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Excess costs of alcohol-dependent patients in German psychiatric care compared with matched non-alcohol-dependent individuals from the general population: a secondary analysis of two datasets

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ABSTRACT

Objectives Heavy alcohol use can cause somatic and mental diseases, affects patients' social life and is associated with social isolation, unemployment and reduced quality of life. Therefore, societal costs of alcohol dependence are expected to be high. The aim of this study was to estimate excess costs of patients with alcohol dependence diagnosed using the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition criteria compared with individuals without alcohol dependence in Germany.

Design In a secondary analysis, baseline data of patients with alcohol dependence enrolled in a randomised controlled trial (German Clinical Trials Register DRS00005035) were compared with data collected via a telephone survey from individuals without alcohol dependence and that had been matched by entropy balancing. Health service use was evaluated retrospectively for a 6-month period.

Settings Four German psychiatric university clinics (patients with alcohol dependence) and the German general adult population (individuals without alcohol dependence).

Participants n=236 adult patients with alcohol dependence and n=4687 adult individuals without alcohol dependence.

Primary and secondary outcome measures The excess costs of health service use, absenteeism and unemployment of patients with alcohol dependence were calculated and compared with individuals without alcohol dependence. In subgroup analyses, the associations between excess cost and gender, comorbidities and the duration of disease were investigated.

Results Total 6-month excess costs of €11 839 (95% CI €11 529 to €12 147) were caused by direct excess costs of €4349 (95% CI €4129 to €4566) and indirect costs of €7490 (95% CI €5124 to €9856). In particular, costs of inpatient treatment, formal long-term care, absenteeism and unemployment were high.

Conclusions Alcohol dependence causes substantial direct and indirect excess costs. Cost-effective interventions to prevent and treat alcohol dependence are urgently needed.

Trial registration number DRKS00005035.

Strengths and limitations of this study

- A new statistical approach was used to derive excess costs for alcohol dependence combining two data sets through entropy balancing to adjust for differences in sociodemographic and clinical characteristics.
- Missing values were managed through multiple imputation.
- The skewness of cost data was taken into account by applying generalised linear models with a gamma distribution and a log-link function.
- Some cost categories were not available, such as data on crime, accidents, medication costs and presentism.
- Recruitment took place in specialised psychiatric university clinics, thus costs due to inpatients psychiatric treatment may be overestimated.

INTRODUCTION

In 2010, German adults consumed on average 11.8 L of pure alcohol per year, with 16.8 L and 7.0 L consumed by men and women, respectively.[1] Approximately 35% of the German population are estimated to have at least one episode of heavy drinking (≥5 glasses of alcohol per day).[2 3] Excessive use of alcohol is harmful to peoples' health and causes severe societal problems. The WHO estimated that 5.9% of all deaths result from the use of alcohol.[4] In persons aged 20–39 years, 25% of deaths are caused by alcohol addiction.[4] Alcohol-related diseases such as hepatitis, pancreatitis and various psychiatric

disorders (eg, depression) cause a reduced quality of life.[5 6] Negative social consequences of alcohol dependence (AD) include unemployment and social isolation.

According to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition criteria,[7] persons are diagnosed with AD if at least three of the following criteria are fulfilled: tolerance; withdrawal symptoms or clinically defined alcohol withdrawal syndrome; use of larger amounts of alcohol for longer periods than intended; persistent desire or unsuccessful efforts to cut down on alcohol use; time is spent obtaining alcohol or recovering from effects; social, occupational and recreational pursuits are given up or reduced because of alcohol use; and use is continued despite knowledge of alcohol-related harm (physical or psychological). Overall, 6.5% of the German population have been estimated to be alcohol dependent, corresponding to 3.4 million persons.[3 8] Thus, the social and economic burden of AD is high.[9 10]

