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Comparing Methods for Estimating Direct Costs of Adverse Drug Events

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ABSTRACT

Objectives: To estimate how direct health care costs resulting from adverse drug events (ADEs) and cost distribution are affected by methodological decisions regarding identification of ADEs, assigning relevant resource use to ADEs, and estimating costs for the assigned resources. **Methods:** ADEs were identified from medical records and diagnostic codes for a random sample of 4970 Swedish adults during a 3-month study period in 2008 and were assessed for causality. Results were compared for five cost evaluation methods, including different methods for identifying ADEs, assigning resource use to ADEs, and for estimating costs for the assigned resources (resource use method, proportion of registered cost method, unit cost method, diagnostic code method, and main diagnosis method). Different levels of causality for ADEs and ADEs' contribution to health care resource use were considered. **Results:** Using the five methods, the maximum estimated overall direct health care costs resulting from ADEs ranged from Sk10,000 (Sk = Swedish krona; ~€1,500 in 2016 values) using the diagnostic code method to more than Sk3,000,000 (~€414,000) using the unit cost method in our study population. The most conservative definitions for ADEs' contribution to health care resource use and the causality of ADEs resulted in average costs per patient ranging from Sk0 using the diagnostic code method to Sk4066 (~€500) using the unit cost method. **Conclusions:** The estimated costs resulting from ADEs varied considerably depending on the methodological choices. The results indicate that costs for ADEs need to be identified through medical record review and by using detailed unit cost data.

Keywords: adverse drug event, health care costs, medical records, pharmacoeconomics.

Introduction

It is well known today that adverse drug events (ADEs) cause considerable resource use in hospitals, but the methods used for estimating their costs vary considerably [1,2]. Moreover, knowledge about costs resulting from ADEs outside hospitals is scarce. Because randomized controlled studies are not possible, studying the economic impact of ADEs is challenging. Studies limited to describing costs for a disease or condition are often referred to as cost-of-illness studies [3]. For example, how to identify ADEs, relevant resource use caused by ADEs, and costs for the resources used need to be managed carefully within such studies [4]. Moreover, identification of ADEs needs to include a method for assessing whether a symptom or a sign is caused by a drug [5]. Using structured methods or algorithms for assessment, the causality assessment can be further elaborated to indicate the relationship likelihood of a suspected ADE, for example, possible, likely, or definite association between drug and symptom [6]. A more conservative definition will result in fewer events judged as ADEs and consequently a lower prevalence of ADEs will be found. Studies estimating costs caused by ADEs have, however, not adjusted for this in their cost estimations or reported costs by, for example, level of causality [7].

To our knowledge, no study has previously compared different methods for assigning resource use and costs to ADEs or compared the resulting costs. Moreover, no previous study has examined the effect of different definitions of causality for including ADEs on estimates of total costs and average costs per patient. By including a lower number of ADEs, the estimated total cost for ADEs in the population should decrease. Nevertheless, if the average cost for each of the "probable" ADEs is small compared with the average cost of "definite" ADEs, the

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decrease in the total cost may be small (less costly ADEs are excluded, whereas more costly ADEs remain). Moreover, the changing number of individuals being included as patients with ADE and the inclusion of costs for resource use associated with specific symptoms also affect the cost per patient with at least one ADE. Thus, there is a lack of knowledge of how the definitions affect both the estimated total costs and the average cost per patient.

Thus, the aim of this study was to estimate how direct health care costs resulting from ADEs and cost distribution are affected by methodological decisions regarding causality assessments of possible ADEs, assessing the contribution of ADEs to health care use, identifying relevant resource use during identified health care (including primary care, other outpatient care, and inpatient care), and estimating costs for used resources.

Methods

In the present study, five cost evaluation methods were developed: resource use method, proportion of registered cost method, unit cost method, diagnostic code method, and main diagnosis method. In each of the five methods, the cost evaluation was performed in three steps: 1) ADE identification, 2) resource use assignment, and 3) estimating costs for the assigned resource use. The five methods and the three steps are shown in Figure 1 and are discussed herein. For examples of how each method was applied to identified cases, see Appendix 1: Case descriptions.

Data Collection and Causality Assessment

The study population consisted of a random sample of 4970 individuals from the Swedish population who were 18 years or older and living in Östergötland County as of December 31, 2007 [8,9]. The sample was randomly divided into four groups and each group was allotted a study quarter during 2008. Characteristics relating to age, sex, country of birth, and assigned study quarters of the study population are presented in Table 1. An ADE was defined as "an injury due to a medical intervention related to a drug" [10].

The first step in the cost evaluation methods was ADE identification (Fig. 1). Manual identification of ADEs was used in three of the five cost evaluation methods (resource use method, proportion of registered cost method, and unit cost method). Primary care, other outpatient care, and inpatient care medical records during the study periods were screened manually for potential ADE cases by a pharmacist trained in reviewing medical records, and data were collected in a standardized data collection sheet. Potential ADEs were analyzed and evaluated individually by two experienced practitioners—one physician with a specialization in clinical pharmacology and one pharmacist with experience from either pharmacovigilance or clinical pharmacy. The final evaluation was discussed to reach consensus. On the basis of a method for causality assessment by Howard et al. [6], ADEs judged at least *possible* (possible, likely, or definite relationship) were further assessed to identify resource use resulting from ADEs.

