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Abstract

Society benefits on a large scale from improved medical care and pharmaceuticals. The prescription of pharmaceuticals, however, also carries risks such as the possibility of an increased risk of falls, which may lead to severe injuries and increased health expenditures associated with these injuries. This study investigates the influence of several fall risk increasing drugs (FRIDs) on the number of injuries of elderly persons using multivariate regression models. Routine data from the Techniker Krankenkasse (TK) of frail elderly persons aged ≥ 65 years is analyzed for the year 2009 by estimating count data models, in order to take the data generating process of the number of injuries into account. The results of the count data model are compared to those from logistic regressions, which is the default regression model in this field of research. The empirical results suggest that antidepressants, anxiolytics, hypnotics and sedatives, antiarrhythmics, and drugs from the Priscus-list have a significant positive effect on the number of injuries, while antihypertensives and anti-parkinsonian agents show no and neuroleptics a significant negative effect. As recurrent injuries are common, the analysis of the number of injuries rather than just the probability of having an injury provides a more informative analysis of FRIDs.

JEL Classification: I12, I19

Keywords: Fall risk increasing drugs; Priscus-List; frail elderly; multivariate regression; count data models

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1 Introduction

Falls can cause serious injuries, disabilities and might even lead to death, in particular in case of elderly persons. About 30 percent of the community-dwelling people aged 65 years or older experience at least one fall every year. People being older than eighty years even fall with a probability of 50 percent per year. The injuries resulting from falls often require extensive medical treatment and – let alone the threat to quality of life of the persons concerned – represent a non-negligible economic factor as these injuries often entail long and expensive rehabilitation periods.[1]

Against this background, the influence of FRIDs on falls or fall-related injuries of elderly persons has been examined extensively throughout the last decades. Meta-analyses and reviews[2,3] reveal that the literature focuses almost exclusively on injuries of certain body regions, such as hip fractures[4], or on certain drugs[5–7] such as psychotropic agents. Furthermore, existing studies predominantly rely on cohort and case-control designs. Both designs should be considered with caution, as they often suffer from a lack of validity due to sample selection bias.[8] Only a few studies are based on randomized control trials[9] or representative cross-sectional data,[10] mainly because of a lack of appropriate data. Furthermore, most existing studies rely on data for the US and Canada.[6,11,12] Only one study investigates the effects of FRIDs using German data.[13] Finally, existing empirical studies predominantly apply logistic regressions[12,14] or Cox proportional hazards models.[4]

Despite these differences in the data and empirical methods used, most studies conclude that it is inevitable to be cautious when prescribing drugs to the elderly, as they can increase the risk of injuries.[1,12,14,15] In particular the following pharmaceuticals are classified as fall-risk increasing drugs (FRIDs): anxiolytics, hypnotics, sedatives, antidepressants, neuroleptics, analgetics, antihypertensives, antiarrhythmics and antiparkinsonian agents as well as drugs from the Beers criteria medication list describing potentially inappropriate medication consumption of older adults.[6,16] However, there are also studies criticizing these results and stating that there are other factors causing fall-related injuries such as morbidity or diseases that were not considered in the analyses. After controlling for these factors, hardly any significant increase in fall risk due to drug consumption can be stated.[11]

Using routine data from a German statutory health insurance fund, this study investigates the specific risk of injuries due to the prescription of FRIDs in older ages. We estimate the influence of FRIDs on the number of injuries using a count data model. This regression model takes the specific data generating process of our dependent variable (the number of fall-related injuries) into account, which results in a non-negative variable with integer values, and hence avoids several limitations of the widely used logistic regression approach.

2 Methods

2.1. Data

The empirical analysis is based on data for the year 2009 from the *Techniker Krankenkasse* (TK) – one of the largest social health insurance funds in Germany. The data are part of the statutory administrative and medical records. We restrict our analysis to individuals aged 65 years and older, who are in need of medical care at least on care level 1.* In contrast to most previous studies our data include both, frail elderly living at their homes and those living in institutions. To avoid a potential source of self-selection bias, we only consider individuals who were insured by the TK for the entire year and did not leave the insurance before the end of 2009. With these restrictions 20,852 insurants remain for the empirical analysis, i.e. about 0.9 percent of all frail elderly in Germany in 2009.[17]

2.1.1. Sample Description

Table 1 provides definitions and descriptive statistics of the variables used in our analysis. On average, the individuals in our sample are 79 years old and about 53 percent are females. They have been in need of care on average for 49 months at the end of the year 2009. Most of them (51 percent) are classified as being in need of care at level 1, followed by 37 percent at care level 2 and 12 percent in the severest care level 3. The distribution concerning the care level is similar to the one reported by the German Federal Statistical Office [17]. Concerning the health status of the frail elderly in our sample, Table 1 shows that most individuals in our sample suffer from diseases of the musculoskeletal system (80 percent), the genitourinary system (72 percent), and dementia (40 percent).