The economic relevance of AD has been assessed by numerous studies.[11–13] In general, total societal costs consist of direct and indirect costs.[14] Direct costs refer to the monetary value of used resources (eg, hospital treatment, outpatient treatment or medication). Indirect costs represent the productivity loss due to morbidity or premature mortality. An international review of cost-of-illness studies summarised existing literature on the economic burden of AD and expressed its findings in US$ purchasing power parities (US$-PPP) (adjusted to the year 2006).[11] Total societal costs were estimated to be between US$-PPP 5228 million for Australia and US$-PPP 216 155 million for the USA. For Germany, total societal costs were estimated to be US$-PPP 32 540 million. Direct costs were estimated to be US$-PPP 9421 million with US$-PPP 3233 million due to inpatient treatment and US$-PPP 6188 million due to outpatient treatment. A recent cohort study (analysing data draw from a large sample size of 606 847 patients with AD from Catalonia) identified healthcare costs of €1290 per person per year.[15] In this study, being male, more extensive alcohol consumption, tobacco use and lower socioeconomic status were associated with higher healthcare costs. As varying cost categories were used by the reviewed studies, results were difficult to compare.

Total societal costs of alcohol consumption have mostly been estimated using the so-called top-down approach, combining aggregated data and using the alcohol attributable fraction (AAF) approach to estimate the contribution of alcohol use disorder in cause-specific morbidity and mortality from different sources.[16 17] However, top-down studies cannot be used to analyse the influence of sociodemographic or clinical patient characteristics on costs. Furthermore, they are limited by the definition of AAF as the proportion of cases attributable to all alcohol consumption. As health economic researchers are often interested in identifying predictors of costs or detecting subgroups of patients with high costs,[11 12] bottom-up studies using patient-level data are needed. Moreover, when calculating the economic burden of a disease, costs are often overestimated due to the inclusion of comorbidities in the calculation of costs. To avoid this problem, excess costs representing the difference between costs of patients with a specific disease and (otherwise identical) individuals without this disease can be calculated, resulting in the calculation of costs solely associated with the disease itself. However, bottom-up studies often only collect data of patients with AD, thus data of individuals without AD are not available. Our statistical approach overcomes this disadvantage by using entropy balancing to combine data of patients with AD and individuals without AD. Our analyses may therefore assist in the use of data from existing bottom-up studies to derive excess costs.

Even though it is well known that the economic burden of AD is high, excess costs of AD were only estimated by one recently published bottom-up study considering the economic burden of AD in Germany.[18] Total costs were reported to be 50% higher among patients with AD compared with individuals without. Calculations of indirect costs in particular differed to results of previous top-down studies. Consequently, the authors called for further cost-of-illness studies, using a bottom-up approach, in order to compare results with widely used top-down studies. Therefore, the aim of this study was to estimate excess costs of patients with AD in Germany using a bottom-up approach.

METHODS

Excess costs were calculated by comparing costs of individuals with and without AD, adjusting for sociodemographic characteristics and comorbidities. The cost calculation of patients with AD was based on the baseline assessment of patients enrolled in a multicentre clinical trial. Cost calculation of the comparison group of individuals without AD was based on data collected via a nationally representative telephone survey.

Study population with AD in inpatient withdrawal treatment

Data on patients with AD were taken from baseline interviews of patients included in a randomised clinical trial (Measurements in the Addictions for Triage and Evaluations - Levels of Care (MATE-LOC)) evaluating the effect of assessment-based recommendations for referral to subsequent treatment. Assessment of healthcare utilisation at baseline was retrospective for the preceding 6-month period. The trial was registered by the German Clinical Trials Register (DRS00005035). Data were collected between June 2013 and August 2014 in specialised alcohol withdrawal treatment units in four German psychiatric university clinics (Essen, Freiburg, Hamburg and Muenster). University clinics in Germany are maximum care hospitals in Germany financed by the public healthcare system and offer a wild range of treatment options. Psychiatric clinics participating in the MATE-LOC trial were specialised in detoxification and inpatient withdrawal treatment for AD. Patients

with a primary diagnosis of AD were eligible to take part in the study. Patients were diagnosed by the attending psychologists/psychotherapists or psychiatrists/neurologist of the patients previous to and independent of the study inclusion. Only patients with AD and willing to have a withdrawal treatment were recommended for the MATE-LOC trial. Exclusion criteria included treatment for reasons other than AD, severe cognitive impairment and psychotic disorder. Furthermore, participants were required to have German language skills and be literate. Even though patients were not selected by the severity of AD, included patients were expected to be more strongly affected by AD than the average German patient with AD (see discussion section).

