


**ORIGINAL REPORT**

# Prevalence and incidence rate of hospital admissions related to medication between 2008 and 2013 in The Netherlands

Fouzia Lghoul-Oulad Saïd<sup>1,2</sup>  | Karin Hek<sup>3</sup> | Linda E Flinterman<sup>3</sup> |  
Ron MC Herings<sup>4</sup> | Margaretha F Warlé-van Herwaarden<sup>5</sup> | Sandra de Bie<sup>6</sup> |  
Vera E Valkhoff<sup>7</sup> | Jelmer Alsmas<sup>8</sup> | Mees Mosseveld<sup>9</sup> | Ann M Vanrolleghem<sup>9</sup> |  
Bruno HCH Stricker<sup>9</sup> | Miriam CJM Sturkenboom<sup>10</sup> | Peter AGM De Smet<sup>11</sup> |  
Patricia MLA van den Bemt<sup>2</sup>

<sup>1</sup>Division of BioTherapeutics, Leiden Academic Centre for Drug Research (LACDR), Gorlaeus Laboratories, Leiden University, Leiden, The Netherlands

<sup>2</sup>Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen, The Netherlands

<sup>3</sup>Nivel, Netherlands Institute for Health Services Research, Utrecht, The Netherlands

<sup>4</sup>PHARMO Institute for Drug Outcomes Research, Utrecht, The Netherlands

<sup>5</sup>Pharmacy Groesbeek, Groesbeek, The Netherlands

<sup>6</sup>Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, The Netherlands

<sup>7</sup>Department of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, The Netherlands

<sup>8</sup>Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands

<sup>9</sup>Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands

<sup>10</sup>Department of Epidemiology, University Medical Center Utrecht, Utrecht, The Netherlands

<sup>11</sup>Departments of IQ healthcare and of clinical pharmacy, Radboud university medical centre, Radboud Institute for Health Sciences, Nijmegen, The Netherlands

**Correspondence**

Fouzia Lghoul-Oulad Saïd, PO box 9502, 2300 RA Leiden, The Netherlands  
Email: f.lghoul@lacdr.leidenuniv.nl

**Funding information**

Ministry of Public health, Welfare and Sports

**Abstract**

**Purpose:** In 2009 a Dutch guideline was published containing recommendations to reduce Hospital Admissions Related to Medications (HARMs). This study aims to examine time-trends of HARMs and their potential preventability between 2008 and 2013 in The Netherlands.

**Methods:** A retrospective prevalence study was conducted using the Dutch PHARMO Database Network. A semi-automated pre-selection was used to make a crude identification of possible HARMs of which four samples were selected. These were independently assessed with respect to causality and potential preventability by a physician and pharmacist. The results were stratified by age into 18-64 years and 65 years and older. For these groups the net prevalences and incidence rates of HARMs and potentially preventable HARMs were calculated for the years 2008, 2009, 2011 and 2013.

**Results:** Four samples of 467 (2008), 447 (2009), 446 (2011) and 408 (2013) admissions were assessed. The net prevalence of HARMs in the 18-64 years group was approximately four times smaller compared to the older group with a mean prevalence of 2.7% (95% confidence interval [CI]:2.4%-3.0%) and 10.2% (95%CI:

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2020 The Authors. *Pharmacoepidemiology and Drug Safety* published by John Wiley & Sons Ltd.

9.7%-10.7%) respectively. The potential preventability was 25.1% (18.4%-31.8%) and 48.3% (95%CI: 44.8%-51.8%), respectively. The prevalence of HARMs in both groups did not change significantly between 2008 and 2013 with 2.4% (95%CI: 1.9%-3.0%) and 10.0% (95%CI: 9.0%-11.0%) in 2008 and 3.1% (2.7%-3.5%) and 10.4% (95%CI: 9.4%-11.4%) in 2013, respectively.

**Conclusion:** Despite efforts to reduce HARMs, the prevalence did not decrease over time. Additional measures are therefore necessary, especially in the elderly population.

#### KEYWORDS

adverse drug reactions, drug-related, hospitalization, incidence, pharmacoepidemiology, prevalence, side effects

## 1 | INTRODUCTION

Besides being beneficial, drugs can have unwanted effects which can be mild, but can also lead to serious adverse effects, hospital admission or even death.

Hospital admissions related to medication (HARMs) are a worldwide problem.<sup>1-9</sup> A review published in 2016 showed a calculated median prevalence of 6.3% of all unplanned hospital admissions in developed countries and 5.5% in developing countries. In The Netherlands, one prospective and two retrospective studies have been performed to estimate the prevalence of possible HARMs in 2003, 2005, 2006 and 2008.<sup>10-12</sup> These studies have shown a prevalence of possible HARMs between 3.9 and 5.6% of acute admissions. The Quick Assessment of Drug-Related Admissions over Time (QUADRAT) study showed a decreasing trend of possible HARMs in The Netherlands between 2005 (4.65%) and 2008 (3.91%).<sup>11</sup> These results are comparable to findings in other Western countries.<sup>13-15</sup>

The percentage of potentially preventable HARMs only showed a small decreasing trend in the QUADRAT study with 20.5% in 2005 and 18.4% in 2008.<sup>11</sup> This potential preventability was lower compared to the other Dutch studies which calculated a percentage of 29.0% and 46.0%. but the QUADRAT study did not include non-adherence as a preventable cause.<sup>10,12</sup>