In two of the five cost evaluation methods, *International Statistical Classification of Diseases and Related Health Problems* (*ICD*), version 10-SE, codes were used for ADE identification

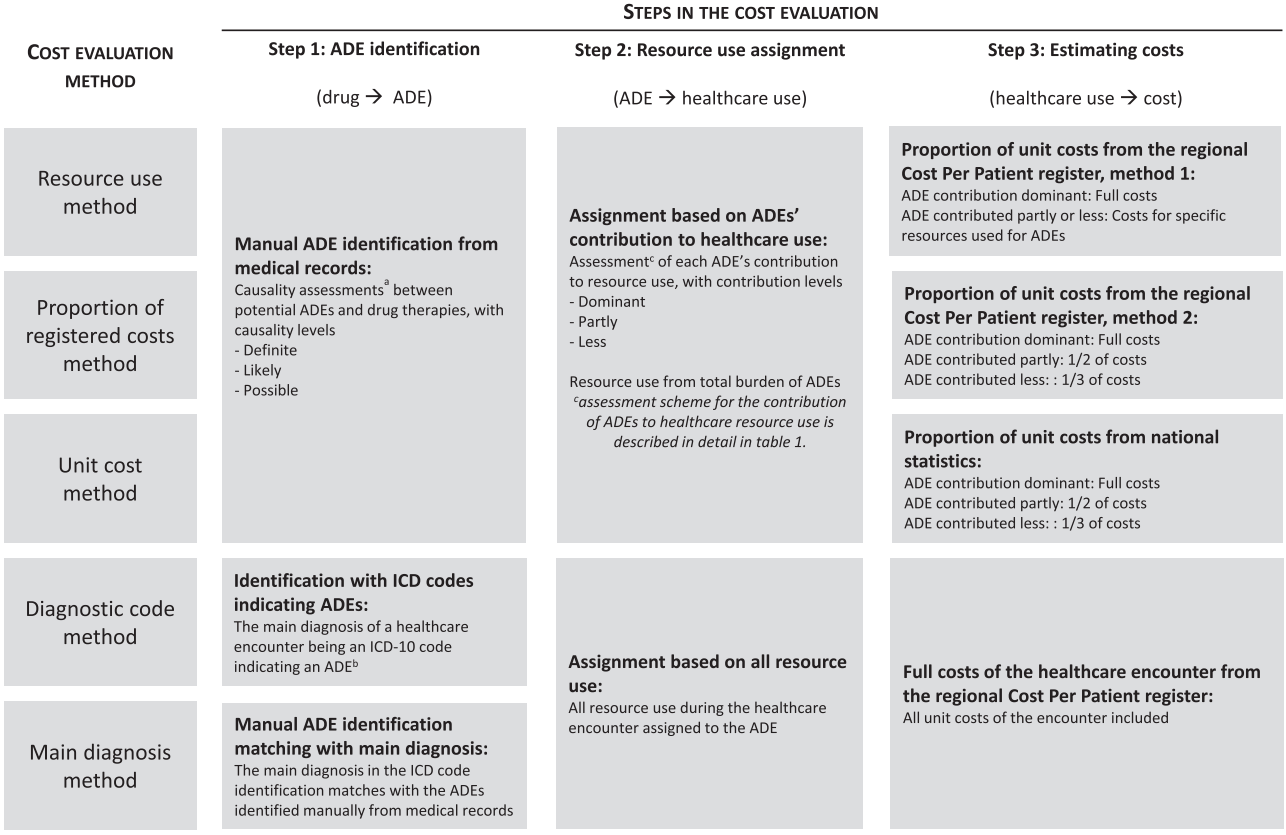

Fig. 1 – Description of the five cost evaluation methods. ADE, adverse drug event; *ICD, International Statistical Classification of Diseases and Related Health Problems*. **[a]Method described by Howard et al. [6]. [b]We considered** *ICD* **version 10 codes F11, F13, T36–T50, U82–U85, and Y40–Y59 to indicate ADEs. [c]The assessment scheme for the contribution of ADEs to health care resource use is described in detail in Table 2.**

Table 1 – Characteristics of the study population.

Characteristic	Study population	
	n (%)	Mean ± SD
Age (y)		
18–34	1,380 (28)	26 ± 5
35–64	2,437 (49)	50 ± 9
≥65	1,153 (23)	75 ± 8
Sex		
Men	2,427 (49)	NA
Women	2,543 (51)	NA
Country of birth		
Sweden	4,437 (89)	NA
Outside Sweden	532 (11)	NA
Health care cost (Sk)*		
Study quarter	**n (%)**	**Mean ± SD, median (IQR)**
Study quarter 1	1,247 (25)	3,822 ± 17,458, 0 (0–1,965)
Study quarter 2	1,245 (25)	3,338 ± 17,689, 0 (0–1,677)
Study quarter 3	1,244 (25)	3,152 ± 15,216, 0 (0–1,331)
Study quarter 4	1,234 (25)	3,919 ± 21,966, 87 (0–2,039)

IQR, interquartile range (quartile 1–quartile 3); NA, not applicable; Sk, Swedish krona.

* Health care costs were skewed in the total population, with most of the population (n = 2,410) not attending health care during their assigned study quarter.

(Fig. 1). *ICD* codes registered in the Care Data Warehouse, the Östergötland County administrative register of health care encounters [11], were extracted. In the diagnostic code method, main diagnoses of health care encounters that indicated an ADE (i.e., F11, F13, T36–T50, U82–U85, and Y40-Y59) were considered as ADEs. The main diagnosis method included encounters for which the identified ADE through the manual identification from medical records matched with the registered main diagnosis (*ICD* code). The main diagnosis did not directly have to indicate an ADE, as in the diagnostic code method.

Resource Assignment and Costs

The second and third steps of the evaluation discerned the costs resulting from ADEs (Fig. 1), that is, costing. The second step concerned methods for assigning resource use to ADEs, that is, to decide which resource use/proportion of resource use was caused by the ADE. The third step was estimating costs, that is, how to set a cost to the resource use assigned to ADEs.

Two approaches, top-down and bottom-up calculations, are important methodological aspects of cost-of-illness studies [12]. When using a top-down approach, resource use is estimated from an aggregate level (e.g., from a hospital budget) to estimate the proportion of the total resources that are used for that specific illness [13]. Using a bottom-up approach, resources are assigned through the identification of actual resources used in the treatment of the illness [12], using, for example, patient questionnaires, information from medical records, or other sources of detailed resource use. Regardless of which approach is used, knowledge is required of which resources should be assigned to the illness under study, as indicated in the second step of the evaluation described hereafter. Resource use assignment to ADEs will further affect the availability of prices or costs to use, for example, availability of detailed administrative cost data or relevant unit costs, as indicated in our third step.