Baseline assessment included a short questionnaire on sociodemographic and clinical data and a measure of addiction severity, the severity of mental and somatic comorbid disorders and the level of functioning. The addiction severity was assessed using the Measurements in the Addictions for Triage and Evaluations questionnaire,[19] which is a validated instrument assessing characteristics of people with drug and/or alcohol problems for triage and evaluation in treatment. It is conceptually constructed according to the International Classification of Diseases, the International Classification of Functioning, Disability and Health and World Health Organization classification system[20] and includes consideration of the lifetime duration of heavy alcohol use. A total of 299 alcohol-dependent patients were enrolled; data from 250 participants were included in the analysis of the RCT. After exclusion of patients with cost outliers, 236 participants remained in the data set. Detailed description of the study protocol can be found elsewhere.[21]

Study population without AD

Individuals without AD were taken from a representative telephone survey of the German adult population. Five thousand and five adults (≥18 years) were interviewed between March and April 2014. One hundred and forty participants were excluded due to missing values, as well as a further 35 participants due to being outliers in total costs. Furthermore, only participants who did not self-report an addiction disorder were considered. A total of 4687 individuals were included in the study as individuals without AD. Further information on the study design and results of healthcare utilisation have been published elsewhere.[22]

Patient and public involvement

The current study constitutes a secondary analysis of two datasets. Therefore, patients and the public were not directly involved in the development of the study protocol, including design, recruitment of patients and conduction of the study. Results will be available for participants through the journal publication.

Health service use and costs

We combined baseline trial data on healthcare utilisation of patients with AD included in the MATE-LOC trial with data of individuals without AD collected in the representative telephone survey of the German adult population. Differences in costs between patients with AD of the MATE-LOC trial and matched individuals without AD of the retrospective telephone survey are called 'excess-costs', as they represent costs that were solely due to AD and independent of further diseases and treatment choices.

In both groups, healthcare utilisation and sickness absence days in the preceding 6 months were assessed retrospectively. A modified version of the Client Socio-demographic and Service Receipt Inventory[23] was used to evaluate direct and indirect costs from the societal perspective. Direct costs refer to the monetary value of used resources (eg, hospital treatment, outpatient treatment or medication), whereas indirect costs represent the productivity loss due to disease-related absence from work.[24] Resource use and productivity losses were monetarily valued using German unit costs (online supplementary table S1).[25 26] If unit costs were not available for 2014, they were adapted to the year 2014 by using the German consumer price index.[27]

Only costs available in both data sets were included. Direct costs included costs for outpatient physician and non-physician services (eg, occupational therapy, physiotherapy, logopaedics, sports therapy and alcohol-specific counselling) as well as formal and informal care. Formal care included care delivered by outpatient nursing services as well as professional household help. Informal care included care provided by family members and friends. Inpatient costs included stays in general hospitals, psychiatric hospitals or rehabilitation hospitals. Unfortunately, data on medication costs were not available for individuals without AD assessed by the telephone survey, because a serious recall bias for medication intake surveyed by telephone was expected. Therefore, it was not possible to calculate medication excess costs. Indirect costs included absenteeism and unemployment. The human capital approach was used to monetarily value time absent from work using full-time and part-time labour costs for manufacturing and service sectors.[26 28]

Statistical analysis

We used a statistical approach to estimate excess costs for patients with AD compared with individuals without AD that consisted of three steps: (1) imputing missing values in the MATE-LOC patient data set, (2) combining the data sets and (3) estimating excess costs using regression analyses.

Imputation of missing values

Imputation of missing values in data sets is recommended when the missing rate is above 5%–10%.[29] As the maximum missing rate per variable in the data set of individuals without AD was 0.8%, no missing values were replaced and only complete cases were used. In contrast, the missing rate per variable in the data set of the MATE-LOC trial ranged between 0.0% and 34.8%.