To reduce the number of potentially preventable HARMs multiple initiatives were developed and implemented. For example, educating prescribers on medication-related patient harm has been studied. However, no firm evidence was found to support or reject this type of intervention according to a systematic review conducted in 2016.<sup>16</sup> In The Netherlands a multidisciplinary taskforce composed 40 recommendations with the aim to reduce HARMs. These recommendations were based on the most common potentially preventable HARMs from the earlier mentioned studies<sup>10,12</sup> and were published in November 2009 (Dutch version).<sup>17</sup> In the years thereafter it led to several initiatives to reduce HARMs such as the development of clinical decision support systems. Additionally checklists and toolkits were implemented and protocols and guidelines were drafted or revised.<sup>18</sup> These initiatives did not lead to significant improvements in the

### KEY POINTS

- Hospital admissions related to medication (HARM) occur four times more often in patients of 65 years and older compared to 18-64 years.
- 2.7% of all hospital admissions in patients between 18 and 65 years are HARMs of which 25.1% is also possibly preventable.
- 10.2% of all hospital admissions in patients of 65 years and older are HARMs of which 48.3% is also possibly preventable.
- Between 2008 and 2013 the prevalence of HARMs did not change over time in The Netherlands.
- Measures to reduce HARMs should focus on the prevention of fractures, syncope and GI complications in the elderly.

QUADRAT study,<sup>11</sup> but implementation of protocols and guidelines takes time and thus this study may have come too early.

Therefore, a study was designed with the primary aim to determine whether these initiatives have led to a reduction in the prevalence and incidence rate of possible HARMs and potentially preventable HARMs in The Netherlands in the years 2008 to 2013.

## 2 | METHODS

### 2.1 | Data source

For this retrospective population based prevalence study we used the Dutch PHARMO Database Network, which combines data from different primary and secondary settings in The Netherlands and enables the follow-up of more than four million residents of a well-defined

population for an average of ten years. For this study drug dispensing data from community pharmacies and admission information of the hospitalization Database from the Dutch Hospital Data Foundation were used.

## 2.2 | Study period

To determine whether the multidisciplinary recommendations influence the number of possible HARMs the gross prevalence was calculated over the period between 2005 and 2013.<sup>17</sup> The net prevalence was calculated by using a sample extracted from the years 2008, 2009, 2011 and 2013. These years were chosen strategically. 2008 because the prior study investigated this year as well and we wanted to be able to compare these methods. 2009 was included since this was the year the HARM-Wrestling recommendations were published in Dutch. 2011 to see whether the recommendations have led to a decrease and this was also the year the English version of the recommendations were released<sup>17</sup> and 2013 to see whether there was a decrease 4 years after publication of the recommendations.

## 2.3 | Study design

This study is a retrospective population based prevalence study. To reduce the number needed to review in order to find a possible HARM a triggerlist was composed using the cause for hospitalization (event) and the concurrent drug use from the Dutch PHARMO Database Network (see Supporting Information, Data S1). All admissions between 2005 and 2013 identified by the triggerlist in the Dutch PHARMO Database Network were included to calculate the gross prevalences and incidence rates. Patients under the age of 18 were excluded. From the admissions included by the triggerlist a random sample was taken for the years 2008, 2009, 2011 and 2013 in order to calculate the positive predictive value (PPV) of possible HARMs and their preventability.

## 2.4 | Assessment of causality and preventability

Each included admission was assessed independently by a physician (JA/SdB/VV) and a pharmacist (FL/MW). The assessment of the causality was performed according the six axes of the algorithm of Kramer.<sup>19</sup> For all possibly causally associated HARMs, the potential preventability was also assessed by applying an adjusted version of the algorithm of Schumock and Thornton (Supporting Information, Data S2).<sup>20</sup> Both assessments resulted in either "yes" (possible causal and/or potentially preventable), "no" (probably not causal and in that case preventability not assessed) or "too little information to assess the causality and/or preventability". The interrater agreement was calculated using the kappa statistic in IBM SPSS Statistics for Windows version 22.0 (IBM Corporation, Armonk, USA).

In case assessments differed between the independent assessors, consensus was reached by a final assessment performed by two

experts (medical (BS) and pharmacist (PdS/PvdB)) independently. In case the assessments of these experts differed, consensus was reached during a consensus meeting.

The PPV for possible causality was calculated by dividing the number of assessed possible HARMs by the total number of admissions triggered by the triggerlist. In the same way a PPV for potentially preventability was calculated.

## 2.5 | Type of potentially preventable HARM

For all potentially preventable HARMs the event and associated drug was registered. The reason for preventability was also registered. Using the adjusted version of the algorithm of Schumock and Thornton the outcome could be one of the following: previously occurred adverse effect; drug was inappropriate for the condition of the patient, the dose, frequency or way of administration was inappropriate for the age, weight or severity of disease of the patient, wrong drug was dispensed, wrong drug was administrated, lack of monitoring of drug or other monitoring which was required, unacceptable drug-drug interaction, non-adherence or additional measures not taken or inadequate (eg, lack of or ineffective dosage of gastric protection when using a Non-Steroidal Anti-Inflammatory Drugs NSAID). Assessors were given the instructions to choose at least one of these reasons for preventability, but could choose more if applicable.

## 2.6 | Outcome measures

The primary outcome of this study was the net prevalence of potential HARMs in two age-groups: 18-64 years and 65 years and older. This division is based on the Dutch guideline for medication reviews (2013) which indicates to perform reviews on patients of 65 years or older with additional risk factors. The secondary outcomes were the incidence rate of potential HARMs, the type of HARMs and the reason for potential preventability for each age-group.