2.1.2. Injuries

As dependent variable we employ injuries and fractures of all body parts, i.e., injuries with the codes S00-T98 in the International Classification of Diseases (ICD-10). On average, the individuals in our sample had 2.51 injuries in 2009. Figure 1 shows that about 53 percent of the frail elderly experienced at least one injury in the considered period of time. Even though the maximum number of recorded injuries is 60, Figure 1 presents the distribution up to 15 injures as more than 15 injuries occur very rare. As the majority of injuries, such as fractures and soft-

* In Germany, the long-term care insurances which are part of the health insurances distinguish between three care levels with increasing severity of care which are formally assessed by an independent Medical Review Board of the Statutory Health Insurance Funds.

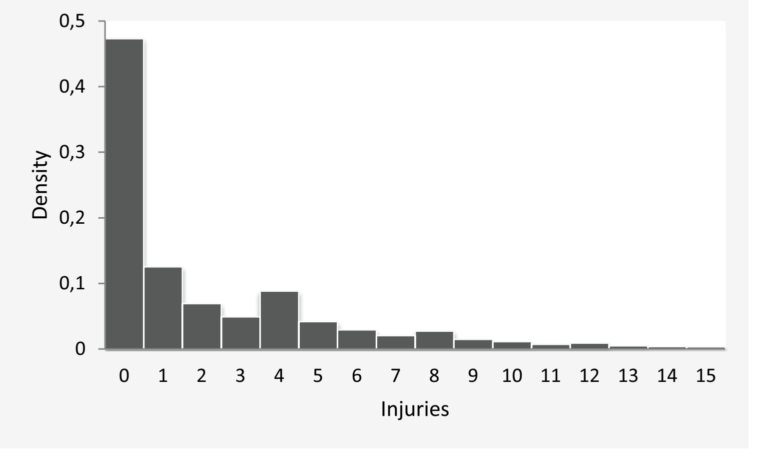
tissue injuries of the elderly are related to falls, the number of recorded injuries can also be considered as a proxy for falls.[15]

Table 1: Description of variables and descriptive statistics

Variable	Description	Mean	Std. Dev.
Dependent Variable			
Injuries	number of injuries (ICD-10: S00-T98)	2.51	(4.06)
Injuries dummy	=1 if individual suffered at least one injury	0.53	(0.50)
Independent Variables:			
Characteristics			
Age	age of individual	79.49	(8.04)
Age squared	squared age of individual	6382.71	(1286.34)
Female	=1 if female, 0 otherwise	0.53	(0.50)
Living alone	=1 if living alone – without any family, 0 otherwise	0.25	(0.43)
Care dependency			
Time in need of care	number of months since becoming care dependent at least at care level 1	49.01	(41.83)
Care Level 2	=1 if care dependent on care level 2, 0 otherwise	0.37	(0.48)
Care Level 3	=1 if care dependent on care level 3, 0 otherwise	0.12	(0.33)
Nursing home resident	=1 if living in a nursing home, 0 otherwise	0.21	(0.40)
Psychotropic drugs			
Antidepressants	sum of prescribed DDDs of antidepressants in 2009	85.18	(185.50)
Anxiolytics	sum of prescribed DDDs of anxiolytics in 2009	11.97	(57.32)
Hypnotics and Sedatives	sum of prescribed DDDs of hypnotics and sedatives in 2009	18.23	(79.46)
Neuroleptics	sum of prescribed DDDs of neuroleptics in 2009	22.58	(113.74)
Cardiovascular drugs			
Antihypertensives	sum of prescribed DDDs of antihypertensives in 2009	14.95	(89.63)
Antiarrhythmics	sum of prescribed DDDs of a antiarrhythmics in 2009	4.66	(38.97)
Miscellaneous drugs			
Antiparkinsonian agents	sum of prescribed DDDs of antiparkinsonian agents in 2009	1.38	(16.64)
Drugs from the Priscus-List	sum of prescribed DDDs of drugs from the Priscus-List in 2009	90.12	(187.10)
Health status			
Dementia	=1 if dementia (ICD-10: F00-F03) diagnosed in 2008/2009, 0 otherwise	0.40	(0.49)
Schizophrenia, schizotypal and delusional disorders	=1 if Schizophrenia, or schizotypal and delusional disorders (ICD-10: F20-F29) diagnosed in 2008/2009, 0 otherwise	0.06	(0.24)
Stroke	=1 if stroke (ICD10: I61, I63, I64) diagnosed in 2008/2009, 0 otherwise	0.33	(0.47)
Cardiac infarction	=1 if cardiac infraction (ICD-10: I21-I22) diagnosed in 2008/2009, 0 otherwise	0.09	(0.29)
Other diseases of the circulatory system	=1 if other diseases of the circulatory system (ICD-10: I00-I99 without I21-I22, I61, I63, I64) diagnosed in 2008/2009, 0 otherwise	0.95	(0.22)
Invasive neoplasms	=1 if invasive neoplasms (ICD-10: C00-C97) diagnosed in 2008/2009, 0 otherwise	0.29	(0.46)
Diseases of the musculoskeletal system	=1 if diseases of the musculoskeletal system (ICD-10: M00-M99) diagnosed in 2008/2009, 0 otherwise	0.80	(0.40)
Diseases of the genitourinary system	=1 if diseases of the genitourinary system (ICD-10: N00-N99) diagnosed in 2008/2009, 0 otherwise	0.72	(0.45)