Therefore, we decided to impute missing values using Multiple Imputation by Chained Equations (MICE).[30 31] As imputation method predictive mean matching with 50 imputations was used.[32–34]

Combining data sets

Data on sociodemographic and clinical characteristics (age, sex, living situation, education and comorbidities) and healthcare utilisation, as well as productivity loss, were extracted from the data sets of MATE-LOC and the telephone survey. As both data sets were collected independently, the sociodemographic and clinical characteristics of participants with and without AD were different. To estimate excess cost solely caused by AD, differences in sociodemographic and clinical characteristics were balanced using entropy balancing.[35] The imputed MATE-LOC data set was used as a reference and remained unchanged. Data of the telephone survey were balanced for each of the 50 imputed MATE-LOC data sets, in order to ensure similar means and SEs of sociodemographic and clinical characteristics.

Estimation of excess costs

Excess costs were analysed using weighted regression analyses with costs as the dependent variable and the presence of AD as the independent variable. Weights derived by entropy balancing were included to adjust for differences in sociodemographic and clinical characteristics. In particular, two-part models (TPM)[36] and generalised linear models (GLMs) with a gamma distribution and a log-link function[37] were applied to account for skewed cost distributions. TPMs were used for analyses of cost categories with a substantial share of zero values (costs of outpatient non-physician treatment, costs of hospital treatment and indirect costs). GLMs were used for cost categories for which almost every participant incurred costs (costs of outpatient physician treatment, direct costs and total costs).

To minimise the impact of cost outliers, we excluded participants above the 99th percentile of total costs (n=49: n=14 for patients with AD and n=35 for individuals without AD). In an additional analysis, we winsorised costs of participants with total costs above the 99th percentile instead.

Subgroup analyses were carried out by gender and AD duration (short ≤7 years <medium ≤16 years <long). Furthermore, costs of patients without any comorbidity were calculated to determine the impact of psychological and somatic comorbidities.

Statistical analyses were conducted with R (V.3.4.1) and STATA V.15.1. The R-package 'mice' was used for multiple imputation.[31] Entropy balancing was performed with the R-package 'ebal'.[38] The STATA module 'twopm' was applied to compute TPMs.[36]

RESULTS

Table 1 presents sociodemographic and clinical characteristics of participants with and without AD before and after entropy balancing. Prebalancing, participants with and without AD differed in sociodemographic and clinical characteristics. Patients with AD had a mean age of 45 years, while those without AD had a mean age of 54.8 years. Of patients with AD, 37% were women, whereas 53% of individuals without AD were female. Forty-nine per cent of the patients with AD were unmarried, whereas 27% of the individuals without AD were unmarried. Furthermore, patients with AD were less educated and had fewer somatic comorbidities but more mental and neurological diseases than individuals without AD. As expected, sociodemographic and clinical characteristics in both groups were similar after entropy balancing.

Table 1 Demographics and clinical sample characteristics prebalancing and postbalancing

	Patients with AD	Individuals without AD prebalancing	Individuals without AD postbalancing
	(n=236)	(n=4687)	(n=4687)
Covariates	**Mean**	**Mean**	**Mean**
Age (mean)	45.03	54.81	43.73
Gender (female %)	37	53	37
Person living not alone (%)	41	62	41
Unemployment (%)	26	4	8
Marital status (%)			
Unmarried	49	27	49
Married	17	43	17
Separated	8	3	8
Divorced	3	15	3
Educational level (%)			
None	3	0	3
Vocational training	30	27	30
Professional school	33	33	33
A-level exam	22	14	22
University	12	25	12
Physical comorbidities (%)			
Lung disease	8	16	8
Joint disease	6	19	6
Metabolic disease	9	26	9
Diabetes	4	11	4
Chronic pain	6	30	6
Gastrointestinal disease	19	19	19
Cancer	1	9	1
Cardiovascular disease	22	34	22
Skin disease	3	14	3
Osteoporosis	1	8	1
Psychiatric/neurological comorbidities (%)			
Mental disorders	36	10	29
Neurological disease	8	1	8

AD, alcohol dependence.