## 2.7 | Sample size

The prevalence of HARMs identified in previous studies was 5.1%,<sup>21</sup> 5.6%,<sup>12</sup> 4.6% and 3.9%.<sup>11</sup> When calculating the sample size the prevalence was estimated at 5.0% and the precision corresponding to this effect size at 0.01. This resulted in a calculated sample size of 1825 for the random sample to be drawn for the years 2008, 2009, 2011 and 2013 from the eligible patients selected by the triggerlist.<sup>22</sup>

## 2.8 | Data analysis

Data from the PHARMO data record linkage (Utrecht, The Netherlands) were analyzed using IBM SPSS Statistics for Windows version

22.0 (IBM Corporation, Armonk, USA). Using descriptive analysis the crude and net prevalence including their confidence intervals were calculated for each year.

For each age-group (18-64 and  $\geq 65$  years) the crude prevalence was calculated by dividing the number of potential HARMs identified with the triggerlist by the total number of admissions recorded in the PHARMO record linkage system for each study year. Using the PPV for causality the net prevalence was calculated for each age-group for each study year. The same was done for the potential preventability, using the PPV for preventability.

For each year between 2005 and 2013 the number of events and the person-time of medication use were collected from the PHARMO database using the triggerlist. The crude incidence rate was calculated for each age-group by dividing the number of these events which indicated potential HARMs by the number of years of use of the medication. These rates were adjusted for lack of supplied data. In 2008 and 2009 10% was lacking and in 2011 16%. For the year 2013 this percentage was unknown. Therefore the percentage of 19% from the previous year (2012) was used. Using the PPV for causality and

preventability obtained from the sample assessment the net incidence rate of possible causal en potentially preventable admissions were determined.

Using the net prevalence and the total number of admissions in the Netherlands for each age-group and year derived from Dutch Hospital Data (DHD), the number of potentially preventable HARMs was extrapolated to The Netherlands.

### 3 | RESULTS

A total of 893 593 and 750 832 admissions from the PHARMO database between 2005 and 2013 could be included for age-group 1 (18-64 years) and age-group 2 ( $\geq 65$  years), respectively. With the trigger list 52 048 and 129 569 admissions were used to calculate the gross prevalence of possible HARMs for each age-group. A sample of 1920 admissions was taken with 397 in age-group 1 and 1523 in age-group 2. The demographic characteristics of the admissions in this sample are shown in Table 1.

**TABLE 1** Demographic characteristics of the sample

	All (n = 1920)	18-64 years (n = 397)	>65 years (n = 1523)
Age (y)			
Mean (SD)	74.2 (14.5)	50.8 (11.7)	80.3 (7.1)
Median (Interquartile range)	78 (68-84)	54 (44-60)	81 (75-85)
Male sex	783 (40.8%)	166 (41.8%)	617 (40.5%)
Renal function			
Good (MDRD >50 mL/min)	513 (26.7%)	124 (31.2%)	389 (25.5%)
Moderate (MDRD 30-50 mL/min)	201 (10.5%)	17 (4.3%)	184 (12.1%)
Severe (MDRD 10-29 mL/min)	92 (4.8%)	6 (1.5%)	86 (5.6%)
Failure (MDRD <10 mL/min)	18 (0.9%)	3 (0.8%)	15 (1.0%)
Unknown	1096 (57.1%)	247 (62.2%)	849 (55.7%)
Hospital ward			
Non-surgical	1426 (74.3%)	282 (71.0%)	1144 (75.1%)
Surgical	489 (25.5%)	115 (29.0%)	374 (24.6%)
Unknown	5 (0.3%)	-	5 (0.3%)
Living conditions			
Independently	447 (23.3%)	127 (32.0%)	320 (21.0%)
Nursing home	75 (3.9%)	5 (1.3%)	70 (2.5%)
Unknown	1398 (72.8%)	265 (66.8%)	1133 (74.4%)
Weekly dosing system			
Yes	320 (16.7%)	22 (5.5%)	298 (19.6%)
No	1331 (69.3%)	284 (71.5%)	1047 (68.7%)
Unknown	269 (14.0%)	91 (22.9%)	178 (11.7%)
Reduced cognition			
Yes	265 (13.8%)	105 (26.4%)	160 (10.5%)
No	235 (12.2%)	14 (3.5%)	221 (14.5%)
Unknown	1420 (74.0%)	278 (70.0%)	1142 (75.0%)

Abbreviations: MDRD, Modification of Diet in Renal Disease formula; n, number; SD, standard deviation; y, years.

The sample of the 18-64 year group was skewed by chance with only six hospital admissions in 2013. To calculate the prevalence of this year the mean of the combined samples over the years of this age-group was used.

### 3.1 | Interrater agreement

The interrater agreement for causality and preventability in age-group 1 was fair with a kappa value of respectively 0.24 and 0.21. For age-group 2 the kappa values were comparable with 0.26 and 0.22 for causality and preventability.<sup>23</sup>

### 3.2 | Positive predictive value of possible HARMs and potentially preventable HARMs

The positive predictive value (PPV) for possible HARMs for age-group 1 and age-group 2 was 45.7% (95% CI 40.7%-50.7%) and

59.3% (95%CI: 56.7%-61.9%) respectively. The PPV of potentially preventable HARMs for age-group 1 and age-group 2 was 25.1% (95%CI: 18.4%-31.8%) and 48.3% (95%CI: 44.8%-51.8%) respectively. 20 (5.0%) admissions were considered to have too little information to assess the causality in age-group 1 and 132 (8.7%) in age-group 2. The PPV for possible HARMs and potentially preventable HARMs distributed by study year are shown in Table 2 for each age-group.

