	Present key elements of study design early in the paper	√ Title, Introduction and Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	√ Abstract and Methods/Participants and data collection
Participants	6	(*a*) ~~*Cohort study*: Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up~~ ~~*Case-control study*: Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls~~ *Cross sectional study*: Give the eligibility criteria, and the sources and methods of selection of participants	√ Methods/Participants and data collection
		(*b*) ~~*Cohort study*: For matched studies, give matching criteria and number of exposed and unexposed~~ ~~*Case-control study*: For matched studies, give matching criteria and the number of controls per case~~	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	√ Aim: Outcomes/diagnostic criteria: self-reported ADE No analysis of predictors, confounders or effect modifiers
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	√ Methods
Bias	9	Describe any efforts to address potential sources of bias	√ Methods: Reminders were sent out.
Study size	10	Explain how the study size was arrived at	√ Methods/Participants and data collection
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	√ Methods/Analyses
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	√ Methods/Analyses (no control for confounding)
		(*b*) Describe any methods used to examine subgroups and interactions	√ Methods/Analyses (no interactions tested)
		(*c*) Explain how missing data were addressed	√ Methods/Analyses (minimum estimation)
		(*d*) ~~*Cohort study*: If applicable, explain how loss to follow-up was addressed~~ ~~*Case-control study*: If applicable, explain how matching of cases and controls was addressed~~ *Cross sectional study*: If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	√ Methods/Analyses

	Item No	Recommendation	Comments about our paper
Results			
Participants	13*	(*a*) Report numbers of individuals at each stage of study: eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	√ Results, paragraph 1
		(*b*) Give reasons for non-participation at each stage	N/A: Lack information about reasons for non-participation
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(*a*)Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	√ Tables 1 and 3
		(*b*) Indicate number of participants with missing data for each variable of interest	√ Table 1 (when relevant)
		(*c*) ~~*Cohort study*: Summarise follow-up time (eg average and total amount)~~	
Outcome data	15*	~~*Cohort study:* Report numbers of outcome events or summary measures over time~~ ~~*Case-control study:* Report numbers in each exposure category, or summary measures of exposure~~ *Cross sectional study:* Report numbers of outcome events or summary measures	√ Results, table 2
Main results	16	(*a*) Report the numbers of individuals at each stage of the study: eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	√ Results
		(*b*) Give reasons for non-participation at each stage	N/A: Lack information about reasons for non-participation
		(*c*) Consider use of a flow diagram	(see item 13c)
Other analyses	17	Report other analyses done: eg analyses of subgroups and interactions, and sensitivity analyses	√ Results, table 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	√ Discussion, paragraph 1
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	√ Direction and magnitude: Discussion/Strengths and weaknesses
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	√ Discussion, Comparison with previous research
Generalisability	21	Discuss the generalisability (external validity) of the study results	√ Discussion, Comparison with previous research
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	√ Funding

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross sectional studies.

Health economic checklist of items to be reported:

	Item No	Checklist item	Page in our paper where the item is dealt with
Study design			
	1	The research question is stated	√ Introduction, paragraph 3
	2	The economic importance of the research question is stated	√ Introduction, paragraph 2
	3	The viewpoint(s) of the analysis are clearly stated and justified	√ Methods/Analyses paragraph 1
	4	The rationale for choosing the alternative programmes or interventions compared is stated	N/A: No programmes or interventions compared
	5	The alternatives being compared are clearly described	N/A: No programmes or interventions compared
	6	The form of economic evaluation used is stated	√ Methods/Analyses paragraph 1
	7	The choice of form of economic evaluation is justified in relation to the questions addressed	√ Introduction, paragraph 2
Data collection			
	8	The source(s) of effectiveness estimates used are stated	N/A: No effectiveness estimates are used.
	9	Details of the design and results of effectiveness study are given (if based on a single study)	N/A: no effectiveness measured
	10	Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	N/A: no synthesis or meta-analysis of effectiveness studies
	11	The primary outcome measure(s) for the economic evaluation are clearly stated	√ Methods/Analyses paragraph 1
	12	Methods to value health states and other benefits are stated	√ Methods/Costs of resource use, paragraphs 1-4
	13	Details of the subjects from whom valuations were obtained are given	√ Methods/Participants and data collection, paragraph 1
	14	Productivity changes (if included) are reported separately	√ Table 2
	15	The relevance of productivity changes to the study question is discussed	N/A: only descriptive data
	16	Quantities of resources are reported separately from their unit costs	√ Table 2
	17	Methods for the estimation of quantities and unit costs are described	√ Methods/Participants and data collection, paragraph 2-3; Methods/Costs of resource use, paragraph 1-4
	18	Currency and price data are recorded	√ Methods, sections about Direct costs, Indirect costs, and Analyses Table 2
	19	Details of currency of price adjustments for inflation or currency conversion are given	√ Methods/Analyses
	20	Details of any model used are given	N/A: No model used
	21	The choice of model used and the key parameters on which it is based are justified	N/A: No model used
Analysis and interpretation of results			
	22	Time horizon of costs and benefits is stated	√ Methods/Analyses paragraph 2
	23	The discount rate(s) is stated	N/A: No discounts made
	24	The choice of rate(s) is justified	N/A: No discounts made
	25	An explanation is given if costs or benefits are not discounted	√ Methods/Indirect costs
	26	Details of statistical tests and confidence intervals are given for stochastic data	√ Methods/Analyses

Item No	Checklist item	Page in our paper where the item is dealt with
27	The approach to sensitivity analysis is given	√ Methods/Analyses paragraph 2
28	The choice of variables for sensitivity analysis is justified	√ Methods/Sensitivity analyses
29	The ranges over which the variables are varied are stated	N/A: Costs based on national statistics, no ranges tested
30	Relevant alternatives are compared	N/A: No programmes or interventions compared
31	Incremental analysis is reported	N/A: No incremental analysis made
32	Major outcomes are presented in a disaggregated as well as aggregated form	√ Tables 2-3
33	The answer to the study question is given	√ Results, paragraphs 2-3
34	Conclusions follow from the data reported	√ Conclusions
35	Conclusions are accompanied by the appropriate caveats	√ Conclusions

Authors may enter N/A if an item on the checklist is not appropriate, but this is only acceptable for items 9, 10, 12-15, 20, 21, 23-29, and 31.

Cost-of-Illness of patient-reported Adverse Drug Events – A population-based cross-sectional survey

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-002574.R1
Article Type:	Research
Date Submitted by the Author:	02-May-2013
Complete List of Authors:	Gyllensten, Hanna; Nordic school of public health NHV, Rehnberg, Clas; Karolinska Institutet, Department of Learning, Informatics, Management and Ethics – LIME Jönsson, Anna; Faculty of Health Sciences, Linköping University, Department of Drug Research/Clinical Pharmacology; County Council of Östergötland, Department of Clinical Pharmacology Petzold, Max; Sahlgrenska academy, University of Gothenburg, Department of Public Health and Community Medicine Carlsten, Anders; Nordic school of public health NHV, Andersson Sundell, Karolina; Nordic school of public health NHV, ; Sahlgrenska Academy, University of Gothenburg, Department of Public Health and Community Medicine
Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology, Health economics, Health services research, Pharmacology and therapeutics
Keywords:	EPIDEMIOLOGY, HEALTH ECONOMICS, Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PUBLIC HEALTH, Adverse events < THERAPEUTICS

TITLE

Cost-of-Illness of patient-reported Adverse Drug Events – A population-based cross-sectional survey

Authors

Hanna Gyllensten, doctoral student (**corresponding author**)
Nordic School of Public Health NHV, Box 121 33, SE-402 42 Gothenburg, Sweden
Phone: +46-31-693925
Fax: +46-31-691777

Clas Rehnberg, Professor
Department of Learning, Informatics, Management and Ethics – LIME, Karolinska Institutet, Stockholm, Sweden

Anna K. Jönsson, PhD
Department of Drug Research/Clinical Pharmacology, Faculty of Health Sciences, Linköping University, Linköping, Sweden, and Department of Clinical Pharmacology, County Council of Östergötland, Linköping, Sweden

Max Petzold, Professor
Akademistatistik – Centre for applied biostatistics, Sahlgrenska academy, University of Gothenburg, Department of Public Health and Community Medicine, Gothenburg, Sweden

Anders Carlsten, Associate professor
Nordic School of Public Health NHV, Gothenburg, Sweden, and
Medical Products Agency, Uppsala, Sweden

Karolina Andersson Sundell, Associate professor
Nordic School of Public Health NHV, Gothenburg, Sweden, and
Unit of Social Medicine, Department of Public Health and Community Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Keywords

adverse drug event
drug therapy
cost of illness
quality of life
survey

Word count: 4782 (excl. tables and figures)

ABSTRACT

Objectives
To estimate the cost-of-illness (COI) of individuals with self-reported adverse drug events (ADE) 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 (ADR) and sub-therapeutic 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 7,099 responded, 1,377 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% confidence interval) 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 to other respondents (COI: 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 have been reported not only to cause harm but also cause resource use from patients attending hospitals.
- Even though adverse drug events have been identified also 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 adverse drug events and compare to those without adverse drug events.

Key messages

- Our study suggests high overall costs of illness for individuals with self-reported adverse drug events, estimated to more than 500 international dollars per person monthly in Sweden when including those with adverse drug reactions, drug dependence, drug intoxications, sub-therapeutic effects of medication therapy and untreated indications.
- The estimated direct costs for prescribed drugs and healthcare use resulting from treatment of two of the adverse drug event categories, i.e. adverse drug reactions and sub-therapeutic effects of medication therapy, were 30 international dollars per person monthly. 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 adverse drug events 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 underrepresented in the analysis.

INTRODUCTION

Adverse drug events (ADEs), "an injury resulting from medical intervention related to a drug", [1] have been identified as a public health problem that causes harm to patients and considerable resource use. According to previous research, 5-6 % of hospitalizations are drug-related, [2,3] and hospitalized patients experiencing adverse drug effects cause additional hospital costs of USD 2284-5640 per 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 e.g. 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, sub-therapeutic effects of medication therapy (STE), drug dependence, drug intoxications and untreated indications. This deviates from common ADE inclusions used in many previous studies, focusing on ADRs and medication errors, [3] but were developed from exploring also e.g. 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 days 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 e.g. been defined as events that occur during drug treatment without a causal relationship to the drug, [11] or according the definition used in this study, [1] that indicates 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 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 occur also at normal doses (often referred to as non-responders to the medication). [14] Moreover, untreated indication has been suggested to cause e.g. 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. Due 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 (e.g. 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 effect than expected, drug dependence were 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 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 January 1st 2010. The sample size was calculated by assuming a one-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% confidence interval of the preventable proportion. The estimated sample size (7,013) 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 February 1st 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 (OTC) 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]: [ten 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, e.g. stopped or dose adjustment; Yes, a new other treatment was initiated (e.g. 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 was 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: i.e. 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 co-payments 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, that was dispensed during the study period according to data from the Swedish Prescribed Drug Register. Costs for adjustments to the drug treatment related to e.g. 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, i.e. self-reported by the respondents. Results from pre-specified questions and from free text were categorized 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 hospitalizations. 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 1/3 of the cost of visiting a nurse, and home healthcare as 2 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 two weeks is not reported in the Social Insurance Agency's register. Because of 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 was 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, that was transferred using the stated value set to the respondents' EQ-5D index value: ranging from dead (=0) tofull 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 to the non-respondents, and compared based on ADE status (table 1), using register data for: age (young adults age 18-34, middle aged 35-64 years old, or individuals above the Swedish retirement age ≥65 years old), country of birth (Sweden or other than Sweden), educational level (mandatory education, intermediate education, i.e. high school and up to two years of university education, or high education, i.e. more than two 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 chi square tests.