Costs were evaluated retrospectively for 6 months in 2014 in both datasets. Total costs per patient with AD were €16 378 (SE €1060), whereas total costs for individuals without AD were €4539 (SE €150) (table 2). Thus, total excess costs of patients with AD compared with

Table 2 Average 6-month costs and excess costs in euros of participants with and without AD in 2014

	AD (n=236)	Without AD (n=4687)	Differences		
	Mean (SE)	Mean (SE)	Excess	95% CI	P values
Direct costs					
Outpatient sector					
Psychologist/psychotherapist	100 (26)	45 (3)	55	0 to 110	0.050
Psychiatrist/neurologist	46 (12)	22 (1)	24	−2 to 50	0.075
Other physicians*	195 (17)	175 (3)	20	12 to 27	<0.001
Non-physician specialists	375 (73)	65 (3)	310	163 to 458	<0.001
Inpatient sector					
General hospital	616 (140)	278 (21)	338	−29 to 703	0.071
Psychiatric hospital	2129 (317)	69 (15)	2060	1415 to 2704	<0.001
Rehabilitation hospital	579 (173)	74 (9)	505	139 to 871	0.007
Home care sector					
Formal care	1184 (403)	73 (11)	1111	318 to 1904	0.006
Informal care	56 (16)	130 (11)	−74	−155 to 7	0.073
Total direct costs*	**5280 (568)**	**931 (44)**	**4349**	**4129 to 4566**	**0.000**
Indirect costs					
Absenteeism	2084 (326)	753 (36)	1331	623 to 2040	<0.001
Unemployment	9014 (997)	2855 (139)	6159	5121 to 7196	<0.001
Total indirect costs	**11 098 (968)**	**3608 (140)**	**7490**	**5124 to 9856**	**<0.001**
Total cost*	**16 378 (1.060)**	**4539 (150)**	**11 839**	**11 529 to 12 147**	**<0.001**

*Estimated with generalised linear models (GLM); the rest was estimated with two-part models .
AD, alcohol dependence.

individuals without were €11 839 (95% CI €11 529 to €12 147). Direct excess costs were €4349 (95% CI €4129 to €4566) for patients with AD and were mainly caused by excess costs of inpatient treatment in general, psychiatric and rehabilitation hospitals, as well as formal care. Indirect excess costs of patients with AD amounted to €7490 (95% CI €5124 to €9856). In summary, all cost categories were higher for patients with AD than for individuals without AD, except for costs due to informal care (€−74; 95% CI €−155 to €7). All differences between costs for patients with AD and individuals without AD were statistically significant, with the exceptions of outpatient treatment by psychologists/psychotherapist, psychiatrist/neurologist, inpatient treatment in general hospitals and informal care.

Results of analyses stratified by the lifetime duration of heavy alcohol use are presented in table 3 and table 4. The analyses revealed differences in direct excess costs. Patients with a short lifetime duration of heavy alcohol use had direct excess costs of €3504 (95% CI €3101 to €3911) compared with individuals without AD, whereas direct excess costs for patients with a long lifetime duration of heavy alcohol use were €5925 (95% CI €5448 to €6403). Indirect excess costs of patients with a short, medium or long lifetime duration of heavy alcohol use were €7571 (95% CI €4206 to €10 935), €6786 (95% CI €3183 to €10 389) and €7902 (95% CI €3876 to €11 929), respectively.

Results of analyses by gender are presented as online supplementary table S2. Direct excess costs were €4284 (95% CI €3873 to €7247) for women with AD compared with women without AD and €4165 (95% CI €3862 to €4472) for men with AD compared with men without AD. Women had higher direct excess costs for inpatient treatment in psychiatric hospitals and rehabilitation, whereas men had higher direct excess costs for formal care. Furthermore, indirect excess costs for men with AD were €7164 (95% CI €4203 to €10 127) compared with men without AD, whereas indirect excess costs for women with AD were €6621 (95% CI €2635 to €10 607) compared with women without AD.