### 3.3 | Prevalence of possible HARMs

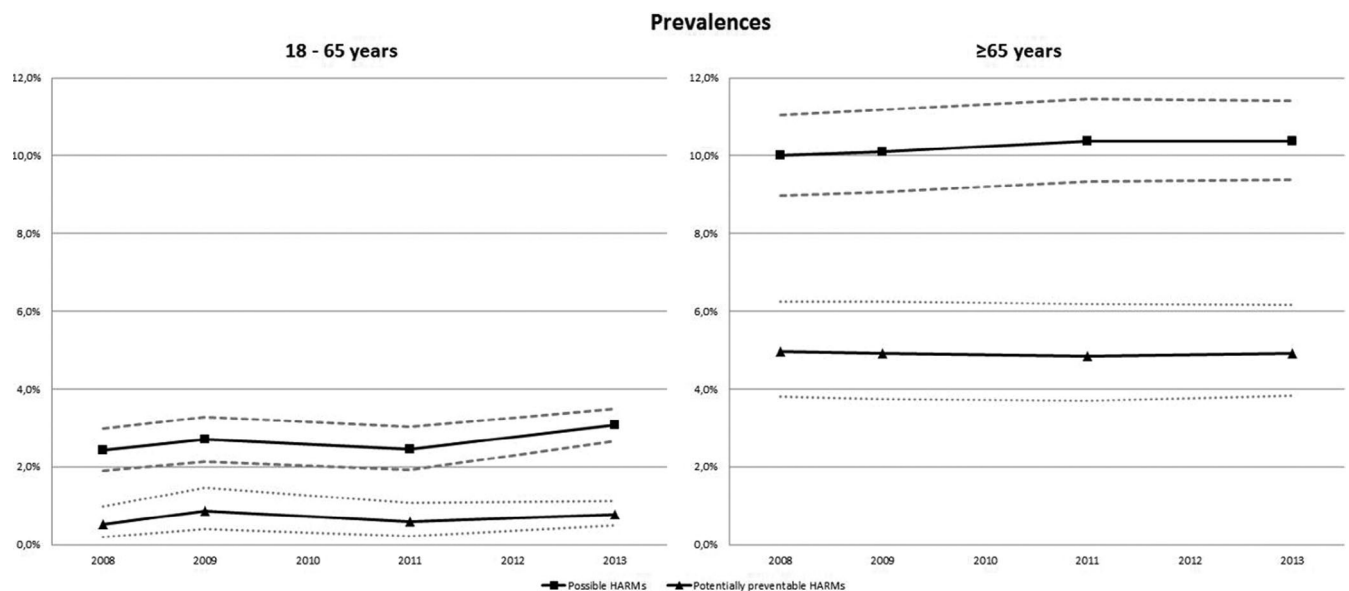
The net prevalences of possible HARMs are shown in Figure 1. The net prevalence was approximately four times smaller in age-group 1 compared to age-group 2 with a mean net prevalence of 2.7% (95% CI: 2.4%-3.0%) and 10.2% (95%CI: 9.7%-10.7%) respectively.

The net prevalence in age-group 1 did not change over the years with 2.4% (95%CI: 1.9%-3.0%) in 2008 and 3.1% (95%CI: 2.7%-3.5%) in 2013. In age-group 2 the net prevalence also remained similar with

**TABLE 2** Positive predictive values of causality and preventability and their 95% Confidence Intervals

	2008	2009	2011	2013
<b>Causality</b>				
18-64 years	43.7% (35.1-52.3%)	46.5% (37.6-55.4%)	43.1% (34.4-51.8%)	<sup>a</sup>
≥ 65 years	59.0% (53.8-64.2%)	58.8% (53.5-64.1%)	60.7% (55.4-66.0%)	57.9% (53.1-62.7%)
<b>Preventability</b>				
18-64 years	21.7% (10.8-32.6%)	32.0% (19.3-44.7%)	23.7% (12.0-35.4%)	<sup>a</sup>
≥ 65 years	49.6% (42.5-56.7%)	48.6% (41.3-55.9%)	46.8 (39.5-54.1%)	47.4% (40.8-54.0%)

<sup>a</sup>The prevalence in 2013 was calculated with the mean positive predictive value (PPV) for the 18-64 year olds because of the skewed sample.



**FIGURE 1** Net prevalences of potential and potentially preventable Hospital Admissions Related to Medication (HARMs) for each age-group. (■: potential HARMs; ▲: potentially preventable HARMs; dashed lines: 95% CI)

10.0% (95%CI: 9.0%-11.0%) in 2008 and 10.4% (9.4%-11.4%) in 2013.

### 3.4 | Prevalence of potentially preventable HARMs

The net prevalence of potentially preventable HARMs are also shown in Figure 1. This was 0.7% (95%CI: 0.4%-1.0%) and 4.9% (95%CI: 4.3%-5.5%) for age-groups 1 and 2 respectively and also remained similar over the years for both age-groups.

### 3.5 | Incidence rates

The net incidence rates of possible HARMs for each age-group per year are shown in Figure 2. The net incidence rates did not increase significantly with an incidence rate of 3.26 (95%CI: 2.66-3.97) in 2008 and 3.71 (95%CI: 3.05-4.53) admissions per 10 000 person-years in 2013 for age-group 1 and an incidence rate of 12.80 (11.72-13.98) in 2008 and 13.50 (12.42-14.69) admissions per 10 000 person-years in 2013 in age-group 2. The incidence rates of potentially preventable HARMs are also shown in Figure 2 and did not change over time either.

