

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<u>http://bmjopen.bmj.com</u>).

If you have any questions on BMJ Open's open peer review process please email <u>info.bmjopen@bmj.com</u>

BMJ Open

A registry-based cohort study of disease- and drug-related 30-day hospital readmissions among polymedicated older inpatients

	1
Journal:	BMJ Open
Manuscript ID	bmjopen-2021-052755
Article Type:	Original research
Date Submitted by the Author:	25-Apr-2021
Complete List of Authors:	Pereira, Filipa; University of Porto, Institute of Biomedical Sciences Abel Salazar; HES-SO University of Applied Sciences and Arts Western Switzerland, School of Health Sciences Verloo, Henk; HES-SO University of Applied Sciences and Arts Western Switzerland, School of Health Sciences; Lausanne University Hospital, Service of Old Age Psychiatry Zhivko, Taushanov; University of Geneva Di Giovanni, Saviana; HES-SO University of Applied Sciences and Arts Western Switzerland, School of Health Sciences; Pharmacy Benu Tavil- Chatton Meyer-Massetti, Carla; University of Bern, Institute for Primary Health Care Von-Gunten, Armin; Lausanne University Hospital, Service of Old Age Psychiatry Martins, Maria Manuela; Porto Higher School of Nursing; University of Porto, Institute of Biomedical Sciences Abel Salazar Wernli, Boris; University of Lausanne, FORS, Swiss Centre of Expertise in the Social Sciences
Keywords:	Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, GERIATRIC MEDICINE, CLINICAL PHARMACOLOGY, EPIDEMIOLOGY
	·





I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our <u>licence</u>.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which <u>Creative Commons</u> licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

reliez oni

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

A registry-based cohort study of disease- and drug-related 30-day hospital readmissions among polymedicated older inpatients

Pereira Filipa¹, Verloo Henk², Taushanov Zhivko³, Di Giovanni Saviana⁴, Meyer-Massetti Carla⁵, von Gunten Armin⁶, Martins Maria Manuela⁷, Wernli Boris⁸

¹Institute of Biomedical Sciences Abel Salazar, University of Porto
Rua de Jorge Viterbo Ferreira, 228 4050-313 Porto, Portugal
School of Health Sciences, HES-SO University of Applied Sciences and Arts Western Switzerland
5, Chemin de l'Agasse, CH-1950 Sion, Switzerland
Email: <u>filipa.pereira@hevs.ch</u>; Phone: +41 78 666 17 00; Fax: +41 27 606 84 00
ORCID: https://orcid.org/0000-0001-9207-4856

² School of Health Sciences, HES-SO University of Applied Sciences and Arts Western Switzerland 5, Chemin de l'Agasse, CH-1950 Sion, Switzerland Service of Old Age Psychiatry, Lausanne University Hospital Email: <u>henk.verloo@hevs.ch</u>; Phone: +41 27 606 84 34 ORCID: http://orcid.org/0000-0002-5375-3255

PLICA

³University of Geneva CH-1205 Geneva, Switzerland Email: <u>zhivko.taushanov@unige.ch</u> ORCID: <u>https://orcid.org/0000-0002-3798-757X</u>

⁴ School of Health Sciences, HES-SO University of Applied Sciences and Arts Western Switzerland 5, Chemin de l'Agasse, CH-1950 Sion, Switzerland Pharmacy Benu Tavil-Chatton Grand rue 11, CH-1110 Morges, Switzerland Email: saviana.digiovanni@gmail.com

⁵Institute for Primary Health Care, University of Bern Mittelstrasse 43, CH-3012 Bern, Switzerland Email: <u>carla.meyer-massetti@biham.unibe.ch</u> ORCID: <u>https://orcid.org/0000-0002-3523-5729</u>

⁶ Service of Old Age Psychiatry, Lausanne University Hospital Route de Cery 60, 1008 Prilly, Switzerland Email: <u>armin.von-gunten@chuv.ch</u>; Phone: +41 21 314 52 67