Assigning Resource use to ADEs

In the second step, resource use was assigned to ADEs in three different ways (Fig. 1). In three of the five costing methods (resource use method, proportion of registered cost method, and unit cost method), resource use was assigned to ADEs on the basis of ADEs' contribution to health care use. An assessment scheme (Table 2), which was developed by one of the authors, was used on the basis of a method for assigning hospitalizations to ADEs [14]. The final assessment scheme was discussed between the authors and the pharmacists making the assessments. Using the scheme, a pharmacist assessed potentially ADE-related health care resource use, registered in the data collection sheet, to the patient's ADEs on the basis of all ADEs identified in the patient's medical records. Health care encounters judged as not associated with ADEs (i.e., the ADEs of the patient were not contributing to the encounter) were not included.

In the remaining two cost evaluation methods (diagnostic code method and main diagnosis method), all resource use during the health care encounter was assigned to the ADE (Fig. 1).

Estimating Costs for the Assigned Resource Use

In the third step, costs of the assigned resource use were estimated in three different ways in the five cost evaluation methods (Fig. 1). The resource use method included all costs for encounters for which the contribution of ADEs was assessed as dominant (Fig. 1) and costs for specific resources used to diagnose, monitor, or treat ADEs during encounters for which ADEs were partly contributing or less important [9]. The costs were identified from a cost-per-patient register (KPP), the Östergötland County register of health care costs for encounters and specific resource use. The proportion of registered cost method included full costs if dominant association, half the costs if partly contributing, and one-third of the costs if less contributing to a health care encounter, using costs from the same KPP register as was used in the resource use method. The unit cost method included costs in the same proportion to the assessed associations as was used in the proportion of registered cost method, but it used unit costs for health care encounters identified from national cost statistics [15]. In the national statistics, average costs are reported for physician visits in primary care and specialized care, respectively, and for hospitalizations. Costs for other encounters are calculated as follows: 40% of the costs for physician visits apply to encounters with other health care professionals, one-third of the costs for visits apply to phone contacts, and 2 times the costs of encounters apply to home health care [15].

Both the diagnostic code method and the main diagnosis method used costs from the KPP register, and cost estimation was based on the full cost of identified encounters (Fig. 1). The rationale for this was that the clinician's choice of a "main" diagnosis or condition, when there are many to choose from, should reflect the use of resources. That is, according to instructions from the Swedish National Board of Health and Welfare, the label "main" should indicate the most resource-demanding condition of an encounter [16].

Analyses

All cost analyses were prevalence-based, that is, included costs incurred during the quarter to which each individual patient was sampled. Costs outside the study period were censored. Statistical analyses were performed using STATA/IC 11.1 (StataCorp, College Station, TX). The average per-patient direct health care costs for patients with an ADE and total direct health care costs resulting from ADEs were estimated using the five different costing methods. Selected findings were inflated to 2016 values

Table 2 – Assessment scheme for ADEs' contribution to health care, used for resource use, assignment (step 2).

ADEs' contribution to health care resource use	Description of original criteria [9]	Application of the criteria for specific health care encounters
Dominant	"The suspected symptoms were the main reason for [admission], and no other symptoms contributed significantly."	The main diagnosis or reason for encounter was associated with ADEs. ADEs were the only "plausible" reason for the encounter; without ADEs the patient would not have attended health care. Temporal relationship between ADEs and the health care encounter. *Also*: The health care encounter was mainly intended for primary prevention to identify an ADE, and resulted in identifying the said ADE. The health care encounter was mainly intended for secondary prevention of a current or recent ADE.
Partly contributing	"The suspected symptoms played a substantial role in [admission], but other factors also contributed significantly."	A diagnosis or partial reason for encounter was associated with ADEs. ADEs were a "plausible" reason for the encounter, but there were additional reasons for the patient to attend health care. Temporal relationship between ADEs and the health care encounter. *Also*: The health care encounter was partially intended for primary prevention to identify an ADE, and resulted in identifying the said ADE. The health care encounter was partially intended for secondary prevention of a current or recent ADE.
Less important	"The suspected symptoms played a minor or uncertain role, and the patient would probably have been [admitted] without them."	An encountered symptom was associated with ADEs. ADEs caused health care resource use (diagnosis, monitoring, or treatment of symptoms) during the encounter, but there were more important reasons for the patient to attend health care. Temporal relationship between ADEs and the health care encounter.
Not contributing	"Other symptoms/circumstances were the main reason for [hospitalization]."	Previous ADEs or potential future ADEs were discussed during the health care encounter. Neither the health care encounter nor health care resource use during the encounter were caused by ADEs. *Also*: The health care encounter was intended for primary prevention to identify an ADE, but no ADE was identified.

ADE, adverse drug event.

using the Swedish health care inflation index (the Swedish health care inflation index (LPI), including medicines; the index was 111.0 in 2008 and 132.5 in 2016) [17] and converted to euros using the 2016 average exchange rate (€1 = Sk9.47 [Swedish krona]) [18]. The relationship between costs in the 2 years is thus approximately €1 in 2016 for Sk8 in 2008.

Costs for prescribed drugs and other resource use resulting from ADEs outside the health care setting are unaccounted for in this study.

Analyses by Definitions of Causality

The resulting costs were reported for more conservative to more inclusive definitions on the basis of the causality assessment, that is, only those with 1) definite causality, 2) definite or likely causality, and 3) definite, likely, or possible causality assessment. Because patients could have more than one ADE, costs during each health care encounter were assigned on the basis of the ADE with the most conservative definition for the causality assessment during each encounter in this analysis. Costs were not adjusted on the basis of causality assessment.

Analyses by Definitions for ADEs' Contribution to Health Care Resource Use and Diagnoses

Finally, results were reported using different definitions for ADEs' contribution to health care resource use, that is, only those of 1) dominant association, 2) dominant association or partly contributing, and 3) dominant association, partly contributing, or less contributing. For the three methods in which resource use was

assigned on the basis of the assessment scheme for ADEs' contribution to health care resource use (resource use method, proportion of registered cost method, and unit cost method), the distribution of resource use by types of health care use and costs were reported using the aforementioned definitions. For the two methods based on registered diagnoses (diagnostic code method and main diagnosis method), the identified ADE-related diagnoses were reported.