### 3.6 | Types of HARMs

In Tables 3 and 4 the events and associated drug(s) are shown for each age-group. The majority of these potentially preventable admissions in the younger group were related to fractures (17.5%), hyper-

or hypoglycemia (17.5%) and gastro-intestinal (GI)-complications (15.0%). In the older group the majority of the potentially preventable admissions were related to fractures (30.1%), syncope/dizziness (17.5%) and GI-complications (13.4%). In Table 5 the reasons for potentially preventable HARMs are shown for each age-group. In age-group 1 the most frequent reason for potential preventability was that additional measures were not taken or were inadequate (39.0%). In age-group 2 the main reason was that the dose, frequency or way of administration was inappropriate for the age, weight or severity of disease of the patient.

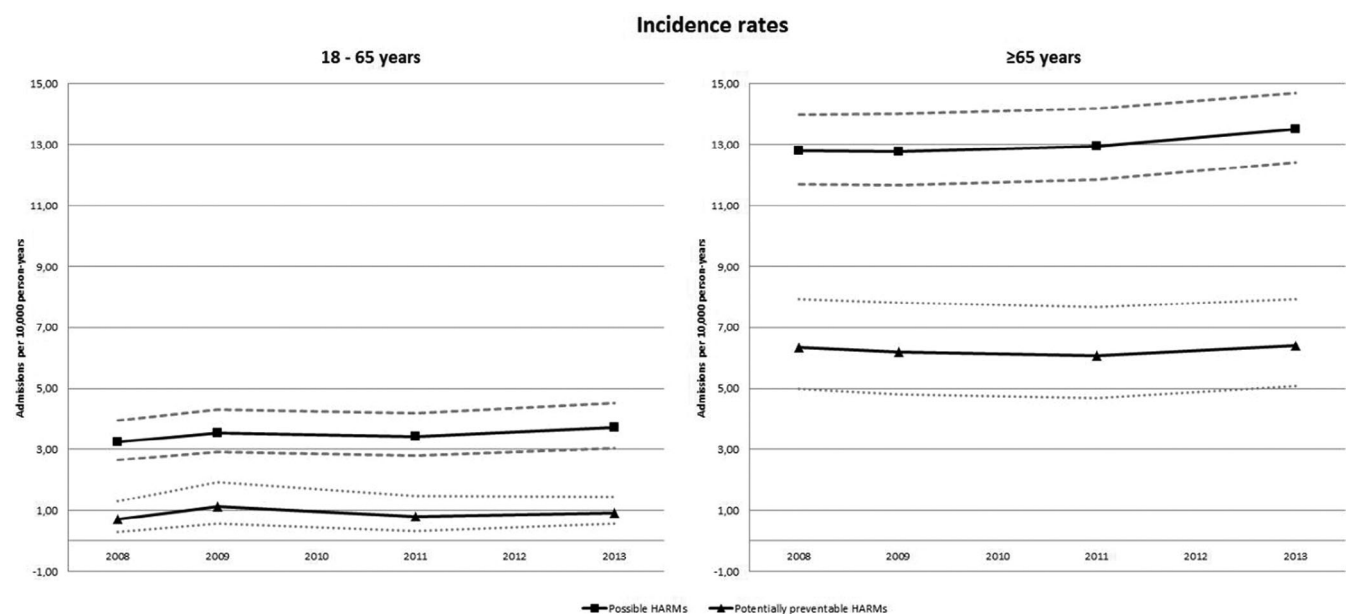
### 3.7 | Extrapolation to the Dutch population

We observed an increase of almost 6000 admissions in the absolute number of possible HARMs in age-group 1 from 11 409 (95%CI: 8934-13 990) in 2008 to 17 161 (95%CI: 14 907-19 508) in 2013. In the second age-group a larger increase of approximately 10 000 admissions was found, from 38 739 (95%CI: 34 794-42 786) in 2008 to 48 779 (95%CI: 44 119-53 550) in 2013.

The number of potentially preventable HARMs in age-group 1 increased from 2475 (95%CI: 965-4 561) in 2008 to 4307 (95%CI: 2743-6 203) admissions in 2013, and from 19 214 (95%CI: 14 787-24 260) in 2008 to 23 121 (95%CI: 18 000-28 917) admissions in 2013 admissions in 2013 in age group 2.

## 4 | DISCUSSION

This study showed the prevalence of hospital admissions related to medication (HARMs) to be stable between 2008 and 2013, both for



**FIGURE 2** Net incidence rates of possible and potentially preventable Hospital Admissions Related to Medication (HARMs) for each age-group. ■: potential HARMs; ▲: potentially preventable HARMs; dashed lines: 95% CI