1	
2 3	
4	ORCID: <u>https://orcid.org/0000-0001-7852-3803</u>
5	
6	⁷ Higher School of Nursing of Porto
7 8	Institute of Biomedical Sciences Abel Salazar, University of Porto
9	Rua Dr. António Bernardino de Almeida
10	4200-072 Porto, Portugal
11 12	Email: mmartins@esenf.pt; Phone: +351 22 507 35 00
13	ORCID: https://orcid.org/0000-0003-1527-9940
14	okeid. <u>https://oreid.org/0000-0005-1527-7740</u>
15	
16 17	⁸ FORS, Swiss Centre of Expertise in the Social Sciences, University of Lausanne
18	Géopolis, CH-1015 Lausanne, Switzerland
19	Email: boris.wernli@fors.unil.ch; Phone: +41 21 692 37 23
20	ORCID: https://orcid.org/0000-0002-5567-1317
21 22	
23	Corresponding author:
24	Pereira F
25 26	Institute of Biomedical Sciences Abel Salazar, University of Porto
27	Rua de Jorge Viterbo Ferreira, 228 4050-313 Porto, Portugal
28	
29	School of Health Sciences, HES-SO University of Applied Sciences and Arts Western Switzerland
30 31	5, Chemin de l'Agasse, CH-1950 Sion, Switzerland
32	Email: <u>filipa.pereira@hevs.ch</u> ; Phone: +41 78 666 17 00; Fax: +41 27 606 84 00
33	ORCID: <u>https://orcid.org/0000-0001-9207-4856</u>
34 35	ORCID: <u>https://orcid.org/0000-0001-9207-4856</u>
35	
37	
38	
39 40	
40 41	
42	
43	
44 45	
45	
47	
48	
49 50	
50	
52	
53	
54 55	
55	

1 2

3 4	1	Abstract
5	2	Objectives: The present study analysed four years of a hospital register (2015–2018) to investigate
6 7	3	associations between 30-day hospital readmission risk and the medical conditions and drug regimens of
8	4	polymedicated, older inpatients discharged home.
9 10	5	Design: Population-based longitudinal study.
11	6	Setting: A public general hospital centre in the French-speaking part of Switzerland.
12 13	7	Participants: We explored the electronic records of 20,422 inpatient stays by polymedicated, home-
14	8	
15		dwelling older adults held in the hospital's patient register. We identified 13,802 separate patients over 64
16 17	9	years old.
18	10	Outcome measures: Sociodemographic characteristics, medical conditions, and drug regimen data
19 20	11	associated with readmission within 30 days of discharge.
20	12	Results: The overall 30-day hospital readmission rate was 7.8%. Higher risks of hospital readmission
22	13	were associated with longer hospital length of stay ($OR = 1.014$), impaired mobility ($OR = 1.218$),
23 24	14	multimorbidity (OR = 1.419), tumoural disease (OR = 2.538), polypharmacy (OR = 1.043), and certain
25	15	specific drugs, including antiemetics and antinauseants (OR = 3.216), antihypertensives (OR = 1.771),
26 27	16	drugs for functional gastrointestinal disorders (OR = 1.424), systemic hormonal preparations
28	17	(OR = 1.207), and vitamins $(OR = 1.201)$, as well as the concurrent use of beta-blocking agents and
29	18	proton pump inhibitors (OR = 1.367).
30 31	19	Conclusions: Thirty-day hospital readmission risks were associated with longer hospital length of stay,
32	20	health disorders, polypharmacy and drug regimens. The drug regimen patterns increasing the risk of
33 34	21	hospital readmission were very heterogeneous. Further research is needed to explore hospital
35	22	readmissions caused solely by specific drugs and drug-drug interactions.
36 27	23	
37 38	24	Keywords: polypharmacy; odds ratio; logistic regression; hospital register; ATC Classification System;
39	25	adverse-drug events; hospital readmission.
40 41	26	
42	27	Strengths and limitations of this study:
43 44	28	• The records of 20,422 separate hospitalisations involving 13,802 polymedicated home-dwelling
45	29	older patients were investigated for the prevalence of 30-day hospital readmission.
46	30	• The study includes four years' data from an exhaustive hospital register (2015–2018).
47 48	31	• A whole series of sociodemographic and clinical parameters, medical conditions and prescribed
49	32	drugs were used to predict the probability of hospital readmission.
50 51	33	• Analyses were correlational and no causality could be demonstrated.
52	34	• Although the study considered statistical associations between drugs and rehospitalisations, it
53 54	35	did not use clinically diagnosed drug–drug interactions.
54 55	36	
56	37	
57 58	38	
59		
50		