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

	Respondents reporting ADE	**Respondents not reporting ADE**	**All respondents**	**Non-respondents**
	Total = 1,377	Total = 5,722	Total = 7,099	Total = 6,832

	N (%)	N (%)	N (%)	N (%)
Age[#]				
18 – 34 years	294(21.4)	1036(18.1)	1330(18.7)	2328(34.1)
35 – 64 years	675(49.0)	2935(51.3)	3610(50.9)	3357(49.1)
65 – years	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$ ≤ 13,848	322(23.4)	1046(18.3)	1368(19.3)	2248(32.9)
Int$ 13,848-22,490	299(21.7)	1162(20.3)	1461(20.6)	1267(18.5)
Int$ 22,490-30,245	290(21.1)	1192(20.8)	1482(20.9)	1279(18.7)
Int$ 30,245-39,661	259(18.8)	1235(21.6)	1494(21.0)	1109(16.2)
Int$ 39,662 ≥	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 which 11 were ADE cases, and 203 of the non-respondents (3.0%).
[†] Occupation was missing for 60 respondents, of which 20 were ADE cases.

Abbreviations: ADE = adverse drug events; Int$ = international dollars; NA = not applicable.

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 United States dollar (US$) in the Unites States of America, allowing for differences in price levels between countries. [29] Means and standard deviations 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 ADRs or STEs, 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 ADRs or STEs, using one-way anova (for age categories) and a two-tailed t-test with unequal variances (for sex). All statistical analyses were made using the STATA 10.1 software.

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)	26,436	-
Healthcare use:			
Phone calls	106 (7.7)	267	18.5
Nurse visits	93 (6.8)	182	55.4
Physicians 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
Hospitalizations	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 disabled	38 (2.8)	420	29.8
Other transportation	240 (17.4)	2793	2.5
INDIRECT COSTS:			
Sick-leave (by age):			
18-24 years	24 (23.1)	1000	12.1[*]
25-34 years	35 (18.4)	1690	15.7[*]
35-44 years	36 (19.1)	1852	18.2[*]
45-54 years	29 (13.0)	1186	18.5[*]
55+ years	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.

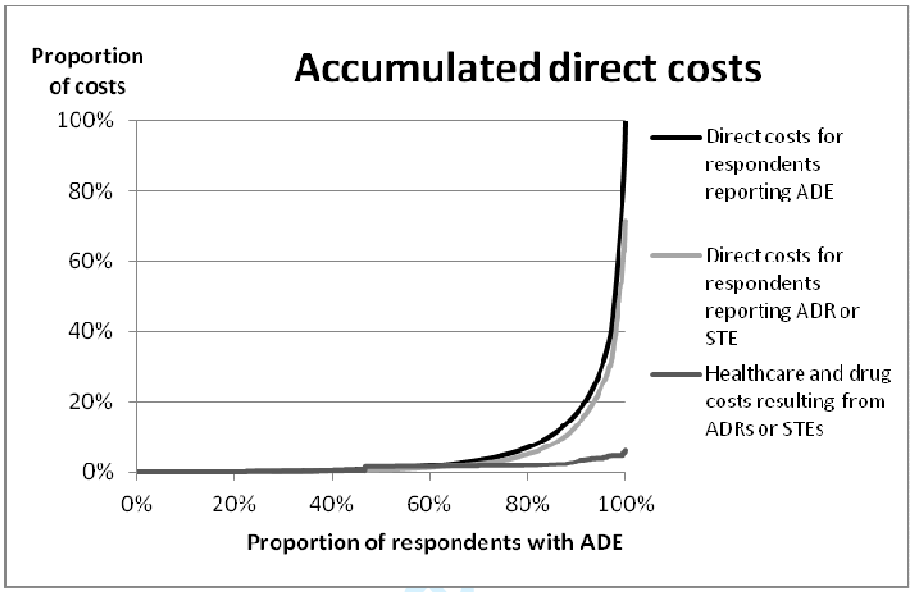
[*] The unit cost indicated was the average wage per hour in each age group [24], which was then multiplied by the general payroll tax. For citizens <26 years of age the general payroll tax was 15.49% and for citizens ≥26 years of age it was 31.42%. [25] For the informal care, the indicated unit cost was the average wage per hour, which was then multiplied by the general payroll tax for citizen's ≥26 years of age.

Abbreviations: ADE = adverse drug events; ED = emergency department; Int$ = international dollars; N = number; NA = not applicable; Q = quartile.

Sensitivity analyses

Sensitivity analyses were made based on available register data for hospitalizations and respondents' lost productivity from sick-leave. Due to 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 interquartile range 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 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 calipers (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.

Figure 1: Accumulated direct costs of individuals with self-reported ADEs, including the subgroup reporting ADRs or STEs.



Abbreviations: ADE = adverse drug events; ADR = adverse drug reaction; STE = sub-therapeutic effect of medication therapy.

RESULTS

A total of 7,099 questionnaires were collected (response rate 51 %). At least one ADE was reported by 1,377 (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 to other respondents (table 1). Resource use for respondents with self-reported ADE is presented in table 2. Healthcare was attended by 239 (17.4%) of respondents reporting ADEs, of which 96 (40.2%) were hospitalized or visited a specialist physician (including psychiatrist visits). Among all respondents, 717 (10.1%) attended healthcare. Resource use among respondents with ADE included also outpatient care in hospitals with other healthcare personnel and primary care visits (e.g. nurse visits and physician visits). In addition, home-help services or a nursing home was attended by 51 (4.5%), of the 1,138 respondents with ADE that did not attend 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 ± standard deviation, 95% confidence interval) Int$ 521.2 ± 1,485.7, Int$ 442.7 to 599.8, of which direct costs were measured at Int$ 349.8 ± 1,328.7, 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 to 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 ± 1,149.6 for those with self-reported ADEs and Int$ 133.0 ± 728.5 for other respondents ($p < 0.001$). The COI of respondents with ADR or STE was Int$ 560.9 ± 1,439.8, 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.

Table 3. Average cost-of-illness for patients with and without self-reported ADEs.

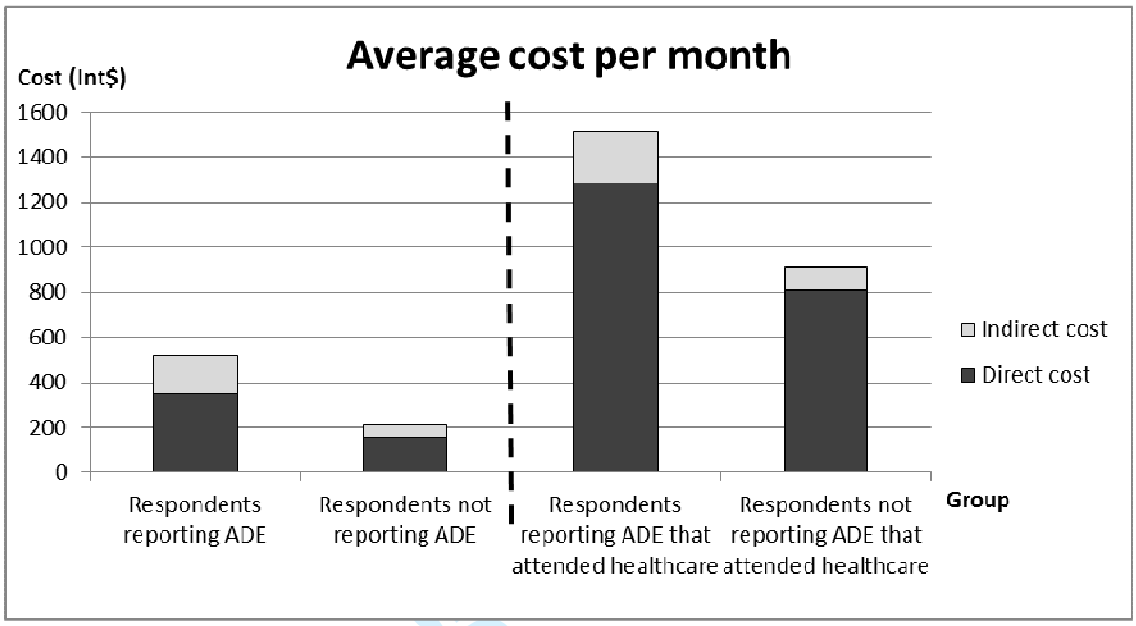
	COI with ADE N = 1377 average ± SD	**COI without ADE** N = 5722 average ± SD
Dispensed prescription medicines (Int$)[#]	48.6 ± 119.0	24.7 ± 103.3
Healthcare use (Int$)[#]	164.9 ± 935.3	40.1 ± 360.7
Social services (Int$)	122.1 ± 778.8	83.6 ± 673.5
Transportation (Int$)[#]	14.3 ± 84.8	6.9 ± 67.2
Total direct cost (Int$)[#]	**349.8 ± 1,328.7**	**155.2 ± 805.3**
Productivity loss, sick-leave (Int$)[#]	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 ± 1,485.7***	***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.

Abbreviations: 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; SD = standard deviation.

Figure 2: The average monthly cost-of-illness of respondents based on reported ADE-status and healthcare attendance, divided into direct and indirect costs.



Abbreviations: ADE = adverse drug events; Int$ = international dollars.

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 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).

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 the ADRs or STEs**[*] average ± SD, Int$
Total resource use among the respondents with ADRs or STEs (N = 943)			
Cost-of-illness	-	560.9 ± 1,439.8	NA
Direct costs	-	*(365.6 ± 1,279.4)*	NA
Indirect costs	-	*(195.3 ± 564.7)*	NA
Age			
18 – 34 years	209 (22.2)	556.5 ± 1,580.8	31.4 ± 241.7
35 – 64 years	473 (50.2)	511.5 ± 1,154.4	41.5 ± 326.9
65 – years	261 (27.7)	653.9 ± 1,754.8	14.3 ± 77.3
Sex			
Men	346 (36.7)	486.4 ± 1,182.8	32.1 ± 232.4
Women	597 (63.3)	604.0 ± 1,568.9	31.5 ± 276.7
Type of ADE[†]			
ADR	554 (58.7)	659.0 ± 1,613.6	36.6 ± 290.8
STE	539 (57.2)	566.0 ± 1,446.1	47.5 ± 335.5
Self-reported preventability			
Preventable[¥]	208 (22.1)	717.6 ± 1,897.3	56.8 ± 342.9
Non-preventable	735 (77.9)	516.5 ± 1,279.2	24.7 ± 232.7

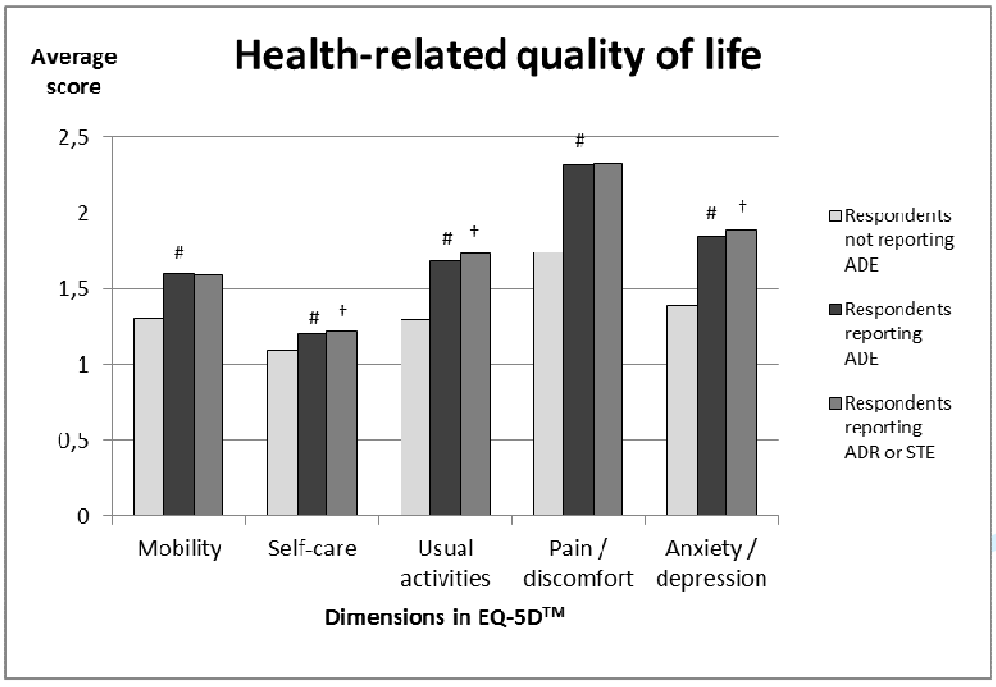
Percentages and costs are rounded.