**TABLE 3** Types of potential HARMs and associated drugs in patients between 18 and 65 years

Event category	Events in category	Number of potentially preventable HARMs (%)	Associated drugs (more than one was possible)
Fractures	low- (3) and high impact (4) fractures	7 (17.5%)	Benzodiazepines (6), GABA-receptor agonist (1), SSRI (1), Flufenazine (1)
Hyper- or hypoglycemia	Keto-acidosis (5), hypoglycemia (2)	7 (17.5%)	insulins (7)
GI-complications	GI-bleeding (6)	6 (15%)	TAls (3), VKAs (3) NSAIDs (3), dipyridamol (1)
Ileus/obstipation	Obstipation/Ileus	4 (10%)	Opioids (3), mebeverin (1)
Electrolytes disorder	Hypo-osmolality (2), hypovolemia (1)	3 (7.5%)	Thiazide diuretics (2), antidiuretic hormone (1)
Syncope/ dizziness/ hypotension/ collapse	hypotension (1), syncope (2)	3 (7.5%)	RAS-inhibitors (1), thiazide diuretics (1), nitrates (1), dihydropyridinederivatives (1), selective beta blockers (1)
Bleeding (other than GI-tract)	Chronic blood loss (2)	2 (5%)	TAls (2), VKAs (1)
Respiratory disorder	Asthma (1), Other lower respiratory disorders (2)	2 (5%)	Benzodiazepines (1), selective beta2 sympathomimetic (1)
Central nervous system	Epilepsy (1), migraine (1)	2 (5%)	SSRI (1), NSAID (1), Opioid (1)
Other		4 (10%)	Glucocorticoids (1), dihydropyridinederivatives (1), estrogens/progestogens (1), insulins (1),

Abbreviations: GABA, Gamma-Aminobutyric acid; GI, Gastrointestinal; HARM, Hospital Admission Related to Medication; NSAID, Nonsteroidal anti-inflammatory drug; RAS, Renin-angiotensin system; SSRI, Selective serotonin reuptake inhibitor; TAI, Thrombocyte aggregation inhibitor; VKA, Vitamin K antagonist.

patients between 18 and 65 years as for patients of 65 years and older. The incidence rate also remained constant in both age-groups. Since the total number of hospital admissions in The Netherlands increased with 20% (18-64 years) and 21% (> 65 years) between 2008 and 2013 the absolute number of potential HARMs in The Netherlands also increased with approximately 6.000 (18-64 years) and 10.000 (> 65 years) admissions. The associated numbers of potentially preventable HARMs increased by approximately 1.800 (18-64 years) and 4.000 (> 65 years) admissions.

A review from 2016 which included 30 studies from developed countries showed a median prevalence of HARMs of 6.3% (IQR 3.3-11.0).<sup>2</sup> This corresponds to the mean of the prevalences of the two age-groups. Our study is the first to investigate the number of possible HARMs for two age-groups which shows the prevalence in the >65 group to be approximately four times higher with a mean prevalence of 10.2% compared to 2.7% in the 18-64 group. This is as expected since older people have more comorbidities and therefore use more drugs which increases the risk of HARMs.<sup>12</sup> This confirms recommendations from previous studies that initiatives to reduce HARMs should be especially targeted on patients of 65 years and older.<sup>10-12,17</sup>

By analyzing two age-groups we could also show the difference in reason for admission, related drugs and reason for preventability. Fractures are responsible for most HARMs in both groups (18-64y: 17.5%; >65y: 30.1%) and GI-complications has the third place in both groups. The second most frequently occurring HARM however differs

with hyper- or hypoglycemia in the younger group and syncope/ dizziness/ hypotension/ collapse in the older group. This shows that different age-groups need different attention when trying to reduce the number of HARMs.

By investigating multiple years we could follow the trend of potential HARMs over multiple years. This showed no increase or decrease. The HARM-Wrestling recommendations were based on the HARM- and IPCI study which were also included in this study, but this study also included a number of types of HARMs which were not included in previous studies. This could be the reason why a clear effect of efforts taken to reduce the number of HARMs was not seen in this study since these efforts were not targeted on the new types of HARMs. In the QUADRAT study bleeding outside the GI tract, serious GI events, and constipation due to ileus had the highest PPVs.<sup>11</sup> As stated earlier GI complications were found as the third most frequent event in both age-groups. In this study fractures was the most frequent event in both age-groups due to predominantly benzodiazepines. This type of HARM was included in the QUADRAT study but did not show the same results. This is because the recommendation to avoid benzodiazepines (especially in elderly) was assessed more strictly in this study.

As stated before a major strength of this study is the stratification of the results by age. Other strengths are the large number of patients included and the robust method of analysis. However, this study also has several limitations. First, the random sample included visits to the emergency department which did not lead to an admission. These

**TABLE 4** Types of potential HARMs and associated drugs in patients of 65 years and older

Event category	Events in category	Number of potentially preventable HARMs (%)	Associated drugs (more than one was possible)
Fractures	Pathological (3), low- (73) and high impact (34) fractures	110 (30.1%)	Benzodiazepines (96), opioids (10), thiazide diuretics (8), SSRIs (6), antipsychotics (6), other antidepressants (5), mirtazapine (5), glucocorticoid (3), dementia (2), selective beta blockers (2), RAS-inhibitors (2), urologic spasmolytic (2), atypical antipsychotics (2)
Syncope/ dizziness/ hypotension/ collapse	Dizziness (3), hypotension (6), syncope (55)	64 (17.5%)	RAS-inhibitors (46), thiazide diuretics (25), nitrates (20), dihydropyridinederivatives (16), selective beta blockers (10), digoxin (7), benzodiazepines (6), Lis diuretics (4), diltiazem (3), non-selective beta blockers (3), alpha- and beta blockers (3), SSRIs (3), opioids (2), spironolactone (2)
GI-complications	Gastro-duodenal ulcers (5), gastritis (2), GI-bleeding (42)	49 (13.4%)	TAIs (32), VKAs (17), NSAIDs (11), coxibs (2)
Bleeding (other than GI-tract)	Anemia (12), cerebral bleeding (10), nose bleeding (2), internal bleeding (2), urinal bleeding (1)	27 (7.4%)	TAIs (16), VKAs (14)
Electrolytes disorder	Hypo-osmolality (9), hypovolemia (14), hyperkalemia (4)	27 (7.4%)	Lis diuretics (13), thiazide diuretics (12), Potassium saving drugs (14), RAS-inhibitors (5), SSRIs (2)
Hyper- or hypoglycemia	Hypoglycemia	21 (5.7%)	Sulfonylurea derivatives (14), insulins (7)
Ileus/obstipation	Obstipation/Ileus	17 (4.6%)	Opioids (11), dihydropyridinederivatives (5), ferritins (4), TCAs (2), loperamide (2), serotonin-antagonists (2)
Heart failure	Congestive heart failure	14 (3.8%)	NSAIDs (9), diltiazem (3), glucocorticoids (2), thiazolidinedione's (2)
Respiratory disorder	Asthma (1), Other lower respiratory disorders (4)	5 (1.4%)	Benzodiazepines (4), selective beta blocker (1)
Kidney disorder	Acute renal failure	5 (1.4%)	RAS-inhibitors (5), spironolactone (3), thiazide diuretics (1),
Heart rhythm disorder	Atrial fibrillation	4 (1.1%)	Verapamil (2)
Fever/infection	Urinary tract infection	2 (0.5%)	Urologic spasmolytic (2)