2 3		
4 5	39	Introduction
5 6	40	Longitudinal studies have demonstrated that approximately 20% of the home-dwelling older adults
7	41	supported by home health-care services experienced hospital readmission within 30 days of their
3 9	42	discharge (1-3). For many older adults, readmission to an acute hospital is associated with a functional
10	43	decline that has not always recovered by the time they are discharged (4). However, the systematic review
11 12	44	by Hansen et al. revealed wide-ranging estimates (5%-79%) of how many hospital readmissions were
13	45	preventable (5). The period between hospital discharge and readmission has not always been clearly
14	46	stated in the literature, ranging from 30 days to 3 years. However, 30 days is the most frequently used in
5 6	47	public health policy when measuring health-care system performance (6-8).
17	48	
8 9	49	Numerous determinants have been identified and associated with hospital readmissions, e.g.
20	50	sociodemographic and individual characteristics, multimorbidity and medical events (9, 10). A substantial
1 2	51	risk of 30-day hospital readmission has been associated with older inpatients treated for different diseases
3	52	and surgical interventions involving hip fracture, cancer, bypass, acute cardiovascular events or complex
4	53	surgery (11). The reasons for hospital readmission after a surgical intervention are often not directly
.5 6	54	related to the surgery itself but rather to underlying chronic health conditions (12). Thus, chronic diseases
27	55	may play an important role in readmission risk, independently of the reason for the initial hospitalisation
.8 .9	56	(13, 14). Chronic diseases are not isolated health conditions among older inpatients: they can influence
0	57	each other and treatment for one disease may adversely affect another (15). For all these reasons, patterns
1	58	of 30-day hospital readmissions may be very complex (16).
2 3	59	of so day nospital readmissions may be very complex (10).
4	60	Multimorbidity, in the case of two or more diseases (17, 18), may require taking multiple medicines (19),
5 6	61	known as polypharmacy (PP) when daily intake involves five or more drugs (20). Increasing incidences
7	62	of multimorbidity with age, and consequently PP, add to the complexity of managing older inpatients'
8 9	63	drug prescriptions, particularly at hospital discharge (21, 22). PP and inadequate drug management are
0	64	significant risk factors for adverse drug events (ADEs)—the most common post-discharge
1	65	complications—alongside hospital-acquired infections and procedural complications (23, 24). ADEs
2 3	66	resulting from inappropriate drug prescribing, discrepancies between prescribed and current regimens,
4	67	poor adherence and the inadequate surveillance of adverse effects frequently lead to hospital admissions,
5 6	68	readmissions (8) and other undesirable consequences such as increased morbidity, decreased autonomy,
7	69	institutionalisation and even early death (25, 26). A systematic review by Morabet <i>et al.</i> indicated ADE
8	69 70	rates of 18%–38% after hospital discharge and 4.5%–24% hospital readmission rates due to those ADEs
.9 0		
1	71 72	(27). Because older adults use more drugs, they are at a greater risk of drug-related readmission.
2 3	72 72	Numerous studies have found that nearly 30% of older inpatients experienced ADEs within three weeks
4	73	of hospital discharge, almost three-quarters of which could have been prevented or lessened (10, 28, 29).
55	74 75	
56 57	75 76	Despite the significant overall impact of ADEs on hospital readmission rates, little is known about
58 59	76	hospital readmission risk's associations with medical conditions and drug regimens (30, 31). Morabet <i>et</i>
	77	al. revealed the high prevalence of antibiotics, diuretics, vitamin K antagonists, opioids, antidiabetics,