Results

The estimated overall direct health care costs resulting from ADEs in our study population of 4970 adults (Table 3) ranged from Sk12,200 (€1,538) to Sk3,282,780 (€413,770) using the different costing methods and the most inclusive definitions. More conservative definitions for ADEs' contribution to health care resource use did not affect the number of individuals with ADEs, but affected the number of included encounters: of the total 1941 encounters, ADEs were the dominant cause of 991, partly contributing to 526, and less contributing to 424. Moreover, more conservative definitions for the causality of ADEs resulted in decreasing number of individuals with ADEs in the analysis of average patient costs: 43 with definite causality, 278 with definite or likely causality, and 596 with definite, likely, or possible causality assessment. Costs varied from Sk74 (€9) to Sk7059 (€890) with the most conservative definitions (i.e., only those with definite causality of ADEs and dominant cause to the health care encounter). The cost per patient ranged between Sk20 to Sk74 using the diagnostic code method and Sk3793 to Sk9706 using the unit cost method, by different definitions.

Examining the distribution of costs by type of encounter (the resource use method and the proportion of registered cost method) (Table 4) or by using the most inclusive definitions for ADEs' contribution to health care resource use and causality (the unit cost method) (Table 5), all methods found the largest total costs resulting from ADEs in hospitalized patients (total cost Sk969,314–Sk1,892,443 [€122,175–€238,528]) and from specialist physician visits (€38288-€54156). All other categories (Tables 4 and 5) had costs less than Sk300,000, except the costs for primary care physician visits as estimated by the unit cost method (Sk368,107). Using the resource use method, the average cost per encounter varied between Sk31,879 for hospitalizations dominantly caused by ADEs and Sk214 for partly contributing and Sk406 when less contributing (Table 4). The corresponding figures using the proportion of registered cost method were Sk31,879 for dominant cause, Sk13,857 for partly contributing, and Sk18,586 for less important.

The diagnostic code method identified six encounters with main conditions that indicated an ADE, including *ICD* codes: F11 and F13 (indicating drug abuse); T41 and T50 (indicating poisoning, adverse effect, or underdosing of a drug). Identified costs resulting from ADEs by the main diagnosis method are presented in Table 6, by *ICD* chapter. Mental and behavioral disorders and diseases of the respiratory system were the *ICD* chapters with the highest costs resulting from ADEs—Sk359,752 and Sk192,769, respectively. All other *ICD* chapters were associated with costs less than Sk100,000.

Discussion

In our population-based sample, the estimated overall direct health care costs ranged from Sk0 to more than Sk3,000,000 (>€400,000 in 2016 values) on the basis of the costing method and from conservative to more inclusive definitions for including ADEs and associated costs. With the most inclusive definitions for ADEs' contribution to health care resource use and causality, costs estimated by the unit cost method were still more than 100 times the costs estimated by the diagnostic code method. Costs resulting from ADEs were thus highly affected by methodological decisions regarding costing methods and definitions for included ADEs, of which the most important determinants appear to be how ADEs are identified (step 1 in the cost evaluation) followed by how the relationship between resource use and ADEs was identified (step 2). Although the overall direct health care costs resulting from ADEs were affected by the conservative definitions for ADEs' contribution to health care resource use and causality, the average cost per patient was for most methods less affected.

The main strengths of this study were the availability of detailed data from regional health care registers and the combination of register data and information from medical records, which enabled us to estimate costs resulting from ADEs by several different methods. In Sweden, health care is mostly tax-funded, and mainly provided by county councils (i.e., the state), although there are private alternatives particularly in primary care and some specialties [19]. The registers used to identify resource use and costs in this study are examples of useful registers for this type of research [11], among many registers of health data available in Sweden [19]. There are, however, limitations to the register data, for example, encounters and resource use without registered costs. This can be illustrated by the three methods using the assessment scheme in Table 2 for assigning costs to ADEs. The unit cost method assigned costs to all 1941 encounters assigned to one or more ADEs. The proportion of registered cost method and the resource use method relied on data from the KPP register, wherein some encounters lacked data on costs. For this reason, costs could be assigned to 1703 (88%) encounters only (of which the ADE was a dominant cause in 854, partly contributing in 470, and less important in 379) using the proportion of registered cost method. For the resource use method, registered costs for specific resources used to diagnose, monitor, and treat ADEs were identified only in 92 (10%) of 950 encounters for which the ADE was judged as partly contributing (n = 45) or as less contributing (n = 47). For encounters for which an ADE was the dominant cause, the full costs were used. Thus, a large proportion of costs resulting from ADEs during encounters for other main diagnoses was probably unaccounted for by the resource use method. This was also seen when exploring costs for specific resources on the basis of ADEs' contribution to health care resource use, in which the costs during encounters with ADEs assessed as partly contributing or less important were particularly low compared with, for example, the proportion of registered cost method and the unit cost method (cost per encounter not shown because it was only the unit cost multiplied by the stated proportions of costs included by each definition). Also, the diagnostic code method identified only six encounters with main diagnoses that indicated an ADE. Of these, five had previously been assigned to be dominantly caused by an ADE but one encounter had not been assigned to ADEs. The main condition causing this encounter was F13, indicating dependence on a drug, but the only ADE identified during medical record review for this patient was a skin disorder. The main diagnosis method resulted in few encounters (n = 217) resulting from ADEs, also if comparing with the encounters assessed, by our manual search and consecutive evaluation, to be dominantly caused by ADEs (22% of 991 encounters). Moreover, of these, ADEs had previously been judged the dominant cause of 108, partly contributing to 86, and less contributing to 23 encounters. This may indicate that our medical record review and two-step procedure to identify and evaluate ADEs did not identify all health care resulting from ADEs, or that the main diagnosis method overestimates resource

Table 3 – ADE-related direct costs for five different costing methods, by definitions for the contribution of ADEs to health care resource use and ADE causality assessment.