Abbreviations: GI, Gastrointestinal; HARM, Hospital Admission Related to Medication; NSAID, Nonsteroidal anti-inflammatory drug; RAS, Renin-angiotensin system; SSRI, Selective serotonin reuptake inhibitor; TAI, Thrombocyte aggregation inhibitor; TCA, Tricyclic antidepressants; VKA, Vitamin K antagonist.

admissions were not excluded from the sample because the overall PHARMO data linkage included these visits as well. By including these emergency department visits in the numerator as well as the denominator the number of admissions was corrected. Second, the interrater agreement between the first assessors which consisted of a physician and a pharmacist was fair for possible causality as well as for the potential preventability.<sup>23</sup> This is less than what we aimed to achieve since the interrater agreement in the QUADRAT study was also insufficient. However, as we used consensus methodology, this limitation did not influence our results. Third, the preselection of possible

HARMs was based on the event and drug used according to the dispensing data of community pharmacies. However, medication administered in the hospital (ie, chemotherapy) and over the counter medications are not registered and thus cannot be taken into account when calculating the prevalence of possible HARMs. This means the results of this study provide an underestimation of reality. Fourth, it is unknown whether other alterations besides the HARM-Wrestling recommendation could have influenced the prevalence such as the implementation of other guidelines. Finally, the letters of discharge which were assessed varied substantially in content from highly



**TABLE 5** Reasons for potentially preventable HARMs for both age-groups

	18-64 years	≥65 years
Previously occurred adverse effect	8 (13.6%)	39 (7.0%)
Drug was inappropriate for the condition of the patient	6 (10.2%)	73 (13.1%)
The dose, frequency or way of administration was inappropriate for the age, weight or severity of disease of the patient	4 (6.8%)	171 (30.7%)
Case of wrong drug delivery	0 (0%)	1 (0.2%)
Case of wrong drug administration	1 (1.7%)	9 (1.6%)
Lack of monitoring of drug or other monitoring which was required	6 (10.2%)	41 (7.4%)
Case of unacceptable drug-drug interactions	6 (10.2%)	68 (12.2%)
Case of noncompliance	5 (8.5%)	8 (1.4%)
Additional measures were not taken or were inadequate	23 (39.0%)	148 (26.5%)

Abbreviation: HARM, Hospital Admission Related to Medication.

detailed to almost no information about the reason for admission. This resulted in a high number of admissions which could not be assessed.

Despite these limitations, this study adds to our knowledge on medication related hospital admissions. It showed that efforts taken by healthcare providers may have contributed to a stable number of HARMs, but further efforts are needed. The preventive measures and initiatives developed up to now are shown insufficient to reduce the prevalence of HARMs.

To decrease the number of HARMs multidisciplinary initiatives are needed. The first recommendation is to further implement the protective measures, but also to be strict in upholding the national and international guidelines. For example to be strict in not prescribing benzodiazepines to older patients, especially not during a long period of time. The use of this drug was intended for a short period of time.<sup>24</sup> The second recommendation is to further improve our pharmacy and physician prescribing systems. These systems should facilitate the protective measures and monitoring recommended in the guidelines. A third recommendation is to train emergency personnel to identify a HARM in order to give the right care. In almost none of the admissions included in the sample the doctor suspected a HARM. Support from an emergency pharmacist may assist in improving this identification. Finally, implementation studies are needed in order to identify facilitators and barriers for implementation of the protective measures.

In conclusion, the prevalence and incidence rate of potential HARMs and potentially preventable HARMs remain stable between 2008 and 2013. Furthermore, to prevent HARMs more initiatives should especially target older patients (65 years and older) since they have a four times higher prevalence of potential HARMs than younger patients (18-64 years). These measures should focus on the prevention of fractures, syncopes and GI complications since these events have the highest prevalence of potentially preventable HARMs among older patients.

## ETHICS STATEMENT

According to Dutch legislation the study is exempt from medical ethical approval as patient integrity is not compromised and only retrospective data are used.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## AUTHOR DISCLOSURE INFORMATION

Fouzia Lghoul - Oulad Saïd: None. Karin Hek: None. Linda E. Flinterman: None. Ron MC Herings: None. Margaretha F Warlé-van Herwaarden: None. Sandra de Bie: None. Vera E Valkhoff: None. Jelmer Alisma: None. Mees Mosseveld: None. Ann M. Vanrolleghem: None. Bruno HCH Stricker: None. Miriam CJM Sturkenboom: None. Peter AGM De Smet: None. Patricia MLA van den Bemt: None.