[#] Include persons with at least one self-reported ADR or STE.
[*] Include resource use reported for both ADRs and STEs.
[†] Categories overlap, both includes persons with at least one self-reported ADR or STE respectively.
[¥] Includes persons with at least one preventable self-reported ADR or STE.

Abbreviations: ADR = adverse drug reaction; Int$ = international dollars; N = subgroup sample size; NA = not applicable; STE = sub-therapeutic effect of medication therapy.

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, 1,448 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, 2,510 days of lost leisure time (n = 187), 857 days of sick-leave (n = 88), and 1,171 days with informal care (n = 92). The health-related quality of life scores were significantly lower for respondents with ADEs compared to other respondents (figure 3): the EQ-5D™ summary estimates were 0.84 ± 0.18 vs. 0.71 ± 0.22 ($p < 0.001$), and results from the visual analogue scale were 69.79 ± 20.69 vs. 81.17 ± 16.94 ($p < 0.001$).

Figure 3: Dimensions of health-related quality of life, health profile results from the EQ-5D™ instrument, the severity reported for each domain used as 1-5 point Likert scale (from 'no problem' to 'extreme problem'), categorized based on reported ADE-status.



[#] Statistically significant difference between respondents with/withoutADEs ($p<0.05$).
[†] Statistically significant difference between respondents with at least one ADR or STE compared to other respondents with ADEs ($p<0.05$).

Abbreviations: ADE = adverse drug events; ADR = adverse drug reaction; EQ-5D™ = The EuroQol Group's five dimension health state questionnaire with five levels of severity; STE = sub-therapeutic effect of medication therapy.

Sensitivity analyses

The hospitalization rate reported in the survey (19 respondents reported 24 hospitalizations during the study period) was compared to the hospitalization rate identified from register data: 85 respondents had 101 hospitalizations covering a total of 365 days during the 5 weeks before answering the survey. Thus the sensitivity of the reporting of hospitalizations in the questionnaire was 59% and the specificity was 99% compared to register data. Among the 85 respondents, 24 hospitalisations lasted only one day or night, 10 hospitalisations occurred less than one 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 the specificity was 99%, compared to 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 reported to be on long-term sickness absence, seeking a job or on parental leave, 45 persons had not reported the sick-leave identified in the register. Of those 390 persons reporting sick-leave that were 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 persons did not receive sickness benefit for their absence. Additional deviations were not possible to explain using 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 1,377 individuals with self-reported ADEs was Int$ 717,750.4 and the direct costs resulting from self-reported ADRs and STEs in 943 individuals was Int$ 29,935.9. Thus, the extrapolated annual direct costs in Sweden resulting from ADRs and STEs, was Int$ 370 million in 2010. Our results suggest that ADEs cause costs also outside hospitals, and 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 further analysing in future studies. Those reporting ADEs were more extensive users of prescription drugs, healthcare resource use, transportation services, and informal care, compared to other respondents. Moreover, they had more short-term sick-leave and disability pension than other respondents. Much of this increase in resource use will be due to co-morbidities, and will be involved in causing the ADE, 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 underrepresented among respondents, e.g. 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 citizens being less prone to respond. Previous research suggests the bias is mainly towards survey respondents being healthier than those not responding. [32] 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 e.g. resulting from the underlying disease rather than the drug use, and other relevant symptoms may not have been perceived to be related to the drug use by the respondent or not being 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, [33] thus we may underestimate the prevalence and resulting resource use of ADEs by not including also the physicians' experiences. However, previous research has identified patients themselves as important actors in reporting adverse events, also due to drug use. [34] 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 the resource use to what was reported in national registers, including data for hospitalizations and sick-leave. The register analyses indicated an underreporting rather than overestimation of the resource use. Moreover, our main cause for underestimating the 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. [35] Lost wages and household production has 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). [36] Our design (time frame and data collection method) did not allow estimation of indirect costs from disability pension and mortality, thus underestimating the economic impact of ADEs.

Our ADE definition was more inclusive than some previous studies', [3] although the included categories' associations with drug treatment and drug-related problems has previously been acknowledged. Based on the ADE definition applied, the prevalence and associated costs will differ. Limiting the inclusion to only e.g. 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. [37] Our estimated one-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 suggests that the drug users experience ADEs and associated consequences that have so far not been included in studies of injuries resulting from medical intervention related to drugs, and thus needs to be further explored to identify causes, consequences and possibilities for prevention. In our study, less than one fifth of respondents with ADEs attended healthcare during the study period, and on 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 hospitalized due to the ADR during a one year study period, [38] but the disparity may depend on the length of the study period and the age of respondents. Our average direct costs resulting from ADRs (Int$ 37) were, as expected, low compared to previous estimates of approximately Euro 2,800 for ADRs in patients attending hospitals. [39] Though, the small proportion of respondents reporting healthcare contacts due to their ADR or STE (with no respondent reporting hospitalization 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$ 1,283) was similar to the attributable charges previously reported for ADEs identified after a visit to ambulatory care: US$ 926 (2006 value). [40]

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 [42] have previously remarked on the balance between costs of ADRs and benefits of drug treatments, and the two costs of ADRs: costs resulting from treating the ADR 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 of 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 incur healthcare resource use, many of these patients should be possible to

identify in the healthcare system, even when the ADE in itself may not be the main cause of resource use. Based on the perspective of a decision or analysis, our results indicate that such costs will occur also outside the healthcare system, e.g. for sick-leave, informal care and lost leisure time. The result was strengthened by the propensity score analyses, indicating both direct healthcare costs, and indirect costs, attributable to ADEs. Thus the patient's views and experiences of drug treatments needs to be further addressed in treatment decisions.

Future research is needed to further analyze the relationship between ADEs and the associated resource use, to identify when and how the resource use occurs, and 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 estimating the 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 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.

ACKNOWLEDGEMENT

We wish to thank the survey respondents for taking the time to share their experience with us.

ETHICS APPROVAL

The study received ethical approval from the Regional Ethical Review Board in Gothenburg (approval reference number: 238-10), in 2010.

The questionnaire cover letter included information about how and why the research was conducted, contact information, and how to withdraw. Informed consent was implied by returning the questionnaire. The questionnaire and the cover letter were developed in accordance with the declaration of Helsinki.

The ethical approval did not include an approval to share individual responses or register data publicly.

COMPETING INTEREST DECLARATION

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: all authors had financial support from National Corporation of Swedish Pharmacies (Apoteket AB) for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

The opinions or assertions contained herein are the private views of the authors, and are not to be construed as official or as reflecting the views of the Medical Products Agency.

FUNDING

The research is part of the DRUMS project (Drug-related morbidity and mortality in Sweden: prevalence, preventability and costs) funded by an unrestricted grant from the National Corporation of Swedish Pharmacies (Apoteket AB). The study sponsor had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the article; and in the decision to submit it for publication. The researchers work was independent from the sponsor. All authors, external and internal, had full access to all of 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.

DETAILS OF CONTRIBUTORS

KAS was the principal investigator. HG did the analyses and drafted the manuscript. AC, AKJ, CR, HG, KAS and MP contributed to the study design and development of the questionnaire, data

analysis, and interpretation of the results and commented on the draft. Also, Katja M Hakkarainen, Staffan Hägg, Johnny Pettersson and Annika Yeiter contributed to the study design, and the development and piloting of the questionnaire. Tatiana Zverkova Sandström contributed to the data analysis. All authors had full access to all data. HG is the guarantor of the study.

LICENCE FOR PUBLICATION

REFERENCES

1. Bates DW, Boyle DL, Vander Vliet MB, Schneider J, Leape L. Relationship between medication errors and adverse drug events. *J Gen Intern Med* 1995; **10**(4): 199-205. doi:10.1007/BF02600255.

2. Einarson TR. Drug-related hospital admissions. *Ann Pharmacother* 1993; **27**(7-8): 832-40.

3. Krähenbühl-Melcher A, Schlienger R, Lampert M, Haschke M, Drewe J, Krähenbühl S. Drug-related problems in hospitals: a review of the recent literature. *Drug Saf* 2007; **30**(5): 379-407.

4. Rodríguez-Monguió R, Otero MJ, Rovira J. Assessing the economic impact of adverse drug effects. *Pharmacoeconomics* 2003; **21**(9): 623-50.

5. Gyllensten H, Jönsson AK, Rehnberg C, Carlsten A. How are the costs of drug-related morbidity measured?: a systematic literature review. *Drug Saf* 2012; **35**(3): 207-19. doi:10.2165/11597090-000000000-00000; 10.2165/11597090-000000000-00000.

6. Isacson D, Johansson L, Bingefors K. Nationwide survey of subjectively reported adverse drug reactions in Sweden. *Ann Pharmacother* 2008; **42**(3): 347-53. doi:10.1345/aph.1K488.

7. Segel JE. Cost-of-Illness Studies - A Primer. *RTI International* 2006; : 1-39.

8. Hakkarainen KM, Andersson Sundell K, Petzold M, Hägg S. Self-reported adverse drug events equally prevalent across age groups - a population-based survey in Sweden. Manuscript submitted for publication. .

9. Aronson JK, Ferner RE. Clarification of terminology in drug safety. *Drug Saf* 2005; **28**(10): 851-70.

10. Yu K, Nation R, Dooley M. Multiplicity of medication safety terms, definitions and functional meanings: when is enough enough? *Qual Saf Health Care* 2005; **14**(5): 358-63.

11. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet* 2000; **356**(9237): 1255-9. doi:10.1016/S0140-6736(00)02799-9.

12. European Parliament, Council of the European Union. Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use. *Official Journal* 2010; **L 348**: 74-99.

13. Young AM, Glover N, Havens JR. Nonmedical use of prescription medications among adolescents in the United States: a systematic review. *J Adolesc Health* 2012; **51**(1): 6-17. doi:10.1016/j.jadohealth.2012.01.011; 10.1016/j.jadohealth.2012.01.011.

14. Taylor S, Abramowitz JS, McKay D. Non-adherence and non-response in the treatment of anxiety disorders. *J Anxiety Disord* 2012; **26**(5): 583-9. doi:10.1016/j.janxdis.2012.02.010; 10.1016/j.janxdis.2012.02.010.