anti-cancer drugs, antihypertensives, digitalis glycosides, corticosteroids and psychotropic drugs in drug-related hospital readmissions (27). Samoy et al. reported that anticoagulants, hypoglycaemics, beta-blocking agents, antidepressants, calcium channel blockers and lenograstim were associated with high risks of hospital readmission (32). A retrospective patient record study by Teymoorian et al. reported that anticoagulants and antiplatelet agents, diuretics and antihypertensives, and opioids were associated with a high risk of persons aged 80 years old or more being readmitted to hospital within 30 days (33). Blanc et al. reported the readmission scores of different drugs in a large sample of 10,374 adult hospital admissions in general medicine. Taking beta-blocking agents, calcium channel blockers, diuretics, hypoglycaemic drugs or opioids was a significant risk for 30-day readmission (9). Besides higher risks of drug-related hospital readmission, some studies have also investigated associations between combining drugs—a common practice when treating complex diseases or co-existing medical conditions—and drug-related hospital readmissions. Although using multiple drugs may be good clinical practice and compliant with guidelines for treating certain diseases, one significant

92 consequence of combining drugs is that patients face much higher risks of ADEs, which can be caused by
93 drug–drug interactions (34-36). ADEs can emerge because a drug's pharmacokinetics and
94 pharmacodynamics change if taken with another drug (36). Moura *et al.* found that participants with
95 potential drug–drug interactions on their prescription list had a 2.4 times higher adjusted odds ratio (OR)
96 of being readmitted (37).

Even though some studies have reported high numbers of readmissions among home-dwelling older patients for a variety of drugs (38), this health issue was mostly investigated using prospective or cross-sectional studies with small samples. More insight is needed into patterns of drug-related hospital readmissions and risk factors in order to design better interventions for addressing ADEs (39, 40). As part of a broader project (41), the present study's goal was to use hospital register data to prioritise risk factors for hospital readmission. We hypothesised that sociodemographic characteristics, medical conditions (defined using the WHO's International Classification of Diseases, tenth revision: ICD-10, and the Swiss Classification of Surgical Interventions: CHOP), and drug prescriptions (based on the WHO's Anatomical Therapeutic Chemical (ATC) Classification System) were significant risk factors for 30-day hospital readmission for discharged older adults.

109 Material and Methods

110 Study Design

This population-based longitudinal study investigated the associations between the risks of discharged, polymedicated, home-dwelling older patients being readmitted to hospital within 30 days and their drug prescriptions and medical conditions. The study was performed with close regard to the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) statement (42).

1 2 3 4 5 6 7	
8 9 10 11 12 13 14 15 16 17	
18 19 20 21	
22 23 24 25 26 27 28 29	
30 31 32 33 34 35 36	
37 38 39 40 41 42 43	
44 45 46 47 48 49 50	
51 52 53 54 55 56 57	
58 59 60	

138

117 **Population and Data Collection**

118 Our custom, four-year, population-based dataset was composed of polymedicated (five or more drugs 119 prescribed at hospital discharge), multimorbid (two or more ICD-10 diagnoses), home-dwelling older 120 adult participants (65 years old and above) admitted and readmitted to a public general hospital in the 121 French-speaking part of Switzerland. This specific population was selected because of its increased risk 122 of hospital readmission (10, 28, 29). The hospital register contains a comprehensive and exhaustive 123 electronic health record (43). However, no electronic patient records were available for adult psychiatry 124 for 2015–2018. The extracted patient data contained sociodemographic characteristics, medical and 125 surgical diagnoses, routinely assessed clinical data (such as gait, falls risk or hearing) from hospitalised 126 patients with at least five prescribed drugs and their prescribed drugs at discharge. Medical and surgical 127 diagnoses were coded based on the ICD-10 and CHOP (44). Drug classification was based on the WHO's 128 ATC Classification System (45). 129 The strategy for transforming and synthesising the data extracted from the register's multiple dataset