Most conservative definition of causality for ADEs*	Most conservative definition of ADEs' contribution to health care resource use†					
	ADE *dominant* cause		ADE at least *partly contributing*		ADE at least *less contributing*	
	Per-patient cost (Sk), mean ± SD; median (IQR)	Total cost (Sk)	Per-patient cost (Sk), mean ± SD; median (IQR)	Total cost (Sk)	Per-patient cost (Sk), mean ± SD; median (IQR)	Total cost (Sk)
Resource use method‡						
ADE definite (n = 43)	2,006 ± 3,877; 87 (0–2,489)	86,245	2,040 ± 3,863; 272 (0–2,489)	87,707	2,151 ± 3,928; 385 (0–2,489)	92,476
ADE at least likely (n = 278)	3,624 ± 19,406; 81 (0–1,449)	1,007,408	3,661 ± 19,405; 104 (0–1,497)	1,017,634	3,748 ± 19,415; 202 (0–1,517)	1,042,063
ADE at least possible (n = 596)	2,899 ± 14,975; 56 (0–1,410)	1,727,592	2,933 ± 14,977; 80 (0–1,443)	1,747,918	2,994 ± 14,983; 126 (0–1,505)	1,784,513
Proportion of registered cost method§						
ADE definite (n = 43)	2,006 ± 3,877; 87 (0–2,489)	86,245	2,274 ± 3,852; 699 (0–2,515)	97,796	5,255 ± 11,742; 1,449 (572–4,591)	225,978
ADE at least likely (n = 278)	3,624 ± 19,406; 81 (0–1,449)	1,007,408	4,260 ± 21,817; 616 (0–2,070)	1,184,359	5,702 ± 22,952; 917 (284–2,547)	1,585,225
ADE at least possible (n = 596)	2,899 ± 14,975; 56 (0–1,410)	1,727,592	3,590 ± 17,006; 510 (0–2,074)	2,139,732	4,625 ± 17,896; 882 (169–2,599)	2,756,581
Unit cost method‖						
ADE definite (n = 43)	7,059 ± 17,677; 879 (0–5,284)	303,551	7,804 ± 17,726; 1,201 (240–5,472)	335,554	9,706 ± 17,867; 2,402 (879–8,881)	417,343
ADE at least likely (n = 278)	4,475 ± 16,903; 801 (0–2,636)	1,244,111	5,248 ± 17,579; 1201 (160–2,783)	1,459,050	6,185 ± 17,906; 1,361 (601–3,292)	1,719,356
ADE at least possible (n = 596)	3,793 ± 14,022; 480 (0–2529)	2,260,696	4,675 ± 15,034; 1,201 (0–1,639)	2,786,373	5,508 ± 15,371; 1,361 (524–3,287)	3,282,780
Diagnostic code method¶						
ADE definite (n = 43)	74 ± 472; 0 (0–0)	3,166	74 ± 472; 0 (0–0)	3,166	74 ± 472; 0 (0–0)	3,166
ADE at least likely (n = 278)	44 ± 428; 0 (0–0)	12,200	44 ± 428; 0 (0–0)	12,200	44 ± 0; 0 (0–0)	12,200
ADE at least possible (n = 596)	20 ± 293; 0 (0–0)	12,200	20 ± 293; 0 (0–0)	12,200	20 ± 293; 0 (0–0)	12,200
Main diagnosis method#						
ADE definite (n = 43)	243 ± 629; 0 (0–0)	10,457	307 ± 674;0 (0–0)	13,184	307 ± 674; 0 (0–0)	13,184
ADE at least likely (n = 278)	1,376 ± 12,495; 0 (0–0)	382,579	1,972 ± 19,428;0 (0–0)	548,238	2,063 ± 19,435; 0 (0–0)	573,599
ADE at least possible (n = 596)	1,091 ± 10,162; 0 (0–0)	650,443	1,533 ± 14,567;0 (0–0)	913,708	1,656 ± 14,621; 0 (0–0)	987,124

Note. Approximated euros (2016 values) can be calculated by dividing the listed Sk (2008 values) by 8.

ADE, adverse drug event; Sk, Swedish krona; IQR, interquartile range (quartile 1–quartile 3).

* The most conservative definition for the causality of ADEs, "definite," includes only those encounters during which the relationship likelihood of at least one suspected ADE was judged as "definite" causality [5], whereas the "at least likely" definition included encounters with ADEs judged as "definite" or "likely" causality.

† The most conservative definition for ADEs' contribution to health care resource use, "dominant cause," included only those encounters during which ADEs were judged to be the dominant reasons for the encounter (Table 2). The second most conservative definition, "at least partly contributing," included cases categorized as "dominant" or "partly contributing.

‡ On the basis of unit costs identified from national statistics [12], the resource use resulting from ADEs was identified using an assessment scheme (Table 2) and costs were included as full costs if dominant association, half the cost if partly contributing, and one-third of the cost if less contributing to a health care encounter.

§ On the basis of the resource use resulting from ADEs identified using an assessment scheme (Table 2) and costs identified from the regional cost-per-patient register, including all costs if dominant association, half the cost if partly contributing, and one-third of the cost if less contributing to a health care encounter.

‖ On the basis of the resource use resulting from ADEs identified using an assessment scheme (Table 2) and costs identified from the regional cost-per-patient register, including all costs for encounters with dominant association and specific ADE-related resource use for encounters for which ADEs were partly contributing or less important.

¶ On the basis of encounters for which the main condition was a diagnostic code indicating an ADE and including all costs identified from the regional cost-per-patient register.

On the basis of encounters for which the main condition matched the symptom identified as an ADE and including all costs identified from the regional cost-per-patient register.

Table 4 – Direct health care costs resulting from ADEs assigned by the proportion of registered cost method and the resource use method, by definitions for the contribution of ADEs to health care resource use.