15. Al-Olah YH, Al Thiab KM. Admissions through the emergency department due to drug-related problems. *Ann Saudi Med* 2008; **28**(6): 426-9.

16. Gandhi TK, Seger DL, Bates DW. Identifying drug safety issues: from research to practice. *Int J Qual Health Care* 2000; **12**(1): 69-76. doi:10.1093/intqhc/12.1.69.

17. Gandhi TK, Weingart SN, Borus J, Seger AC, Bates DW. Adverse drug events in ambulatory care. *N Engl J Med* 2003; **348**(16): 1556-64. doi:10.1056/NEJMsa020703.

18. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. The EuroQol Group. *Health Policy* 1990; **16**(3): 199-208.

19. Swedish Association of Local Authorities and Regions. Statistik om hälso- och sjukvård samt regional utveckling 2010. 2011; : 1-216.

20. Swedish Association of Local Authorities and Regions. Kostnad per brukare: jämförelser mellan kommuner inom omsorg om äldre och personer med funktionsnedsättning : utfall 2010. 2011; : 39.

21. Transport Analysis. Special transport service and inter-municipal transport service 2010. 2011; **2011:16**.

22. Transport Analysis. Local and regional public transport 2010. 2011; **2011:19**.

23. Lindgren B. Costs of illness in Sweden 1964-1975. Lund, Sweden: Lund University; 1981.

24. Statistics Sweden. Genomsnittlig grund- och månadslön samt kvinnors lön i procent av mäns lön efter sektor, yrke (SSYK), kön och ålder. År 2005-2010. ; Avalable at: http://www.ssd.scb.se/databaser/makro/Visavar.asp?yp=tansss&xu=C9233001&omradekod=AM&huvudtabell=LonYrkeAlder4&omradetext=Arbetsmarknad&tabelltext=Genomsnittlig+grund%2D+och+m%E5nadsl%F6n+samt+kvinnors+l%F6n+i+procent+av+m%E4ns+l%F6n+efter+sektor%2C+yrke+%28SSYK%29%2C+k%F6n+och+%E5lder%2E+%C5r&preskat=O&prodid=AM0110&deltabell=&deltabellnamn=Genomsnittlig+grund%2D+och+m%E5nadsl%F6n+samt+kvinnors+l%F6n+i+procent+av+m%E4ns+l%F6n+efter+sektor%2C+yrke+%28SSYK%29%2C+k%F6n+och+%E5lder%2E+%C5r&innehall=Antal&starttid=2005&stopptid=2010&Fromwhere=M&lang=1&langdb=1. Accessed 03/06, 2012.

25. Statistics Sweden. Mer om Arbetskostnadsindex (AKI). ; Avalable at: http://www.scb.se/Pages/Standard____23066.aspx. Accessed 11/26, 2012.

26. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011; **20**(10): 1727-36. doi:10.1007/s11136-011-9903-x.

27. EuroQol Group. EQ-5D-5L Crosswalk Value Sets. 2012; Avalable at: http://www.euroqol.org/about-eq-5d/valuation-of-eq-5d/eq-5d-5l-value-sets.html. Accessed 11/26, 2012.

28. Organisation for economic co-operation and development. PPPs and exchange rates. ; Avalable at: http://stats.oecd.org/Index.aspx?DataSetCode=CPL#. Accessed 09/24, 2012.

29. Evans DB, Edejer TT, Adam T, Lim SS. Methods to assess the costs and health effects of interventions for improving health in developing countries. *BMJ* 2005; **331**(7525): 1137-40. doi:10.1136/bmj.331.7525.1137.

30. Leuven E, Sianesi B. PSMATCH2: Stata module to perform full Mahalanobis and propensity score matching, common support graphing, and covariate imbalance testing. *Statistical Software Components* 2003; **April 2012 revision**.

31. Statistics Sweden. Svenska hälsoräkenskaper 2001-2010. ; Avalable at: http://www.scb.se/Pages/ProductTables____231546.aspx. Accessed 06/28, 2012.

32. Suominen S, Koskenvuo K, Sillanmaki L, et al. Non-response in a nationwide follow-up postal survey in Finland: a register-based mortality analysis

of respondents and non-respondents of the Health and Social Support (HeSSup) Study. *BMJ Open* 2012; **2**(2): e000657. doi:10.1136/bmjopen-2011-000657.

33. Morimoto T, Gandhi TK, Seger AC, Hsieh TC, Bates DW. Adverse drug events and medication errors: detection and classification methods. *Qual Saf Health Care* 2004; **13**(4): 306-14. doi:10.1136/qhc.13.4.306.

34. Zhu J, Stuver SO, Epstein AM, Schneider EC, Weissman JS, Weingart SN. Can we rely on patients' reports of adverse events? *Med Care* 2011; **49**(10): 948-55. doi:10.1097/MLR.0b013e31822047a8; 10.1097/MLR.0b013e31822047a8.

35. Ramsberg J, Ekelund M. Stuprörstänkande gör samhällets kostnader för ohälsa onödigt höga. *Ekonomisk debatt* 2011; **39**(5): 41,53. Swedish.

36. Thomas EJ, Studdert DM, Newhouse JP, Zbar B, Howard KM, Williams EJ, Brennan TA. Costs of medical injuries in Utah and Colorado. *Inquiry* 1999; **36**(3): 255-64.

37. Taché SV, Sönnichsen A, Ashcroft DM. Prevalence of adverse drug events in ambulatory care: a systematic review. *Ann Pharmacother* 2011; **45**(7-8): 977-89. doi:10.1345/aph.1P627.

38. Chrischilles EA, Segar ET, Wallace RB. Self-reported adverse drug reactions and related resource use. A study of community-dwelling persons 65 years of age and older. *Ann Intern Med* 1992; **117**(8): 634-40.

39. Gautier S, Bachelet H, Bordet R, Caron J. The cost of adverse drug reactions. *Expert Opin Pharmacother* 2003; **4**(3): 319-26.

40. Burton MM, Hope C, Murray MD, Hui S, Overhage JM. The cost of adverse drug events in ambulatory care. *AMIA Annu Symp Proc* 2007; : 90-3.

41. Borg S, Persson U, Odegaard K, Berglund G, Nilsson JA, Nilsson PM. Obesity, survival, and hospital costs-findings from a screening project in Sweden. *Value Health* 2005; **8**(5): 562-71. doi:10.1111/j.1524-4733.2005.00048.x.

42. Lundkvist J, Jönsson B. Pharmacoeconomics of adverse drug reactions. *Fundam Clin Pharmacol* 2004; **18**(3): 275-80.

TITLE

Cost-of-Illness of patient-reported Adverse Drug Events – A population-based cross-sectional survey

Authors

Hanna Gyllensten, doctoral student (**corresponding author**)
Nordic School of Public Health NHV, Box 121 33, SE-402 42 Gothenburg, Sweden
Phone: +46-31-693925
Fax: +46-31-691777

Clas Rehnberg, Professor
Department of Learning, Informatics, Management and Ethics – LIME, Karolinska Institutet, Stockholm, Sweden

Anna K. Jönsson, PhD
Department of Drug Research/Clinical Pharmacology, Faculty of Health Sciences, Linköping University, Linköping, Sweden, and Department of Clinical Pharmacology, County Council of Östergötland, Linköping, Sweden

Max Petzold, Professor
Akademistatistik – Centre for applied biostatistics, Sahlgrenska academy, University of Gothenburg, Department of Public Health and Community Medicine, Gothenburg, Sweden

Anders Carlsten, Associate professor
Nordic School of Public Health NHV, Gothenburg, Sweden, and
Medical Products Agency, Uppsala, Sweden

Karolina Andersson Sundell, Associate professor
Nordic School of Public Health NHV, Gothenburg, Sweden, and
Unit of Social Medicine, Department of Public Health and Community Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Keywords

adverse drug event
drug therapy
cost of illness
quality of life
survey

Word count: 4782 (excl. tables and figures)

ABSTRACT

Objectives
To estimate the cost-of-illness (COI) of individuals with self-reported adverse drug events (ADE) 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 (ADR) and sub-therapeutic 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 7,099 responded, 1,377 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% confidence interval) 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 to other respondents (COI: 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 have been reported not only to cause harm but also cause resource use from patients attending hospitals.
- Even though adverse drug events have been identified also 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 adverse drug events and compare to those without adverse drug events.

Key messages

- Our study suggests high overall costs of illness for individuals with self-reported adverse drug events, estimated to ~~8,871 million~~more than 500 international dollars ~~annually~~ per person monthly in Sweden when including those with adverse drug reactions, drug dependence, drug intoxications, sub-therapeutic effects of medication therapy and untreated indications.
- The estimated ~~annual~~ direct costs for prescribed drugs and healthcare use resulting from treatment of two of the adverse drug event categories, i.e. adverse drug reactions and sub-therapeutic effects of medication therapy, were ~~370 million~~30 international dollars per person monthly. 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 adverse drug events 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 underrepresented in the analysis.

INTRODUCTION

Adverse drug events (ADEs), "an injury resulting from medical intervention related to a drug", [1] have been identified as a public health problem that causes harm to patients and considerable resource use. According to previous research, 5-6 % of hospitalizations are drug-related, [2,3] and hospitalized patients experiencing adverse drug effects cause additional hospital costs of USD 2284-5640 per 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 ~~the~~ cost items in the COI ~~could~~ 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 ~~study the development of the associated resource use over time~~. [7] Information about COI could also be useful for developing future intervention studies to address ADEs and to retrieve the costs for modelling e.g. 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, sub-therapeutic effects of medication therapy (STE), drug dependence, drug intoxications and untreated indications. This deviates from common ADE inclusions used in many previous studies, focusing on ADRs and medication errors, [3] but were developed from exploring also e.g. 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 days 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 e.g. been defined as events that occur during drug treatment without a causal relationship to the drug, [11] or according the definition used in this study, [1] that indicates 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 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 occur also at normal doses (often referred to as non-responders to the medication). [14] Moreover, untreated indication has been suggested to cause e.g. 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. Due 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 (e.g. 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 effect than expected, drug dependence were 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 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 January 1st 2010. The sample size was calculated by assuming a one-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% confidence interval of the preventable proportion. The estimated sample size (7,013) 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 February 1st 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 (OTC) 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]: [ten 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, e.g. stopped or dose adjustment; Yes, a new other treatment was initiated (e.g. 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), ~~and cross-examined~~ , 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 was 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: i.e. 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 co-payments 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 ~~in~~ by the survey respondents to be initiated for treating an ADR or STE ~~and~~, that was dispensed during the study period according to data from the Swedish Prescribed Drug Register~~register~~. Costs for adjustments to the drug treatment related to e.g. 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, i.e. self-reported by the respondents. Results from pre-specified questions and from free text were categorized 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 hospitalizations. 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 1/3 of the cost of visiting a nurse, and home healthcare as 2 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 two weeks is not reported in the Social Insurance Agency's register. Because of 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. ~~Lost productivity~~Sick-leave and disability pension during the study period ~~was~~ were identified from the questionnaire~~.~~, ~~Costs~~ and the costs for lost productivity were measured ~~with~~ 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 was 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, that was transferred using the stated value set to the respondents' EQ-5D index value: ranging from dead (=0) tofull 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 to the non-respondents, and compared based on ADE status (table 1), using register data for: age (young adults age 18-34, middle aged 35-64 years old, or individuals above the Swedish retirement age ≥65 years old), country of birth (Sweden or other than Sweden), educational level (mandatory education, intermediate education, i.e. high school and up to two years of university education, or high education, i.e. more than two 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 chi square tests.