Excess costs of participants without mental or somatic comorbidities are shown in the online supplementary table S3. Patients with AD and without any comorbidity had direct excess costs of €2836 (95% CI €1340 to €4333) when compared with healthy individuals. Indirect excess costs were €9103 (95% CI €5360 to €12 847) for patients with AD and without mental or somatic comorbidities, compared with healthy individuals.

Sensitivity analyses on outliers resulted in only small changes. Compared with the main analysis, excess costs were higher in the subgroup with winsorised cost outliers

Table 3 Average 6-month costs in euros of participant with and without AD in 2014 for different lifetime duration of heavy alcohol use

	Short AD	Without AD (balanced to short AD)	Medium AD	Without AD (balanced to medium AD)	Long AD	Without AD (balanced to long AD)
	(n=87)	(n=4687)	(n=73)	(n=4687)	(n=76)	(n=4687)
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)
Direct costs						
Outpatient sector						
Psychologist/psychotherapist	169 (59)	63 (5)	46 (28)	41 (3)	71 (34)	34 (3)
Psychiatrist/neurologist	77 (29)	24 (1)	35 (11)	21 (1)	20 (6)	22 (1)
Other physicians	144 (22)	168 (3)	212 (32)	185 (3)	238 (32)	178 (3)
Non-physician specialists	378 (130)	71 (3)	369 (131)	62 (3)	377 (118)	67 (3)
Inpatient sector						
General hospital	488 (175)	214 (18)	661 (295)	261 (23)	723 (240)	438 (26)
Psychiatric hospital	1949 (597)	90 (17)	1756 (397)	75 (15)	2700 (588)	39 (11)
Rehabilitation hospital	357 (215)	91 (11)	463 (249)	58 (8)	954 (411)	70 (9)
Home care sector						
Formal care	817 (542)	96 (13)	969 (662)	70 (10)	1825 (891)	58 (10)
Informal care	65 (27)	123 (10)	45 (24)	119 (10)	58 (32)	135 (13)
Total direct costs	**4444 (886)**	**940 (47)**	**4556 (850)**	**892 (46)**	**6966 (1178)**	**1041 (43)**
Indirect costs						
Absenteeism	3010 (698)	807 (37)	1387 (413)	719 (38)	1665 (449)	746 (34)
Unemployment	8162 (1581)	2794 (138)	8649 (1785)	2531 (131)	10369 (1855)	3386 (150)
Total indirect	**11172 (1553)**	**3601 (139)**	**10036 (1736)**	**3250 (134)**	**12034 (1779)**	**4132 (150)**
Total cost	**15616 (1695)**	**4541 (151)**	**14592 (1778)**	**4142 (145)**	**19000 (2027)**	**5173 (159)**

*Short ≤7 years <medium ≤16 years <long.
AD, alcohol dependence.

where total excess costs and direct excess costs of patients with AD were €11171 (95% CI €6599 to €11 430) and €5066 (95% CI €2537 to €5250) compared with individuals without AD. Indirect excess costs of €7152 (95% CI €3071 to €11 233)) were almost equal to those of the main analysis.

For all subgroup analyses, differences between patients with AD and individuals without AD in total costs, as well as direct and indirect costs, remained statistically significant, except for the total excess costs of patients without any comorbidity.

DISCUSSION

Our analysis revealed a high economic burden of AD with 6-month total excess costs of €11 839 for patients with AD compared with individuals without. Indeed, costs were almost four times higher for patients with AD compared with individuals without AD.

Approximately 2/3 of the total excess costs were due to indirect excess costs, with 82% of the indirect excess costs caused by unemployment. When compared with results reported by the only other study on excess cost for patients with AD in Germany,[18] indirect excess costs in our study were much higher (€7490 vs €1051), particularly costs due to unemployment (€6159 vs €373). In our analysis, the duration of unemployment was not specifically assessed and therefore assumed to be 6 months.[39] The costs of unemployment may consequently be overestimated.