## PRIOR PRESENTATIONS

ICPE 2018, poster presentation.

## ORCID

Fouzia Lghoul-Oulad Saïd  <https://orcid.org/0000-0001-7518-4236>

## REFERENCES

1. Feinstein JA, Feudtner C, Kempe A. Adverse drug event-related emergency department visits associated with complex chronic conditions. *Pediatrics*. 2014;133(6):e1575-e1585.
2. Angamo MT, Chalmers L, Curtain CM, Bereznicki LR. Adverse-drug-reaction-related hospitalisations in developed and developing countries: a review of prevalence and contributing factors. *Drug Saf*. 2016;39(9):847-857.
3. Rojas-Velandia C, Ruiz-Garzon J, Moscoso-Alcina JC, et al. Characterization of adverse drug reactions causing admission to an intensive care unit. *Br J Clin Pharmacol*. 2017;83(5):1134-1140.
4. Phillips AL, Nigro O, Macolino KA, et al. Hospital admissions caused by adverse drug events: an Australian prospective study. *Aust Health Rev*. 2014;38(1):51-57.
5. Laatikainen O, Sneek S, Bloigu R, Lahtinen M, Lauri T, Turpeinen M. Hospitalizations due to adverse drug events in the elderly—a retrospective register study. *Front Pharmacol*. 2016;7:358.
6. Noguchi C, Sakuma M, Ohta Y, Bates DW, Morimoto T. Prevention of medication errors in hospitalized patients: the Japan adverse drug events study. *Drug Saf*. 2016;39(11):1129-1137.
7. Al Hamid A, Ghaleb M, Aljadhey H, Aslanpour Z. A systematic review of hospitalization resulting from medicine-related problems in adult patients. *Br J Clin Pharmacol*. 2014;78(2):202-217.
8. Ferrah N, Lovell JJ, Ibrahim JE. Systematic review of the prevalence of medication errors resulting in hospitalization and death of nursing home residents. *J Am Geriatr Soc*. 2017;65(2):433-442.
9. Shehab N, Lovegrove MC, Geller AI, Rose KO, Weidle NJ, Budnitz DS. US emergency department visits for outpatient adverse drug events, 2013-2014. *JAMA*. 2016;316(20):2115-2125.
10. Mosis G, Dieleman JP, Stricker B, van der Lei J, Sturkenboom MC. A randomized database study in general practice yielded quality data but patient recruitment in routine consultation was not practical. *J Clin Epidemiol*. 2006;59(5):497-502.
11. Warle-van Herwaarden MF, Valkhoff VE, Herings RM, et al. Quick assessment of drug-related admissions over time (QUADRAT study). *Pharmacoepidemiol Drug Saf*. 2015;24(5):495-503.

12. Leendertse AJ, Egberts AC, Stoker LJ, van den Bemt PM, Group HS. Frequency of and risk factors for preventable medication-related hospital admissions in The Netherlands. *Arch Intern Med*. 2008;168(17):1890-1896.
13. Wester K, Jonsson AK, Spigset O, Druid H, Hagg S. Incidence of fatal adverse drug reactions: a population based study. *Br J Clin Pharmacol*. 2008;65(4):573-579.
14. Pirmohamed M, James S, Meakin S, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ*. 2004;329(7456):15-19.
15. McDonnell PJ, Jacobs MR. Hospital admissions resulting from preventable adverse drug reactions. *Ann Pharmacother*. 2002;36(9):1331-1336.
16. Bos JM, van den Bemt P, de Smet P, Kramers C. The effect of prescriber education on medication-related patient harm in the hospital: a systematic review. *Br J Clin Pharmacol*. 2017;83(5):953-961.
17. Warle-van Herwaarden MF, Kramers C, Sturkenboom MC, van den Bemt PM, De Smet PA, H-WTF D. Targeting outpatient drug safety: recommendations of the Dutch HARM-Wrestling Task Force. *Drug Saf*. 2012;35(3):245-259.
18. Lambooi MS MC, Limburg LCM, Weda M. *Inventarisatie initiatieven medicatieveiligheid: Relatie met HARM-WRESTLING aanbevelingen*. Bilthoven, The Netherlands: Rijksinstituut voor Volksgezondheid en Milieu; RIVM rapport 360200001. 2012.
19. Kramer MS, Leventhal JM, Hutchinson TA, Feinstein AR. An algorithm for the operational assessment of adverse drug reactions. I. Background, description, and instructions for use. *JAMA*. 1979;242(7):623-632.
20. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. *Hosp Pharm*. 1992;27(6):538.
21. van der Hooft CS, Dieleman JP, Siemes C, et al. Adverse drug reaction-related hospitalisations: a population-based cohort study. *Pharmacoepidemiol Drug Saf*. 2008;17(4):365-371.
22. Pourhoseingholi MA, Vahedi M, Rahimzadeh M. Sample size calculation in medical studies. *Gastroenterol Hepatol Bed Bench*. 2013;6(1):14-17.
23. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. *Fam Med*. 2005;37(5):360-363.
24. Ashton H. Guidelines for the rational use of benzodiazepines. When and what to use. *Drugs*. 1994;48(1):25-40.

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Lghoul-Oulad Saïd F, Hek K, Flinterman LE, et al. Prevalence and incidence rate of hospital admissions related to medication between 2008 and 2013 in The Netherlands. *Pharmacoepidemiol Drug Saf*. 2020;29:1659-1668. <https://doi.org/10.1002/pds.5122>