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

	Respondents reporting ADE Total = 1,377 N (%)	Respondents not reporting ADE Total = 5,722 N (%)	All respondents Total = 7,099 N (%)	Non-respondents Total = 6,832 N (%)
Age[#]				
18 – 34 years	294(21.4)	1036(18.1)	1330(18.7)	2328(34.1)
35 – 64 years	675(49.0)	2935(51.3)	3610(50.9)	3357(49.1)
65 – years	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$ ≤ 13,848	322(23.4)	1046(18.3)	1368(19.3)	2248(32.9)
Int$ 13,848-22,490	299(21.7)	1162(20.3)	1461(20.6)	1267(18.5)
Int$ 22,490-30,245	290(21.1)	1192(20.8)	1482(20.9)	1279(18.7)
Int$ 30,245-39,661	259(18.8)	1235(21.6)	1494(21.0)	1109(16.2)
Int$ 39,662 ≥	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 which 11 were ADE cases, and 203 of the non-respondents (3.0%).
[†] Occupation was missing for 60 respondents, of which 20 were ADE cases.

Abbreviations: ADE = adverse drug events; Int$ = international dollars; NA = not applicable.

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 United States dollar (US$) in the Unites States of America, allowing for differences in price levels between countries. [29] Means and standard deviations 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 ADRs or STEs, 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 ADRs or STEs, using one-way anova (for age categories) and a two-tailed t-test with unequal variances (for sex). ~~Extrapolated annual direct costs, indirect costs and COI were calculated for the adult Swedish population (N = 7,382,226) during 2010.~~ All statistical analyses were made using the STATA 10.1 software.

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)	26,436	-
Healthcare use:			
Phone calls	106 (7.7)	267	18.5
Nurse visits	93 (6.8)	182	55.4
Physicians 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
Hospitalizations	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 disabled	38 (2.8)	420	29.8
Other transportation	240 (17.4)	2793	2.5
INDIRECT COSTS:			
Sick-leave (by age):			
18-24 years	24 (23.1)	1000	12.1[*]
25-34 years	35 (18.4)	1690	15.7[*]
35-44 years	36 (19.1)	1852	18.2[*]
45-54 years	29 (13.0)	1186	18.5[*]
55+ years	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.

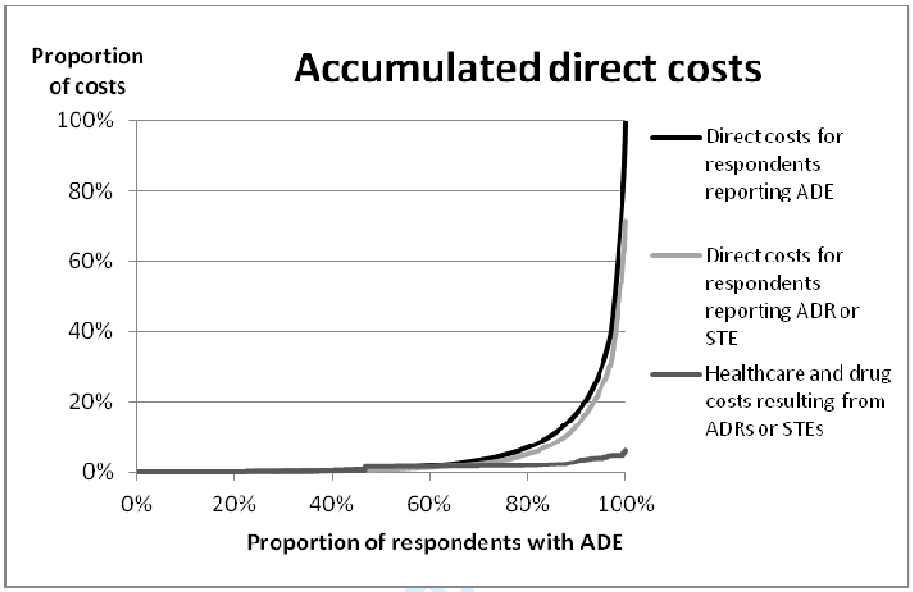
[*] The unit cost indicated was the average wage per hour in each age group [24], which was then multiplied by the general payroll tax. For citizens <26 years of age the general payroll tax was 15.49% and for citizens ≥26 years of age it was 31.42%. [25] For the informal care, the indicated unit cost was the average wage per hour, which was then multiplied by the general payroll tax for citizen's ≥26 years of age.

Abbreviations: ADE = adverse drug events; ED = emergency department; Int$ = international dollars; N = number; NA = not applicable; Q = quartile.

Sensitivity analyses

Sensitivity analyses were made based on available register data for hospitalizations and respondents' lost productivity from sick-leave. ~~Moreover, an additional extrapolation to the annual COI in the Swedish population was made, under the assumption that all ADEs and resource use in the study population was reported by the respondents, thus assuming that non-respondents had no ADEs or resource use. Because of the~~Due to skewed data, ~~with resources corresponding to~~ 80% of the direct costs for respondents with ADEs were reported by 10% of these respondents (figure 1), a ~~proposed~~ sensitivity analysis proposed in the research plan, based on interquartile range of responses~~, in the research plan~~, 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 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 calipers (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.

Figure 1: Accumulated direct costs of individuals with self-reported ADEs, including the subgroup reporting ADRs or STEs.



Abbreviations: ADE = adverse drug events; ADR = adverse drug reaction; STE = sub-therapeutic effect of medication therapy.

RESULTS

A total of 7,099 questionnaires were collected (response rate 51 %). At least one ADE was reported by 1,377 (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 to other respondents (table 1). Resource use for respondents with self-reported ADE is presented in table 2. Healthcare was attended by 239 (17.4%) of respondents reporting ADEs, of which 96 (40.2%) were hospitalized or visited a specialist physician (including psychiatrist visits). Among all respondents, 717 (10.1%) attended healthcare. Resource use among respondents with ADE included also outpatient care in hospitals with other healthcare personnel and primary care visits (e.g. nurse visits and physician visits). In addition, home-help services or a nursing home was attended by 51 (4.5%), of the 1,138 respondents with ADE that did not attend 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 ± standard deviation, 95% confidence interval) Int$ 521.2 ± 1,485.7, Int$ 442.7 to 599.8, of which direct costs were measured at Int$ 349.8 ± 1,328.7, 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 to 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 ± 1,149.6 for those with self-reported ADEs and Int$ 133.0 ± 728.5 for other respondents ($p < 0.001$). The COI of respondents with ADR or STE was Int$ 560.9 ± 1,439.8, Int$ 468.9 to 652.9. ~~Extrapolated to the Swedish population, the annual direct costs, indirect costs and COI of individuals with ADE were: Int$ 5,953.4 million, Int$ 2,917.5 million, and Int$ 8,870.9 million, respectively (figure 3).~~ 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.

Table 3. Average cost-of-illness for patients with and without self-reported ADEs.

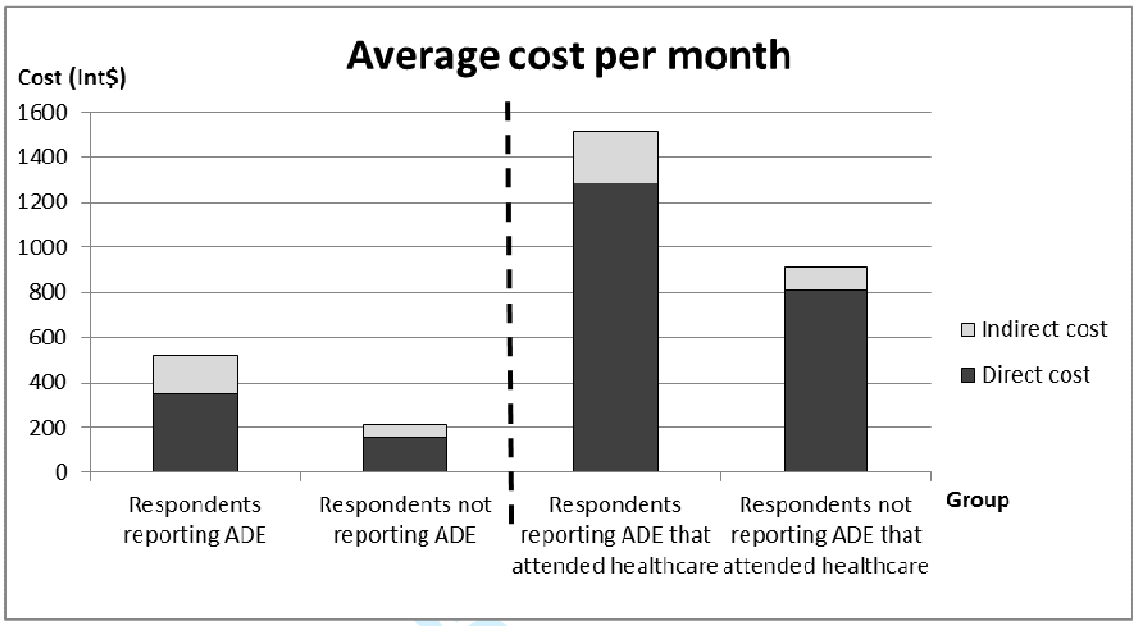
	COI with ADE N = 1377 average ± SD	**COI without ADE** N = 5722 average ± SD
Dispensed prescription medicines (Int$)[#]	48.6 ± 119.0	24.7 ± 103.3
Healthcare use (Int$)[#]	164.9 ± 935.3	40.1 ± 360.7
Social services (Int$)	122.1 ± 778.8	83.6 ± 673.5
Transportation (Int$)[#]	14.3 ± 84.8	6.9 ± 67.2
Total direct cost (Int$)[#]	**349.8 ± 1,328.7**	**155.2 ± 805.3**
Productivity loss, sick-leave (Int$)[#]	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 ± 1,485.7***	***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.

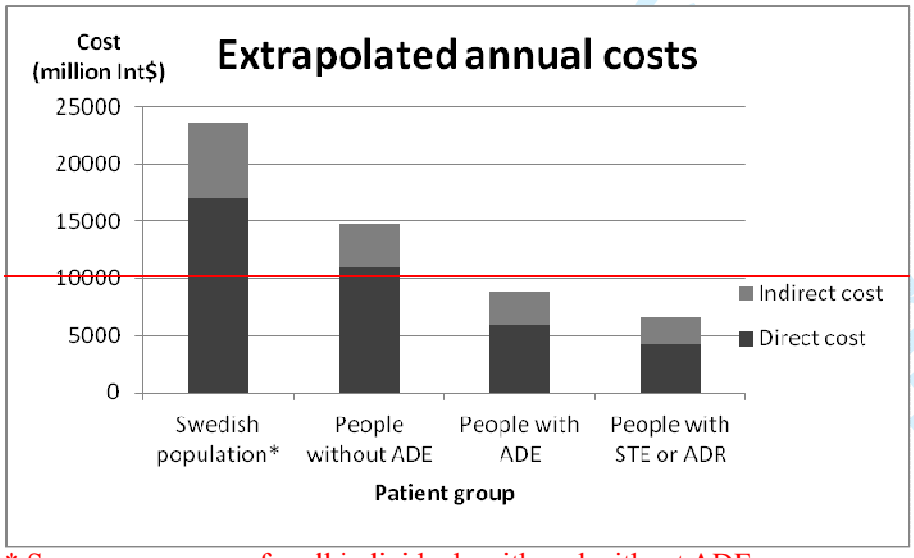
Abbreviations: ADE = adverse drug events; EQ-5D™ = The EuroQol Group's five dimension health state questionnaire with five levels of severity; EQ-VAS = The EuroQol Group's visual analogue scale; Int$ = international dollars; N = population size; SD = standard deviation.