Unexpectedly, indirect costs decreased between a short and medium lifetime duration of heavy alcohol use. In subgroup analyses, patients with a short lifetime duration of heavy alcohol use showed higher indirect excess costs compared with patients with a medium lifetime duration of heavy alcohol use, although the numbers of comorbidities increased. Fifty-five per cent of the patients with a short lifetime duration of heavy alcohol use were employed, whereas only 42% of the patients with a medium lifetime duration of heavy alcohol use were employed. As indirect costs are linked to the employment rate, the higher employment rate among patients with a short lifetime duration of heavy alcohol use is responsible for higher indirect excess costs.

Direct excess costs amounted to only one-third of total excess costs. Cost of inpatient treatment amounted to more than three quarters of direct excess costs. Less

Table 4 Average 6-month excess costs in euros of participant with and without AD in 2014 for different lifetime duration of heavy alcohol use

	Short AD			Medium AD			Long AD		
	Excess	95% CI	P values	Excess	95% CI	P values	Excess	95% CI	P values
Direct costs									
Outpatient sector									
Psychologist /psychotherapist	106	−15 to 228	0.087	5	−52 to 63	0.861	37	−32 to 105	0.294
Psychiatrist/ neurologist	53	−6 to 112	0.077	14	−12 to 39	0.229	−2	−19 to 14	0.803
Other physicians*	−24	−32 to −17	<0.001	27	21 to 34	<0.001	60	48 to 73	<0.001
Non-physician specialists	307	45 to 569	0.021	307	50 to 563	0.019	310	75 to 545	0.010
Inpatient sector									
General hospital	274	−222 to 770	0.278	400	−256 to 1055	0.232	285	−401 to 972	0.415
Psychiatric hospital	1859	669 to 3050	0.002	1681	813 to 2549	<0.001	2661	1472 to 3851	<0.001
Rehabilitation hospital	266	−229 to 763	0.291	405	−147 to 958	0.151	884	79 to 1689	0.031
Home care sector									
Formal care	721	−344 to 1785	0.185	899	−395 to 2191	0.173	1767	29 to 3504	0.046
Informal care	−58	−153 to 36	0.225	−74	−165 to 17	0.109	−77	−177 to 22	0.128
Total direct costs*	**3504**	**3101 to 3911**	**0.000**	**3664**	**3209 to 4117**	**<0.001**	**5925**	**5448 to 6403**	**<0.001**
Indirect costs									
Absenteeism	2203	794 to 3611	0.002	668	−193 to 1528	0.128	919	−7 to 1847	0.052
Unemployment	5368	3804 to 6932	<0.001	6118	4418 to 7819	<0.001	6983	4421 to 8151	<0.001
Total indirect	**7571**	**4206 to 10935**	**<0.001**	**6786**	**3183 to 10389**	**<0.001**	**7902**	**3876 to 11929**	**<0.001**
Total cost*	**11075**	**10513 to 11639**	**<0.001**	**10450**	**9897 to 11001**	**<0.001**	**13827**	**13051 to 14605**	**<0.001**

Short ≤7 years <medium ≤16 years <long.
*Estimated with generalised linear models (GLM); the rest was estimated with two-part models.
AD, alcohol dependence.

than 10% of inpatient treatment costs were incurred in general hospitals, with the remaining costs incurred due to treatment in psychiatric and rehabilitation hospitals, where patients are likely to have received specific AD treatment. Excess costs of inpatient treatment increased with lifetime duration of heavy alcohol use. Furthermore, excess costs of formal care were high, in particular among patients with a long lifetime duration of heavy alcohol use, whereas excess costs of informal care were rather low. This might be explained by the absence of a partner and social contacts and/or their inability to provide support.[40] Even if patients were not living alone, difficulties in relationships existed, thus relatives might not be able to provide support. In the literature, social deficits and isolation were reported for any kind of alcoholism independent of the severity of disease.[41] Therefore, patients with AD may be forced to use formal rather than informal care.