Resource use type	Definition of ADEs' contribution to health care resource use						Total ADE cost (Sk), all encounters
	ADEs *dominant* cause of resource use		ADEs *partly contributing* to resource use		ADEs *less contributing* to resource use		
	Encounters, N	Average ADE cost per encounter (Sk), mean ± SD; median (IQR)	Encounters, N	Average ADE cost per encounter (Sk), mean ± SD; median (IQR)	Encounters, N	Average ADE cost per encounter (Sk), mean ± SD; median (IQR)	
Resource use method*							
Telephone contacts	263	200 ± 559; 68 (30–138)	134	0.5 ± 6; 0 (0–0)	49	19 ± 136; 0 (0–0)	53,673
Nurse visits	227	371 ± 442; 324 (50–522)	119	98 ± 240; 0 (0–0)	99	140 ± 319; 0 (0–0)	109,790
Physician visits in primary care	215	881 ± 821; 1,093 (97–1,300)	115	31 ± 93; 0 (0–0)	102	21 ± 69; 0 (0–0)	195,073
Physician visits in specialized care	123	2450 ± 1,786; 2,515 (1,315–3,457)	42	37 ± 149; 0 (0–0)	57	153 ± 476; 0 (0–0)	311,702
Home health care	61	1,753 ± 2,451; 655 (601–1,453)	67	9 ± 62 0 (0–0)	37	11 ± 70; 0 (0–0)	107,971
Other outpatient visits	72	509 ± 873; 94 (0–540)	36	0	55	7 ± 42; 0 (0–0)	36,990
Hospitalizations	30	31,879 ± 39,566; 14,011 (5,677–43,461)	13	214 ± 379; 0 (0–236)	25	406 ± 787; 0 (0–486)	969,314
Proportion of registered cost method†							
Telephone contacts	263	200 ± 559; 68 (30–138)	134	119 ± 389; 34 (21–69)	49	125 ± 310; 35 (18–45)	74,703
Nurse visits	227	371 ± 442; 324 (50–522)	119	180 ± 169; 162 (20–322)	99	153 ± 107; 149 (79–217)	120,783
Physician visits in primary care	215	881 ± 821; 1,093 (97–1,300)	115	480 ± 396; 498 (71–713)	102	362 ± 253; 393 (53–510)	281,557
Physician visits in specialized care	123	2,450 ± 1,786; 2,515 (1,315–3,457)	42	1176 ± 745; 1,018 (839–1,300)	57	1164 ± 938; 966 (649–1,537)	417,150
Home health care	61	1,753 ± 2,451; 655 (601–1,453)	67	1,139 ± 814; 1,492 (267–1,659)	37	321 ± 198; 327 (157–484)	195,110
Other outpatient visits	72	509 ± 873; 94 (0–540)	36	380 ± 678; 28 (0–621)	55	287 ± 544; 0 (0–326)	66,117
Hospitalizations	30	31,879 ± 39,566; 14,011 (5,677–43,461)	13	13,857 ± 16,025; 8,300 (5,497–14,398)	25	18,586 ± 18,962; 10,223 (8271–21,076)	1,601,162

Note. Approximated euros (2016 values) can be calculated by dividing the listed Sk (2008 values) by 8.

ADE, adverse drug event; IQR, interquartile range (quartile 1–quartile 3); Sk, Swedish krona.

* On the basis of the resource use resulting from ADEs identified using an assessment scheme (Table 2) and costs identified from the regional cost-per-patient register, including all costs for encounters with dominant association and specific ADE-related resource use for encounters for which ADEs were partly contributing or less important.

† On the basis of the resource use resulting from ADEs identified using an assessment scheme (Table 2) and costs identified from the regional cost-per-patient register, including all costs if dominant association, half the cost if partly contributing, and one-third of the cost if less contributing to a health care encounter.

Table 5 – Direct health care costs resulting from ADEs assigned using the unit cost method*, by definitions for the contribution of ADEs to health care resource use.

Resource use type	Unit cost per encounter (Sk)†	Definition of ADEs' contribution to health care resource use			
		ADEs *dominant* cause	ADEs *partly contributing*	ADEs *less contributing*	Total ADE cost (Sk), all encounters
		Encounters, N	Encounters, N	Encounters, N	
Telephone contacts					
Physician in primary care	1,201/3	75	28	15	37,631
Other health care professional in primary care	0.4 × 1,201/3	87	38	11	17,561
Physicians in specialized outpatient care	2,636/3	58	35	11	69,561
Other health care professional in specialized outpatient care	0.4 × 2,636/3	43	33	12	22,318
Physician visits					
In primary care	1,201	215	115	102	368,107
In specialized outpatient care	2,636	123	42	57	429,668
Home health care					
Physicians in primary care	1,201 × 2	5	8	2	23,219
Other health care professional in primary care	0.4 × 1,201 × 2	35	21	19	49,801
Physician in specialized outpatient care	2,636 × 2	8	1	3	44,812
Other health care professional in specialized outpatient care	0.4 × 2,636 × 2	13	37	16	77,674
Other health care visits					
Primary care	0.4 × 1,201	227	119	99	153,488
Outpatient care	0.4 × 2,636	72	36	52	113,172
Hospitalizations					
≤1 d	6,514	–	–	–	6,514
≥1 night	43,562‡	30	13	25	1,892,443

Note. Approximated euros (2016 values) can be calculated by dividing the listed Sk (2008 values) by 8.

ADE, adverse drug event; Sk, Swedish krona.

* On the basis of unit costs identified from national statistics [12], the resource use resulting from ADEs was identified using an assessment scheme (Table 2) and costs were included as all costs if dominant association, half the cost if partly contributing, and one-third of the cost if less contributing to a health care encounter.

† Unit costs from national statistics [12] were reported as costs for physician visits and weighted costs for other encounters: 40% of the costs for physician visits applied to encounters with other health care professionals, one-third of the costs for visits applied to phone contacts, and 2 times the cost of encounters applied to home health care. Costs were assigned as the full cost if dominant association, half the cost if partly contributing, and one-third of the cost if less contributing.

‡ The unit cost for a hospitalization is presented; the estimated costs for hospitalizations were also censored on the basis of the start and end of each person's study period.

use resulting from some types of ADEs (those assessed not to be dominantly caused by ADEs according to our assessment scheme).

Other limitations to the study results include use of medical records that are primarily aimed to provide health information to health care professionals rather than for research purposes, the subjective judgment necessary for both the reviews of medical records and consecutive evaluations of identified ADEs, and the use of secondary data as collected during the review in the evaluations [8,9]. The evaluations were thus based on the data collected during the medical record review rather than the medical records. Nevertheless, standardized tools, such as a standardized data collection sheet for the reviews, a method for causality assessment, and the assessment scheme for ADEs' contribution to health care resource use, were introduced to support the decision processes whenever possible. In addition, costs for prescribed drugs and other resource use resulting from ADEs outside the health care setting are unaccounted for in this study. Studies exploring the effects of methodological decisions in studies of costs for drug use resulting from ADEs are thus warranted. Moreover, a note of caution regarding the interpretation of presented confidence intervals needs to be added: because of the skewed distribution of cost data, the intervals should mainly be viewed as an indication of variation within each cost estimate.