Figure 2: The average monthly cost-of-illness of respondents based on reported ADE-status and healthcare attendance, divided into direct and indirect costs.



Abbreviations: ADE = adverse drug events; Int$ = international dollars.

~~*Figure 3: The annual cost-of-illness during 2010, extrapolated to the Swedish adult population, divided into direct and indirect costs.*~~



~~* Summary measure for all individuals with and without ADEs.~~

~~Abbreviations: ADE = adverse drug events; Int$ = international dollars.~~

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 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).

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 the ADRs or STEs*** average ± SD, Int$
Total resource use among the respondents with ADRs or STEs (N = 943)			
Cost-of-illness	-	560.9 ± 1,439.8	NA
Direct costs	-	*(365.6 ± 1,279.4)*	NA
Indirect costs	-	*(195.3 ± 564.7)*	NA
Age			
18 – 34 years	209 (22.2)	556.5 ± 1,580.8	31.4 ± 241.7
35 – 64 years	473 (50.2)	511.5 ± 1,154.4	41.5 ± 326.9
65 – years	261 (27.7)	653.9 ± 1,754.8	14.3 ± 77.3
Sex			
Men	346 (36.7)	486.4 ± 1,182.8	32.1 ± 232.4
Women	597 (63.3)	604.0 ± 1,568.9	31.5 ± 276.7
Type of ADE†			
ADR	554 (58.7)	659.0 ± 1,613.6	36.6 ± 290.8
STE	539 (57.2)	566.0 ± 1,446.1	47.5 ± 335.5
Self-reported preventability			
Preventable¥	~~207~~ 208 (22.~~0~~1)	~~720~~717.~~9~~ 6 ± 1,~~901~~897.3	~~57~~56.~~1~~ 8 ± ~~343~~342.~~79~~
Non-preventable	~~736~~ 735 (~~78~~77.~~09~~)	~~515~~516.~~9~~ 5 ± 1,~~278~~279.~~42~~	24.~~6~~ 7 ± 232.~~67~~

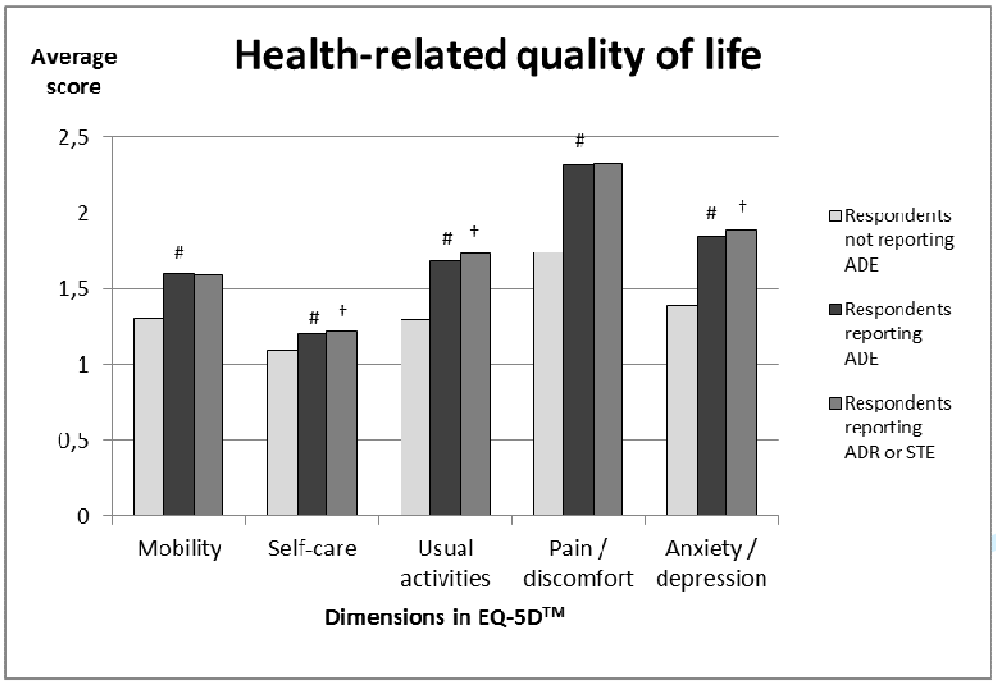
Percentages and costs are rounded.

[#] Include persons with at least one self-reported ADR or STE.
[*] Include resource use reported for both ADRs and STEs.
[†] Categories overlap, both includes persons with at least one self-reported ADR or STE respectively.
[¥] Includes persons with at least one preventable self-reported ADR or STE.

Abbreviations: ADR = adverse drug reaction; Int$ = international dollars; N = subgroup sample size; NA = not applicable; STE = sub-therapeutic effect of medication therapy.

Additional resource use attributed to ADRs by 554 respondents, reported during the 30 days study period, included: 90 medication changes not ~~identified~~ registered in the Swedish Prescribed Drug Register~~register~~, 1,448 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, 2,510 days of lost leisure time (n = 187), 857 days of sick-leave (n = 88), and 1,171 days with informal care (n = 92). The health-related quality of life scores were significantly lower for respondents with ADEs compared to other respondents (figure ~~4~~3): the EQ-5D™ summary estimates were 0.84 ± 0.18 vs. 0.71 ± 0.22 ($p < 0.001$), and results from the visual analogue scale were 69.79 ± 20.69 vs. 81.17 ± 16.94 ($p < 0.001$).

Figure ~~4~~3: Dimensions of health-related quality of life, health profile results from the EQ-5D™ instrument, the severity reported for each domain used as 1-5 point Likert scale (from 'no problem' to 'extreme problem'), categorized based on reported ADE-status.



Statistically significant difference between respondents with/withoutADEs ($p<0.05$).
† Statistically significant difference between respondents with at least one ADR or STE compared to other respondents with ADEs ($p<0.05$).

Abbreviations: ADE = adverse drug events; ADR = adverse drug reaction; EQ-5D™ = The EuroQol Group's five dimension health state questionnaire with five levels of severity; STE = sub-therapeutic effect of medication therapy.

Sensitivity analyses

The hospitalization rate reported in the survey (19 respondents reported 24 hospitalizations during the study period) was compared to the hospitalization rate identified from register data: 85 respondents had 101 hospitalizations covering a total of 365 days during the 5 weeks before answering the survey. Thus the sensitivity of the reporting of hospitalizations in the questionnaire was 59% and the specificity was 99% compared to register data. Among the 85 respondents, 24 hospitalisations lasted only one day or night, 10 hospitalisations occurred less than one 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 the specificity was 99%, compared to 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 reported to be on long-term sickness absence, seeking a job or on parental leave, 45 persons had not reported the sick-leave identified in the register. Of those 390 persons reporting sick-leave that were 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 persons did not receive sickness benefit for their absence. Additional deviations were not possible to explain using 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).

~~Assuming that all ADEs and resource use in the study population was reported by our respondents, resulted in an annual COI of individuals with ADEs in the Swedish population Int$ 746 million (direct costs: Int$ 501 million).~~

DISCUSSION

In this study, the societal COI of 1,377 individuals with self-reported ADEs was Int$ 717,750.4 and the direct costs resulting from self-reported ADRs and STEs in 943 individuals was Int$ 29,935.9. Thus, the extrapolated annual direct costs in Sweden resulting from ADRs and STEs, was Int$ 370 million in 2010. Our results suggest that ADEs cause costs also outside hospitals, and 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 further ~~analyzing~~analysing in future studies. Those reporting ADEs were more extensive users of prescription drugs, healthcare resource use, transportation services, and informal care, compared to other respondents. Moreover, they had more short-term sick-leave and disability pension than other respondents. Much of this increase in resource use will be due to co-morbidities, and will be involved in causing the ADE, 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 underrepresented among respondents, e.g. 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 citizens being less prone to respond. ~~Therefore we report a minimum estimation of the extrapolated annual COI for individuals with ADEs in the Swedish general public, assuming the non-respondents had no ADEs or resource use; thus were healthier than the respondents. This resulted in healthcare costs far below what was expected if compared to the annual healthcare expenditure in Sweden,~~[31] ~~and even comparing our main analysis of extrapolated direct costs for the population, suggest that much resource use was unaccounted for in our analyses, thus we underestimate rather than overestimate the economic impact of ADEs. Moreover, p~~Previous

research suggests the bias is mainly towards survey respondents being healthier than those not responding. [32] 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 e.g. resulting from the underlying disease rather than the drug use, and other relevant symptoms may not have been perceived to be related to the drug use by the respondent or not being included in the five ADE categories included in the questionnaire. ~~Still, p~~Previous research has shown that there is little overlap between ADEs reported by patients and by physicians, [33] thus we may underestimate the prevalence and resulting resource use of ADEs by not including also the physicians' experiences. However, previous research has identified patients themselves as important actors in reporting adverse events, also due to drug use. [34] 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 the resource use to what was reported in national registers, ~~only~~ including data for hospitalizations and sick-leave ~~were available in national registers, which also~~ The register analyses indicated an underreporting rather than ~~overestimating~~ overestimation of the resource use. ~~Yet~~ Moreover, our main cause for underestimating the COI ~~should~~ 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. [35] Lost wages and household production has 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). [36] Our design (time frame and data collection method) did not allow estimation of indirect costs from disability pension and mortality, thus underestimating the economic impact of ADEs.

Our ADE definition was more inclusive than some previous studies', [3] although the included categories' associations with drug treatment and drug-related problems has previously been acknowledged. Based on the ADE definition applied, the prevalence and associated costs will differ. Limiting the inclusion to only e.g. 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. [37] Our estimated one-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 suggests that the drug users experience ADEs and associated consequences that have so far not been included in studies of injuries resulting from medical intervention related to drugs, and thus needs to be further explored to identify causes, consequences and possibilities for prevention.

In our study, less than one fifth of respondents with ADEs attended healthcare during the study period, and on 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 hospitalized due to the ADR during a one year study period, [38] but the disparity may depend on the length of the study period and the age of respondents. Our average direct costs resulting from ADRs (Int$ 37) were, as expected, low compared to previous estimates of approximately Euro 2,800 for ADRs in patients attending hospitals. [39] Though, the small proportion of respondents reporting healthcare contacts due to their ADR or STE (with no respondent reporting hospitalization 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$ 1,283) was similar to the attributable charges previously reported for ADEs identified after a visit to ambulatory care: US$ 926 (2006 value). [40]

~~Our extrapolated annual direct costs for individuals with ADEs (Int$ 5,953.4 million) equals 17% of the total healthcare expenditures in Sweden during 2010 (Int$ 35,257.8 million).~~ [31] ~~The extrapolated direct costs resulting from ADRs and STEs (Int$ 370 million) represented a small part of the total~~

~~healthcare costs, but was comparable to the excess hospital costs estimated for obesity in Sweden (US$ 269 million in 2003).~~ [41]

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 [42] have previously remarked on the balance between costs of ADRs and benefits of drug treatments, and the two costs of ADRs: costs resulting from treating the ADR 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 of 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 incur healthcare resource use, many of these patients should be possible to identify in the healthcare system, even when the ADE in itself may not be the main cause of resource use. Based on the perspective of a decision or analysis, our results indicate that such costs will occur also outside the healthcare system, e.g. for sick-leave, informal care and lost leisure time. The result was strengthened by the propensity score analyses, indicating both direct healthcare costs, and indirect costs, attributable to ADEs. Thus the patient's views and experiences of drug treatments needs to be further addressed in treatment decisions.