Direct excess costs found in our study (€4349) were higher than those reported for Germany in literature (€1836).[18] In particular, excess costs of inpatient treatment (€2903 vs €469) and, to a lesser extent, of outpatient treatment (€409 vs €314) were higher in our sample. However, excess costs for the treatment by physicians other than psychologist/psychotherapists or psychiatrists/neurologists were lower in our study (€20 vs €120). These differences could be explained by differences in the recruitment of samples, as our sample was recruited in psychiatric university hospitals, whereas Manthey *et al*[18] recruited patients via general practitioners. Specifically, when compared with statistics of the federal statistical office on all patients with AD receiving inpatient treatment in Germany, patients of the MATE-LOC trial were on average 10 years younger and more often male (48% vs 65%).[42] These two factors are known to be associated with a more harmful consumption of alcohol.[43] Furthermore, mean length of inpatient-stays of patients in the MATE-LOC trial was approximately 10 days longer compared with other AD patients.[42] Thus, compared with other patients with AD, costs might be overestimated.

Additional analyses revealed men having higher excess costs than women, which is in line with results of the literature.[11–13 18] Gender differences in excess costs in our results were caused by the differences in indirect costs due to absenteeism and unemployment (€7164 vs €6621). Men were more often unemployed and, if employed, were more often absent from work. Direct costs were similar for both groups (€4165 vs €4284).

Patients with AD and without any comorbidity had slightly higher excess costs compared with patients included in the main analysis. As patients with AD and

without any comorbidity were all male and costs for male patients with AD are known to be higher compared with female,[43] cost differences could be explained by gender differences.

Strengths and limitations

Our analysis has several strengths including its statistical approach and the data sets used. We combined different statistical approaches to derive excess costs for participants with and without AD for the German healthcare system. We used two independent data sets, which were combined by entropy balancing to adjust for differences in sociodemographic and clinical characteristics. As randomised controlled trials often do not include healthy controls, it was necessary to match a second data set by entropy balancing, which only controls for observed parameter. To our knowledge, this was the first time this statistical approach was used to derive excess costs for AD. Missing values were managed using MICE, a powerful statistical approach, useful for instances where when missing values occur completely at random or depend on observed data. Furthermore, our statistical approach took the skewness of cost data into account by applying GLMs with a gamma distribution and a log-link function or TPMs. In subgroup analyses, we investigated the effect of different sociodemographic and clinical characteristics.

However, there are some limitations in our study. First, we did not include all cost categories usually assessed in cost-of-illness studies for AD, because data on crime, accidents, medication costs and presentism due to disability and early retirement were not available in both data sets used. These costs categories are known to be increased for patients with AD,[18 44 45] thus excess costs may have been underestimated. Second, SEs especially for inpatient costs, were high. We conducted several analyses to avoid methodological bias. We tested for variations in the number of imputations, iterations and nearest neighbours, for influences of outliers and for the number of missing values. The results of complete case analysis were similar to those received by the main analysis. We came to the conclusion that between variations of imputation were caused by the data itself, because a few patients with AD had very high costs for inpatient treatment. However, it might be possible that missing values were not (completely) random. Third, recruitment took place in specialised psychiatric university clinics, thus cost due to inpatient psychiatric treatment may be overestimated. Fourth, individuals who participated in the telephone survey were included based on self-reported diagnoses. As no clinical diagnoses were made and individuals might have concealed an AD, data of the telephone survey may include some individuals with an addiction disorder. As these individuals with AD are likely to have higher costs than those without AD, this bias would lead to an underestimation of excess costs. Furthermore, excess costs might differ, because individuals were asked to report any addiction disorder and not specifically AD. Fifth, a bias in costs for absenteeism may have occurred. Self-reported absenteeism from work is likely to be concealed,[46 47] thus excess costs may have been underestimated.

Conclusion

Our analysis revealed significant excess costs due to AD. Indirect excess costs were high, particularly those due to unemployment. Furthermore, direct excess costs, especially for inpatient treatment and formal home care, were high. High inpatient costs may have been caused by the recruitment of patients in specialised psychiatric university clinics. Additional analyses revealed that excess costs were higher for men compared with women, and costs increased with lifetime duration of heavy alcohol use. In order to reduce the high costs of AD, cost-effective interventions to prevent and treat AD are urgently needed.

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