Although the methods used in the studies of the economic impact of ADEs have been reviewed [1,2], there is no consensus or "criterion standard" for how costs resulting from ADEs should be measured. According to a recent review of the literature [20], this difficulty in assigning resource use and costs to specific events applies also to studies of medication errors (i.e., avoidable harm resulting from drug therapy). The identification of resource use

Table 6 – Direct health care costs resulting from ADEs assigned by the main diagnosis method*.

ICD chapter† and ICD categories (three-character level)	Encounters, N	MedDRA categories‡, SOC chapter	Average ADE cost per encounter (Sk), mean ± SD; median (IQR)	Total ADE cost (Sk), all encounters
Certain infectious and parasitic diseases (A00–B99): A69	1	Infections and infestation	68; 68 (68–68)	68
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50–D89): D50, D64	5	Blood and lymphatic system disorder	19,693 ± 32,854; 1,544 (1,362–18,653)	98,463
Endocrine, nutritional, and metabolic diseases (E00–E90): E03, E16, E78	4	Endocrine disorder; metabolism and nutrition disorder	1,729 ± 1,163; 2,114 (902–2,557)	6,917
Mental and behavioral disorders (F00–F99): F11, F25, F31, F32, F33, F39, F40, F41	52	Psychiatric disorder; musculoskeletal and connective tissue disorders; injury, poisoning, and procedural complications	6,918 ± 19,564; 3,317 (2,742–3,317)	359,752
Diseases of the nervous system (G00–G99): G20, G25, G40, G43	6	Nervous system disorder; musculoskeletal and connective tissue disorders	3,789 ± 4,393; 2,446 (979–4,610)	22,736
Diseases of the eye and adnexa (H00–H59): H40	2	Eye disorder	612 ± 0; 612 (612–612)	1,224
Diseases of the ear and mastoid process (H60–H95): H60	1	Ear and labyrinth disorder	1,108; 1,108 (1,108–1,108)	1,108
Diseases of the circulatory system (I00–I99): I10, I20, I47, I49, I50, I80	48	Endocrine disorder; psychiatric disorder; cardiac disorder; vascular disorder; respiratory, thoracic, and mediastinal disorders; gastrointestinal disorder; general disorders and administration site conditions	2,012 ± 2,559; 1,409 (762–2,398)	96,558
Diseases of the respiratory system (J00–J99): J01, J06, J18, J22, J32, J44, J45, J70	27	Nervous system disorder; vascular disorder; respiratory, thoracic, and mediastinal disorders	7,179 ± 16,864; 1,449 (1,063–6,113)	193,832
Diseases of the digestive system (K00–K93): K12, K25, K29, K30, K50	7	Gastrointestinal disorder	12,365 ± 26,806; 2,599 (1,353–3,775)	86,558
Diseases of the skin and subcutaneous tissue (L00–L99): L01, L02, L08, L20, L27, L40, L50, L57, L73, L97	10	Skin and subcutaneous tissue disorders	1,958 ± 993; 1,733 (1,335–2,801)	19,576
Diseases of the musculoskeletal system and connective tissue (M00–M99): M06, M07, M10, M17, M25, M54	42	Psychiatric disorder; cardiac disorder; gastrointestinal disorder; musculoskeletal and connective tissue disorders; general disorders and administration site conditions	1,252 ± 1,124; 657 (644–1,432)	52,581
Diseases of the genitourinary system (N00–N99): N18, N30, N34	10	Renal and urinary disorder	4,001 ± 9,332; 1,132 (1,003–1,299)	40,007
Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified (R00–R99): R52, R53, R99	3	General disorders and administration site conditions	2,581 ± 1,144; 3,103 (1,270–3,371)	7,744

Note. Approximated euros (2016 values) can be calculated by dividing the listed Sk (2008 values) by 8.

ADE, adverse drug event; *ICD*, *International Statistical Classification of Diseases and Related Health Problems*; IQR, interquartile range (quartile 1–quartile 3); Sk, Swedish krona; SOC, System Organ Classes.

* On the basis of encounters for which the main condition matched the symptom identified as an ADE and including all costs identified from the regional cost-per-patient register.

† *ICD-10-SE* chapters, excluding chapters with no identified ADEs: neoplasms (C00–D48); pregnancy, childbirth, and the puerperium (O00–O99); certain conditions originating in the perinatal period (P00–P96); congenital malformations, deformations, and chromosomal abnormalities (Q00–Q99); injury, poisoning, and certain other consequences of external causes (S00–T98); external causes of morbidity and mortality (V01–Y98); factors influencing health status and contact with health services (Z00–Z99); and codes for special purposes (U00–U99).

‡ A standardized medical terminology used for sharing regulatory information for medical products developed by the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Categorized into SOC as described previously [10].

resulting from a disease can be done, for example, through using the registered main condition of each health care encounter [21], what we call the diagnostic code method. Thus, *ICD* codes have been used previously to identify health care use caused by ADEs [22]. Nevertheless, according to our results, costs for ADEs estimated by this method were low compared with costs using other methods. Because studies using review of medical records to identify ADEs have resulted in higher prevalence of medication-related hospitalizations than studies using *ICD* codes [23], costs measured by methods based on registered diagnoses only probably underestimate the economic impact of ADEs. Moreover, little is known of the costs of ADEs outside hospitals, but in hospital settings also, studies often estimate costs on the basis of the full cost of admissions mainly caused by ADEs (similar to our main diagnosis method). In a previous review of methods for estimating costs of ADEs, this method was found to be used in 10 of 29 included articles [1]. Thus, the overall impact on health care would also be underestimated in those studies, because resource use during hospitalization for other reasons will be excluded. This is why our cost estimate using the main diagnosis method is low compared with the three methods using manual assessment of ADEs' contribution to health care resource use (resource use method, proportion of registered cost method, and unit cost method). To our knowledge, there are no previous studies using methods similar to our assessment scheme and consequent assignment of costs to identified resource use resulting from ADEs. The results provided in this study indicate that using registered diagnoses (step 1 in the cost evaluation) results in underestimating the costs of ADEs to a large extent. Moreover, such methods are probably unfit for either following ADEs over time in one setting or comparing between settings because of the sensitivity to differences in coding.