N=20,852

Figure 1: Number of Injuries – Frequency Distribution



2.1.3. Fall Risk Increasing Drugs (FRIDs)

As potentially FRIDs we consider the annual sums of prescribed daily defined doses (DDDs), an internationally comparable statistical unit of measurement for drug consumption.[18] The sums of DDDs are calculated for the following drugs from the Anatomical Therapeutic Chemical (ATC) classification:

- Antidepressants (ATC: N06A),
- Anxiolytics (ATC: N05B),
- Hypnotics and sedatives (ATC: N05C),
- Neuroleptics (ATC: N05A),
- Antihypertensives (ATC: C02),
- Antiarrhythmics (ATC: C01B), and
- Antiparkinsonian agents (ATC: N04).

Attention is also paid to drugs that are included in the Priscus-list, a list of potentially inappropriate medication for frail elderly people in Germany[19] that resembles similar international lists such as the Beers-list.[20] We exclude selected drugs from the Priscus-list having no systemic effects, such as, for example, ointments which have only local effects. With 90.12 DDDs the highest average sums of all prescribed drugs in 2009 are those from the Priscus-list followed by antidepressants with 85.18 DDDs and neuroleptics with 22.58 DDDs.

2.1.4. *Descriptive Analysis*

Table 2 provides descriptive analyses of the effects of FRIDs on the average number of injuries. It appears that frail elderly persons with prescriptions of antidepressants, anxiolytics, hypnotics and sedatives, antiarrhythmics, antiparkinsonian agents or drugs from the Priscus-list experience on average at least 0.6 injuries more within a year than people without such prescriptions, while the number of injuries between consumers and non-consumers of neuroleptics and antihypertensives do not differ significantly and the prescription of antiparkinsonians has only a small but significant effect on injuries.

Table 2: Mean number of injuries with and without prescription of FRIDs

	Mean number of injuries		
	Insurants with prescriptions of considered FRIDs	Insurants without prescriptions of considered FRIDs	Differences
Psychotropic Drugs			
Antidepressants	2.94 (4.47) N=6,273	2.33 (3.86) N=14,579	0.61***
Anxiolytics	3.12 (4.58) N=2,630	2.43 (3.97) N=18,222	0.69***
Hypnotics and Sedatives	3.14 (4.47) N=2,402	2.43 (4.00) N=18,450	0.71***
Neuroleptics	2.55 (4.00) N=4,919	2.50 (4.08) N=15,933	0.05
Cardiovascular Drugs			
Antihypertensives	2.82 (4.66) N=924	2.50 (4.03) N=19,928	0.32
Antiarrhythmics	3.36 (4.40) N=367	2.50 (4.05) N=20,485	0.86***
Miscellaneous drugs			
Antiparkinsonian Agents	2.79 (4.54) N=255	2.51 (4.06) N=20,597	0.28***
Drugs from the Priscus-list	2.85 (4.34) N=9,256	2.25 (3.89) N=11,596	0.60***
All considered Drugs expect Drugs from the Priscus-list	2.76 (4.28) N=11,700	2.21 (3.74) N=9,152	0.55***

Notes: Standard errors in parentheses; Significant at ***: 1% level; **: 5% level; *: 10% level.