Future research is needed to further analyze the relationship between ADEs and the associated resource use, to identify when and how the resource use occurs, and 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 estimating the 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 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.

ACKNOWLEDGEMENT

We wish to thank the survey respondents for taking the time to share their experience with us.

ETHICS APPROVAL

The study received ethical approval from the Regional Ethical Review Board in Gothenburg (approval reference number: 238-10), in 2010.

The questionnaire cover letter included information about how and why the research was conducted, contact information, and how to withdraw. Informed consent was implied by returning the questionnaire. The questionnaire and the cover letter were developed in accordance with the declaration of Helsinki.

The ethical approval did not include an approval to share individual responses or register data publicly.

COMPETING INTEREST DECLARATION

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: all authors had financial support from National Corporation of Swedish Pharmacies (Apoteket AB) for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

The opinions or assertions contained herein are the private views of the authors, and are not to be construed as official or as reflecting the views of the Medical Products Agency.

FUNDING

The research is part of the DRUMS project (Drug-related morbidity and mortality in Sweden: prevalence, preventability and costs) funded by an unrestricted grant from the National Corporation of Swedish Pharmacies (Apoteket AB). The study sponsor had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the article; and in the decision to submit it for publication. The researchers work was independent from the sponsor. All authors, external and internal, had full access to all of 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.

DETAILS OF CONTRIBUTORS

KAS was the principal investigator. HG did the analyses and drafted the manuscript. AC, AKJ, CR, HG, KAS and MP contributed to the study design and development of the questionnaire, data

analysis, and interpretation of the results and commented on the draft. Also, Katja M Hakkarainen, Staffan Hägg, Johnny Pettersson and Annika Yeiter contributed to the study design, and the development and piloting of the questionnaire. Tatiana Zverkova Sandström contributed to the data analysis. All authors had full access to all data. HG is the guarantor of the study.

LICENCE FOR PUBLICATION

REFERENCES

1. Bates DW, Boyle DL, Vander Vliet MB, Schneider J, Leape L. Relationship between medication errors and adverse drug events. *J Gen Intern Med* 1995; **10**(4): 199-205. doi:10.1007/BF02600255.

2. Einarson TR. Drug-related hospital admissions. *Ann Pharmacother* 1993; **27**(7-8): 832-40.

3. Krähenbühl-Melcher A, Schlienger R, Lampert M, Haschke M, Drewe J, Krähenbühl S. Drug-related problems in hospitals: a review of the recent literature. *Drug Saf* 2007; **30**(5): 379-407.

4. Rodríguez-Monguió R, Otero MJ, Rovira J. Assessing the economic impact of adverse drug effects. *Pharmacoeconomics* 2003; **21**(9): 623-50.

5. Gyllensten H, Jönsson AK, Rehnberg C, Carlsten A. How are the costs of drug-related morbidity measured?: a systematic literature review. *Drug Saf* 2012; **35**(3): 207-19. doi:10.2165/11597090-000000000-00000; 10.2165/11597090-000000000-00000.

6. Isacson D, Johansson L, Bingefors K. Nationwide survey of subjectively reported adverse drug reactions in Sweden. *Ann Pharmacother* 2008; **42**(3): 347-53. doi:10.1345/aph.1K488.

7. Segel JE. Cost-of-Illness Studies - A Primer. *RTI International* 2006; : 1-39.

8. Hakkarainen KM, Andersson Sundell K, Petzold M, Hägg S. Self-reported adverse drug events equally prevalent across age groups - a population-based survey in Sweden. Manuscript submitted for publication. .

9. Aronson JK, Ferner RE. Clarification of terminology in drug safety. *Drug Saf* 2005; **28**(10): 851-70.

10. Yu K, Nation R, Dooley M. Multiplicity of medication safety terms, definitions and functional meanings: when is enough enough? *Qual Saf Health Care* 2005; **14**(5): 358-63.

11. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet* 2000; **356**(9237): 1255-9. doi:10.1016/S0140-6736(00)02799-9.

12. European Parliament, Council of the European Union. Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use. *Official Journal* 2010; **L 348**: 74-99.

13. Young AM, Glover N, Havens JR. Nonmedical use of prescription medications among adolescents in the United States: a systematic review. *J Adolesc Health* 2012; **51**(1): 6-17. doi:10.1016/j.jadohealth.2012.01.011; 10.1016/j.jadohealth.2012.01.011.

14. Taylor S, Abramowitz JS, McKay D. Non-adherence and non-response in the treatment of anxiety disorders. *J Anxiety Disord* 2012; **26**(5): 583-9. doi:10.1016/j.janxdis.2012.02.010; 10.1016/j.janxdis.2012.02.010.

15. Al-Olah YH, Al Thiab KM. Admissions through the emergency department due to drug-related problems. *Ann Saudi Med* 2008; **28**(6): 426-9.

16. Gandhi TK, Seger DL, Bates DW. Identifying drug safety issues: from research to practice. *Int J Qual Health Care* 2000; **12**(1): 69-76. doi:10.1093/intqhc/12.1.69.

17. Gandhi TK, Weingart SN, Borus J, Seger AC, Bates DW. Adverse drug events in ambulatory care. *N Engl J Med* 2003; **348**(16): 1556-64. doi:10.1056/NEJMsa020703.

18. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. The EuroQol Group. *Health Policy* 1990; **16**(3): 199-208.

19. Swedish Association of Local Authorities and Regions. Statistik om hälso- och sjukvård samt regional utveckling 2010. 2011; : 1-216.

20. Swedish Association of Local Authorities and Regions. Kostnad per brukare: jämförelser mellan kommuner inom omsorg om äldre och personer med funktionsnedsättning : utfall 2010. 2011; : 39.

21. Transport Analysis. Special transport service and inter-municipal transport service 2010. 2011; **2011:16**.

22. Transport Analysis. Local and regional public transport 2010. 2011; **2011:19**.

23. Lindgren B. Costs of illness in Sweden 1964-1975. Lund, Sweden: Lund University; 1981.

24. Statistics Sweden. Genomsnittlig grund- och månadslön samt kvinnors lön i procent av mäns lön efter sektor, yrke (SSYK), kön och ålder. År 2005-2010. ; Avalable at: http://www.ssd.scb.se/databaser/makro/Visavar.asp?yp=tansss&xu=C9233001&omradekod=AM&huvudtabell=LonYrkeAlder4&omradetext=Arbetsmarknad&tabelltext=Genomsnittlig+grund%2D+och+m%E5nadsl%F6n+samt+kvinnors+l%F6n+i+procent+av+m%E4ns+l%F6n+efter+sektor%2C+yrke+%28SSYK%29%2C+k%F6n+och+%E5lder%2E+%C5r&preskat=O&prodid=AM0110&deltabell=&deltabellnamn=Genomsnittlig+grund%2D+och+m%E5nadsl%F6n+samt+kvinnors+l%F6n+i+procent+av+m%E4ns+l%F6n+efter+sektor%2C+yrke+%28SSYK%29%2C+k%F6n+och+%E5lder%2E+%C5r&innehall=Antal&starttid=2005&stopptid=2010&Fromwhere=M&lang=1&langdb=1. Accessed 03/06, 2012.

25. Statistics Sweden. Mer om Arbetskostnadsindex (AKI). ; Avalable at: http://www.scb.se/Pages/Standard____23066.aspx. Accessed 11/26, 2012.

26. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011; **20**(10): 1727-36. doi:10.1007/s11136-011-9903-x.

27. EuroQol Group. EQ-5D-5L Crosswalk Value Sets. 2012; Avalable at: http://www.euroqol.org/about-eq-5d/valuation-of-eq-5d/eq-5d-5l-value-sets.html. Accessed 11/26, 2012.

28. Organisation for economic co-operation and development. PPPs and exchange rates. ; Avalable at: http://stats.oecd.org/Index.aspx?DataSetCode=CPL#. Accessed 09/24, 2012.

29. Evans DB, Edejer TT, Adam T, Lim SS. Methods to assess the costs and health effects of interventions for improving health in developing countries. *BMJ* 2005; **331**(7525): 1137-40. doi:10.1136/bmj.331.7525.1137.

30. Leuven E, Sianesi B. PSMATCH2: Stata module to perform full Mahalanobis and propensity score matching, common support graphing, and covariate imbalance testing. *Statistical Software Components* 2003; **April 2012 revision**.

31. Statistics Sweden. Svenska hälsoräkenskaper 2001-2010. ; Avalable at: http://www.scb.se/Pages/ProductTables____231546.aspx. Accessed 06/28, 2012.

32. Suominen S, Koskenvuo K, Sillanmaki L, et al. Non-response in a nationwide follow-up postal survey in Finland: a register-based mortality analysis

of respondents and non-respondents of the Health and Social Support (HeSSup) Study. *BMJ Open* 2012; **2**(2): e000657. doi:10.1136/bmjopen-2011-000657.

33. Morimoto T, Gandhi TK, Seger AC, Hsieh TC, Bates DW. Adverse drug events and medication errors: detection and classification methods. *Qual Saf Health Care* 2004; **13**(4): 306-14. doi:10.1136/qhc.13.4.306.

34. Zhu J, Stuver SO, Epstein AM, Schneider EC, Weissman JS, Weingart SN. Can we rely on patients' reports of adverse events? *Med Care* 2011; **49**(10): 948-55. doi:10.1097/MLR.0b013e31822047a8; 10.1097/MLR.0b013e31822047a8.

35. Ramsberg J, Ekelund M. Stuprörstänkande gör samhällets kostnader för ohälsa onödigt höga. *Ekonomisk debatt* 2011; **39**(5): 41,53. Swedish.

36. Thomas EJ, Studdert DM, Newhouse JP, Zbar B, Howard KM, Williams EJ, Brennan TA. Costs of medical injuries in Utah and Colorado. *Inquiry* 1999; **36**(3): 255-64.

37. Taché SV, Sönnichsen A, Ashcroft DM. Prevalence of adverse drug events in ambulatory care: a systematic review. *Ann Pharmacother* 2011; **45**(7-8): 977-89. doi:10.1345/aph.1P627.

38. Chrischilles EA, Segar ET, Wallace RB. Self-reported adverse drug reactions and related resource use. A study of community-dwelling persons 65 years of age and older. *Ann Intern Med* 1992; **117**(8): 634-40.

39. Gautier S, Bachelet H, Bordet R, Caron J. The cost of adverse drug reactions. *Expert Opin Pharmacother* 2003; **4**(3): 319-26.

40. Burton MM, Hope C, Murray MD, Hui S, Overhage JM. The cost of adverse drug events in ambulatory care. *AMIA Annu Symp Proc* 2007; : 90-3.

41. Borg S, Persson U, Odegaard K, Berglund G, Nilsson JA, Nilsson PM. Obesity, survival, and hospital costs-findings from a screening project in Sweden. *Value Health* 2005; **8**(5): 562-71. doi:10.1111/j.1524-4733.2005.00048.x.

42. Lundkvist J, Jönsson B. Pharmacoeconomics of adverse drug reactions. *Fundam Clin Pharmacol* 2004; **18**(3): 275-80.