There are also other methods for analyzing costs from ADEs. Attributable costs from ADEs have been calculated by comparing the costs for hospitalizations between matched pairs with or without ADEs or by regression analysis [1]. Such methodological or statistical control of background characteristics, in theory, enables the isolation of costs resulting from ADEs. There is, however, a high risk of bias because of confounders, because patients with ADEs may differ from other patients in many other aspects than those measured. Arguably, the costs will be overestimated, because patients with ADEs are likely to be frailer and have other risk factors that increase costs of encounters regardless of the ADE. The studies we have found have been limited to inpatient costs analyzed by regression [24–28] or matching [29–34]. Hospitalized patients with or without ADEs in a specific health care setting may have similar probabilities of developing adverse events. Nevertheless, in the general population and outpatient setting, it is probably more difficult to identify a good group of controls or background characteristics for the analyses, which makes standardized methods for assigning costs to relevant (e.g., adverse) outcomes important.

A few other methods have been suggested for assigning resource use to ADEs, also among hospitalized patients. We based our assessment scheme on the method developed by Hallas et al. [14] for assigning hospitalizations to ADE, but to our knowledge no formalized method for assigning other inpatient resource use to ADEs exists [1]. One study used a measure called Imputability score to estimate the marginal costs attributable to ADE [35], but these scores were based on the causal relationship between symptoms and drug rather than on the association between ADEs and health care resource use. Thus, it is unclear how this assessment relates to the costs resulting from ADEs. Such a score would be better applied as definitions for what is a drug-related event, and be combined with an assessment of resource use resulting from ADEs, to enable future adjustments of both aspects in estimates of costs caused by ADEs. Such a method would be in line with how, for example, comorbidities can be handled in some studies [12]. There is, however, no knowledge today of what such an adjustment of costs could be based on (e.g., which proportion of costs should be included if the ADE was judged to be "possible" or "probable," respectively), and no previous studies have reported on the results from causality assessments related to costs for ADEs [7]. The "possible" level (disregarding the variation in methods used to assess causality) is often used in research [36–38], although in routine pharmacovigilance there is no definite level below which suspected cases should be excluded from analyses [39,40]. Our results by different levels of minimum causality level should thus be interpreted as the estimated costs if that level of causality is assumed to indicate an ADE. This highlights the need for a more thorough understanding of how causality should be interpreted in studies of costs related to ADEs.

Using the resource use method and the assessment scheme to identify ADEs' contribution to health care resources and drug use, we recently reported that the average direct costs resulting from ADEs was US $445 per patient with at least one ADE [9]. Although the method enabled assignment of registered costs for specific resources used to diagnose, monitor, and treat ADEs, many identified resources used were not assigned a cost, and thus the economic impact of ADEs was underestimated. The proportion of registered cost method and the unit cost method are attempts to overcome this problem by assigning costs to a larger proportion or all health care encounters, but may instead overestimate costs resulting from ADEs as the proportions (i.e., full costs/half of the costs/one-third of the costs) used were arbitrary. Nevertheless, the total costs estimated using these proportions were actually in line with previous modeling results that the costs resulting from ADEs are similar in magnitude with, or higher than, the costs for prescription drugs in a population. Prescription drugs in our (total) study sample cost approximately Sk3.5 million [9]. Moreover, the distribution of costs of ADEs in different parts of the health care system [9] was sensitive to changes in the methods used; using the resource use method, inpatient care costs corresponded to 54% of all costs for ADEs [9], whereas the unit cost method resulted in inpatient costs corresponding to 58% (Sk1,898,957 of Sk3,282,780) of costs. To our knowledge, there are no previous studies using similar methods with which our results can be compared, and we thus had no previous study on which to base our choice of proportions. The information in the predefined data collection sheet did not support a more detailed unit cost analysis, for example, using unit costs for specific resource use during health care encounters. After the initial screening for possible ADEs, and filling in the data collection sheet, the access to medical records was removed (personal identity numbers were exchanged to a random identification number by Statistics Sweden that enabled linkage between our data files but not to the medical records) for ethical reasons. Nevertheless, the results presented in this study indicate that unless a health care provider registers costs on the basis of each diagnosis present during an encounter, future studies of costs related to ADEs should collect detailed unit cost data. To our knowledge, there are no such studies to date.

According to our findings, the methodological decisions in studies of the economic impact of ADEs greatly affect the estimated costs. This is in line with a study by Frappier et al. [41] that the results of economic evaluations are dependent on the methods used for cost estimations. Because not all resource use is presented together with detailed cost registers, and probably not even all health care resource use, there is a need for more in-depth discussions about what is "good enough" cost data in studies of costs resulting from ADEs. Unit costs may be assigned to the used resources, as we did in the unit cost method, but this also requires making a judgment of what specific

resources were ADE-related. The same applies to studies of the lost productivity resulting from ADEs, without which the full societal economic impact is greatly underestimated. The unit cost method can be further developed, on the basis of detailed clinical data, to provide the best possible measure of costs resulting from ADEs. Unit costs can also be adapted to other settings, regions, and countries. Unless detailed resource use is available, it may be possible to use proportions of the total cost to indicate costs resulting from ADEs, as in our study, but this needs to be further explored. The lack of primary care and other outpatient data in previous research makes comparison of results unfeasible, in particular when taking into account our identified effect of methodological choices on the estimated costs.

Conclusions

The estimated costs for ADEs were highly affected by the choice of the costing methods, and by applying different thresholds for the uncertainty of a causal connection between the drug and the suspected ADE (step 1 of the cost evaluation) as well as between the ADE and the use of health care resources (step 2). In particular, costing methods based on manual assessment of resource use due to ADEs resulted in higher cost estimates than did methods based on registered diagnoses. The latter methods appear to underestimate costs to a large extent, because many ADEs were not assigned any costs, indicating that methods such as our suggested assignment of resource use to ADEs is needed in studies of the economic impact of ADEs. Nevertheless, costs varied also between the methods based on manual assessments, and unless a consensus emerges on how to handle the distribution of costs between conditions during one health care encounter (step 3), a detailed unit cost method, including specific resources used, is needed in future studies in this field of research. A better understanding of the impact of methodological choices on estimated costs is thus needed in studies that measure the costs of ADEs.

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Supplemental Materials

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