2.2. Logistic regression vs. count data models

In order to assess the effect of FRIDs on injuries in a multivariate setting, we apply two types of regression models: (i) a logistic regression, where the dependent variable takes the value "1" if at least one injury occurred in 2009, and "0" otherwise; and (ii) a count data model, where the dependent variable represents the number of injuries in 2009. In both models, we control for a set of variables describing the drugs prescribed to an individual and a set of variables describing the disease patterns, socio-economic characteristics as well as care dependency of the insurants. In the existing literature, the use of specific drugs enters the regression models predominantly as dichotomous variables. In addition to this type specification, we also provide estimation results for regression models in which the use of specific drugs is measured in DDDs. As the drugs from the Priscus-list are part of the other drug categories used in our models, we perform the estimations for the Priscus-list separately.

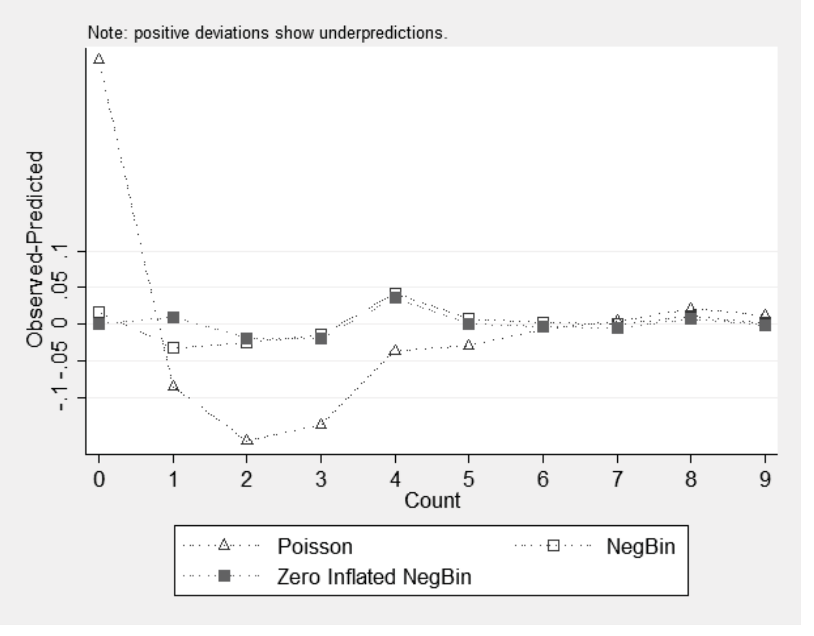
Most existing studies in the relevant literature rely on logistic regressions for dichotomous dependent variables in order to investigate the fall risk increasing effects of certain drugs.[12,14] This type of regression model only allows estimating the probability that one or more injuries occur in a specific time period. Recurrent injuries are considered either just as one injury or the logit estimations are conducted for recurrent and single injuries separately. However, dichotomizing may result in loss of information and the obtained results may be inefficient, inconsistent or biased.[21]

In comparison to logistic regression models, count data models are able to take the non-negative count of the dependent variable into account, i.e. they provide a more adequate description of the underlying data generating process. Furthermore, the model allows us to study not only the effect of FRIDs on the probability of an injury, but also on the frequency of injuries. The classical count data models are the Poisson and the Negative Binomial (NegBin) models. A limitation of the Poisson model is its assumption of equality of the mean and variance of the dependent variable.[22] As this eqidispersion hypothesis in the Poisson model is rejected in our sample[†], we concentrate on the NegBin model. In order to handle the excess of zero injuries in our data, we estimate Zero Inflated NegBin models. Figure 2 shows the observed minus the predicted probabilities for the Poisson, NegBin and Zero inflated NegBin model. The chosen model produces the best fit. The Vuong test further supports the decision to prefer the Zero Inflated NegBin model over the regular NegBin. As the Zero Inflated count models assume that zeros are generated by two distinct processe,[22] we believe that there is a separate population of zeros in our sample formed of those insurants, who are healthier in general, which is in accordance to

[†] The test of overdispersion was conducted according to Cameron and Trivedi (2009).

existing studies in epidemiology.[23] All statistical analyses are performed using STATA 11.[24] (StataCorp LP, Texas, USA).

Figure 2: Observed minus predicted probabilities



3 Results

We use our estimated results from the Logit and Zero Inflated NegBin models to predict the number and the probability of injuries for elderly with and without any prescriptions of FRIDs. In the model with drugs measured in DDDs we use the mean number of DDDs of consumers of the certain drugs to predict the number of injuries for people who take these drugs‡. To demonstrate the quantitative effects of taking FRIDs, we calculate the percentage difference of the predicted number of injuries between consumers and non-consumers of a particular drug normalized by the predicted number of injuries of the non-consumers§. The effects estimated by using the Logit model show the increase of the probability of suffering from injuries when taking the considered drugs compared to not taking FRIDs. Results from the zero inflated NegBin

‡ Means of prescribed DDDs under the condition that the drug is taken at all: Antidepressants: 283.20; Anxiolytics: 94.97; Hypnotics and Sedatives: 158.21; Neuroleptics: 95.70; Antihypertensives: 337.27; Antiarrhythmics: 264.98; Antiparkinsonian agents: 112.90; Drugs from the Priscus-list: 198.86.