STROBE statement checklist of items that should be included in the report:

	Item No	Recommendation	Comments about our paper
Title and abstract			
	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	√ Title: Population-based cross-sectional survey √ Abstract: cross-sectional study
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	√ What was done: Methods √ What was found: Results
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	√ Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	√ Aim in Introduction No prespecified hypotheses, descriptive analysis only
Methods			
Study design	4	Present key elements of study design early in the paper	√ Title, Introduction and Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	√ Abstract and Methods/Participants and data collection
Participants	6	(*a*) ~~*Cohort study*: Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up~~ ~~*Case-control study*: Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls~~ *Cross sectional study*: Give the eligibility criteria, and the sources and methods of selection of participants	√ Methods/Participants and data collection
		(*b*) ~~*Cohort study*: For matched studies, give matching criteria and number of exposed and unexposed~~ ~~*Case-control study*: For matched studies, give matching criteria and the number of controls per case~~	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	√ Aim: Outcomes/diagnostic criteria: self-reported ADE No analysis of predictors, confounders or effect modifiers
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	√ Methods
Bias	9	Describe any efforts to address potential sources of bias	√ Methods: Reminders were sent out.
Study size	10	Explain how the study size was arrived at	√ Methods/Participants and data collection
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	√ Methods/Analyses
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	√ Methods/Analyses (no control for confounding)
		(*b*) Describe any methods used to examine subgroups and interactions	√ Methods/Analyses (no interactions tested)
		(*c*) Explain how missing data were addressed	√ Methods/Analyses (minimum estimation)
		(*d*) ~~*Cohort study*: If applicable, explain how loss to follow-up was addressed~~ ~~*Case-control study*: If applicable, explain how matching of cases and controls was addressed~~ *Cross sectional study*: If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	√ Methods/Analyses

	Item No	Recommendation	Comments about our paper
Results			
Participants	13*	(*a*) Report numbers of individuals at each stage of study: eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	√ Results, paragraph 1
		(*b*) Give reasons for non-participation at each stage	N/A: Lack information about reasons for non-participation
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(*a*)Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	√ Tables 1 and 3
		(*b*) Indicate number of participants with missing data for each variable of interest	√ Table 1 (when relevant)
		(*c*) ~~*Cohort study*: Summarise follow-up time (eg average and total amount)~~	
Outcome data	15*	~~*Cohort study:* Report numbers of outcome events or summary measures over time~~ ~~*Case-control study:* Report numbers in each exposure category, or summary measures of exposure~~ *Cross sectional study:* Report numbers of outcome events or summary measures	√ Results, table 2
Main results	16	(*a*) Report the numbers of individuals at each stage of the study: eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	√ Results
		(*b*) Give reasons for non-participation at each stage	N/A: Lack information about reasons for non-participation
		(*c*) Consider use of a flow diagram	(see item 13c)
Other analyses	17	Report other analyses done: eg analyses of subgroups and interactions, and sensitivity analyses	√ Results, table 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	√ Discussion, paragraph 1
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	√ Direction and magnitude: Discussion/Strengths and weaknesses
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	√ Discussion, Comparison with previous research
Generalisability	21	Discuss the generalisability (external validity) of the study results	√ Discussion, Comparison with previous research
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	√ Funding

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross sectional studies.

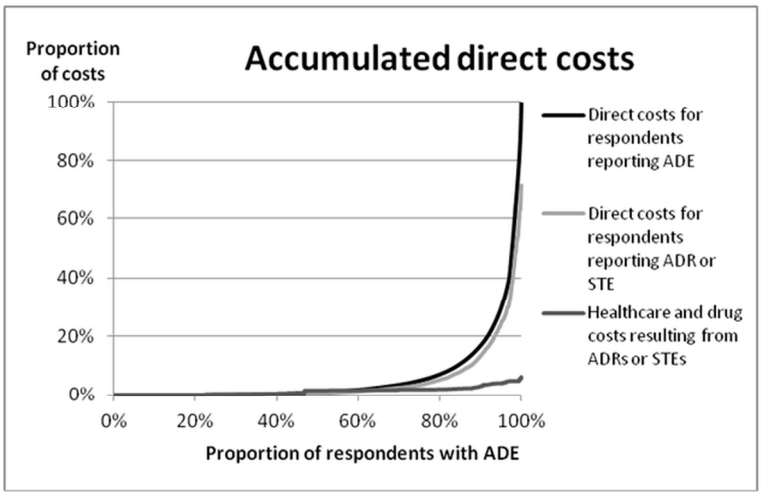
Health economic checklist of items to be reported:

	Item No	Checklist item	Page in our paper where the item is dealt with
Study design			
	1	The research question is stated	√ Introduction, paragraph 3
	2	The economic importance of the research question is stated	√ Introduction, paragraph 2
	3	The viewpoint(s) of the analysis are clearly stated and justified	√ Methods/Analyses paragraph 1
	4	The rationale for choosing the alternative programmes or interventions compared is stated	N/A: No programmes or interventions compared
	5	The alternatives being compared are clearly described	N/A: No programmes or interventions compared
	6	The form of economic evaluation used is stated	√ Methods/Analyses paragraph 1
	7	The choice of form of economic evaluation is justified in relation to the questions addressed	√ Introduction, paragraph 2
Data collection			
	8	The source(s) of effectiveness estimates used are stated	N/A: No effectiveness estimates are used.
	9	Details of the design and results of effectiveness study are given (if based on a single study)	N/A: no effectiveness measured
	10	Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	N/A: no synthesis or meta-analysis of effectiveness studies
	11	The primary outcome measure(s) for the economic evaluation are clearly stated	√ Methods/Analyses paragraph 1
	12	Methods to value health states and other benefits are stated	√ Methods/Costs of resource use, paragraphs 1-4
	13	Details of the subjects from whom valuations were obtained are given	√ Methods/Participants and data collection, paragraph 1
	14	Productivity changes (if included) are reported separately	√ Table 2
	15	The relevance of productivity changes to the study question is discussed	N/A: only descriptive data
	16	Quantities of resources are reported separately from their unit costs	√ Table 2
	17	Methods for the estimation of quantities and unit costs are described	√ Methods/Participants and data collection, paragraph 2-3; Methods/Costs of resource use, paragraph 1-4
	18	Currency and price data are recorded	√ Methods, sections about Direct costs, Indirect costs, and Analyses Table 2
	19	Details of currency of price adjustments for inflation or currency conversion are given	√ Methods/Analyses
	20	Details of any model used are given	N/A: No model used
	21	The choice of model used and the key parameters on which it is based are justified	N/A: No model used
Analysis and interpretation of results			
	22	Time horizon of costs and benefits is stated	√ Methods/Analyses paragraph 2
	23	The discount rate(s) is stated	N/A: No discounts made
	24	The choice of rate(s) is justified	N/A: No discounts made
	25	An explanation is given if costs or benefits are not discounted	√ Methods/Indirect costs
	26	Details of statistical tests and confidence intervals are given for stochastic data	√ Methods/Analyses

Item No	Checklist item	Page in our paper where the item is dealt with
27	The approach to sensitivity analysis is given	√ Methods/Analyses paragraph 2
28	The choice of variables for sensitivity analysis is justified	√ Methods/Sensitivity analyses
29	The ranges over which the variables are varied are stated	N/A: Costs based on national statistics, no ranges tested
30	Relevant alternatives are compared	N/A: No programmes or interventions compared
31	Incremental analysis is reported	N/A: No incremental analysis made
32	Major outcomes are presented in a disaggregated as well as aggregated form	√ Tables 2-3
33	The answer to the study question is given	√ Results, paragraphs 2-3
34	Conclusions follow from the data reported	√ Conclusions
35	Conclusions are accompanied by the appropriate caveats	√ Conclusions

Authors may enter N/A if an item on the checklist is not appropriate, but this is only acceptable for items 9, 10, 12-15, 20, 21, 23-29, and 31.

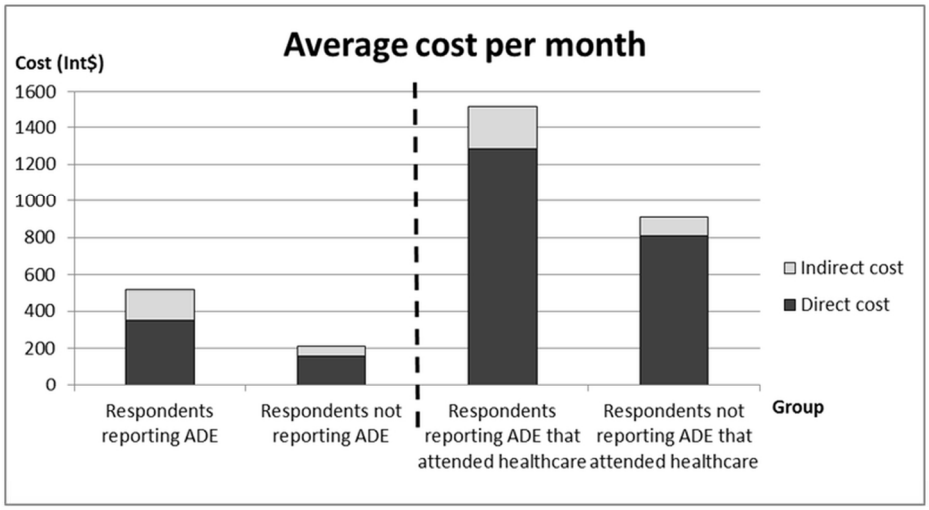
Figure 1: Accumulated direct costs of individuals with self-reported ADEs, including the subgroup reporting ADRs or STEs.



Abbreviations: ADE = adverse drug events; ADR = adverse drug reaction; STE = sub-therapeutic effect of medication therapy.

133x90mm (300 x 300 DPI)

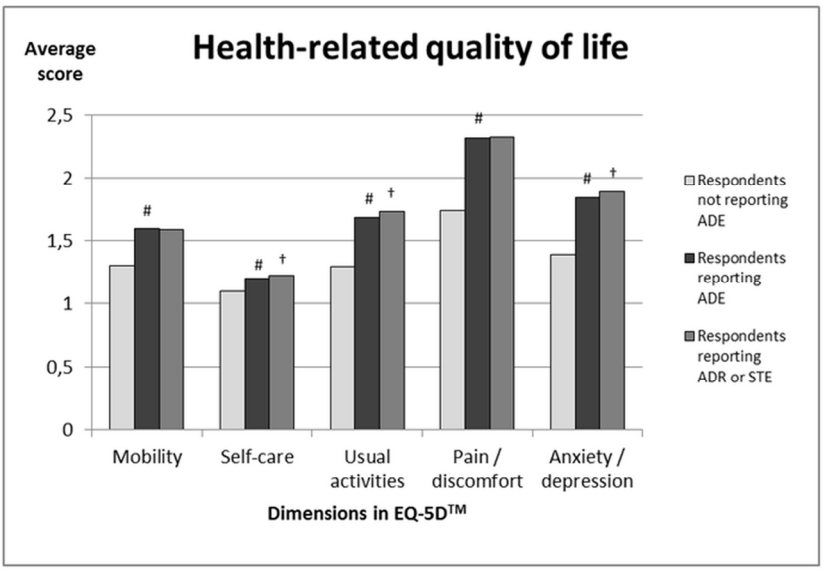
Figure 2: The average monthly cost-of-illness of respondents based on reported ADE-status and healthcare attendance, divided into direct and indirect costs.



Abbreviations: ADE = adverse drug events; Int$ = international dollars.

135x90mm (300 x 300 DPI)

Figure 3: Dimensions of health-related quality of life, health profile results from the EQ-5D™ instrument, the severity reported for each domain used as 1-5 point Likert scale (from 'no problem' to 'extreme problem'), categorized based on reported ADE-status.



132x90mm (300 x 300 DPI)