§ If $\hat{I}_{Ci}$ denotes the predicted number of injuries for consumers of drug i and $\hat{I}_{NCi}$ those of non-consumers, Table 3 shows $\widehat{DI} = \frac{(\hat{I}_{Ci} - \hat{I}_{NCi})}{\hat{I}_{NCi}} * 100$.

model in contrast represent the increase of the number of injuries due to prescriptions of FRIDs in percentage terms. As the Zero Inflated NegBin model with drugs measured in DDDs accounts for all available information regarding the frequency of injuries and dosages of drugs, we consider this model as our benchmark model.

Table 3: Number of Injuries — Changes due to FRIDs

Variables	Logit		Zero inflated NegBin	
	Drugs measured dichotomously	Drugs measured in DDDs	Drugs measured dichotomously	Drugs measured in DDDs
Psychotropic drugs				
Antidepressants	7.26***	13.86***	3.65***	7.39***
Anxiolytics	12.66***	18.50***	3.92***	6.46***
Hypnotics and Sedatives	13.32***	17.81***	3.84***	5.29***
Neuroleptics	1.49	-0.02***	-1.80***	-3.79***
Cardiovascular drugs				
Antihypertensives	0.91	7.00*	-3.53	1.85
Antiarrhythmics	19.09***	31.35***	14.72***	21.75***
Miscellaneous drugs				
Antiparkinsonian agents	4.10	10.21	5.21	2.70
Drugs from the Priscus-list	12.80***	0.00***	7.86***	5.71***

Notes: Significant at ***: 1% level; **: 5% level; *: 10% level. N=20,852. The regression further controls for all independent variables described in Table 1.

The results shown in Table 3 reveal that not all drugs under consideration increase the risk of injuries. In our benchmark model, we find no significant effects for antihypertensives and antiparkinsonian agents, while neuroleptics even appear to have a significant negative effect on injuries. Significant positive effects on injuries are found for antidepressants, anxiolytics, hypnotics and sedatives, antiarrhythmics as well as the drugs from the Priscus-list. In all models, the highest effects are obtained for antiarrhythmics. According to the results from the Logit model, the prescription of this drug increases the risk of experiencing at least one injury on average by 31.35%. The results from the Zero Inflated NegBin model show that the frequency of injuries increases by 21.75% for consumers of antiarrhythmics[**].

4 Discussion

The contribution of our study to existing literature is manifold. First, drugs from the recently published Priscus-list have never been analyzed in terms of the fall increasing effect of these drugs before. Secondly, the empirical analysis is based on routine data with over 20,000 observations, which allows more precise estimates for the effects of FRIDs on injuries than most other previous studies. Thirdly, we are able to control for many confounding factors and

[**] The results refer to people who take the average prescribed amount of DDDs of the considered drug under the condition that they take the drug at all.

variables such as various diseases and the care dependency level of individuals, which are neglected by some recent studies.[5,14] Fourthly, for the first time we rely on a count data model to estimate the influence of FRIDs on injuries. In contrast to previously used models the count data model explicitly allows to take the number of injuries into account. Finally, it is often criticized that the exploration of the influence of FRIDs on falls and fall-related injuries does not consider dosages.[2] We are able to overcome this shortcoming as our data provide information on DDDs.

Despite these advantages, there are also impairments in our study. We are only able to measure drug prescriptions instead of factual drug use. Note however, such a measurement error usually results in an attenuation bias. Hence, if anything we estimate a lower bound of the injury-risk increasing effects of FRIDs. Based on the available data it cannot be detected if the patient took the drugs before or after an injury. In addition, we are not able to determine the circumstances of an injury. Although, most of the injuries of elderly persons are fall-related,[16] this fact could lead to an overestimate of the actual effect of the considered drugs on injuries, as some of the included injuries may arise from external causes others than falls.

Even thought there is a growing literature on models specifically developed for count data, only few studies in epidemiology and public health exploit the advantages of these approaches to model health outcomes, such as injuries.[23] This study shows that when dealing with injuries caused by FRIDs, the use of count data models is recommended rather than relying on dichotomous regression models. In the present application, models specifically developed for count outcomes with excess zeros provide better insights into the analysis of the side effects of certain drugs.

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