130 sources was based on Olsen's register-based methodological considerations (46) and has been 131 documented elsewhere (47). Our dataset was composed of 20,422 hospital admission records running

132 from January 2015 to December 2018, with similar numbers of annual hospital admissions: 5134, 5095,

133 5125, and 5068, respectively.

135 Patient and Public Involvement

136 Neither patients nor public were directly involved in the development of the research questions, study 137 design, outcome measures, recruitment and conduct of the study.

139 **Dataset Customisation for Predictive Analysis**

140 The dataset was recoded and customised to identify the frequency of older patients' hospital admissions. 141 Each subject's unique identifier was used to distinguish their different hospital stays from 2015–2018. 142 The dataset included 13,802 hospital stays involving older inpatients discharged home and whose data 143 were complete (no missing values). These complete datasets related to 8,878 different individuals, with an 144 average of 1.55 inpatient hospital stays. Sociodemographic and clinical data were considered independent 145 variables and used to compute the predictive models. Readmission following discharge home was defined 146 as the dependent variable of interest and was dichotomised $(0 = n_0, 1 = y_{es})$ based on 30-day readmission 147 between 2015 and 2018. Furthermore, the custom dataset was composed of six clinical clusters based on 148 agglomerative hierarchical clustering methods for identifying clinically relevant characteristics and 149 representing older inpatients' health status. Medical status and drugs data were recoded and copied to an 150 exploitable population database (47).

151

152 Sociodemographic Variables and Length of Stay

153 Sex and age were included in the analysis as sociodemographic control variables. The total sample's mean age was 77.77 years old (SD = 7.48), and 57% were women. Age was considered a continuous 154

variable as its progressive impact has been proven in preliminary investigations and previous studies (48).
The average hospital length of stay (LOS) was 8.44 days (SD = 7.58).

160 Health Variables

 Numerous variables were used to describe older patients' health status during each hospital stay. Three of six preliminarily computed hierarchical clusters (47) were included in the modeling analysis as confounding variables: the mobility cluster, the dependency in the activities of daily living cluster and the mental state cluster (47). Twenty-five per cent of the sample had impaired mobility, 4% were impaired in their activities of daily living and 4% showed mental impairment at discharge. Our sample population averaged 4.58 (SD = 0.92) ICD-10 diagnoses, with their individual numbers used to model multimorbidity, and 1.80 (SD = 1.76) surgical interventions (CHOP) performed during the hospitalisation. The selected medical diagnoses distinguished patients affected by circulatory (24%), infectious (3%), and respiratory diseases (11%), as well as trauma (8%) and tumours (11%). Finally, the year of hospitalisation was introduced as a control variable, based on the fact that earlier admission to hospital during this period led to a higher probability of unplanned readmissions during the entire period covered.

174 Included Drugs

Drugs were classified according to the WHO's ATC Classification System (49) and then included in the
predictive model as independent variables. To ensure robust statistical results, the model only included
drug categories prescribed to at least 30 participants (n = 13,802). Drug prescription was considered
continuous, with an average of 8.95 (SD = 3.24) drugs per patient prescribed at hospital discharge. Table
presents the prescribed ATC classified drugs included in the predictive model as independent variables.
[Insert Table 1]

182 Data analysis strategy

Data were extracted into a Microsoft Excel spreadsheet (Microsoft, Redmond, Washington, United States) and then imported into SPSS software, version 26.0 (IBM Corp, Armonk, New York, United States). We examined statistical associations between hospital readmissions and patient age and sex, LOS, principal and related ICD-10 diagnoses, CHOP interventions and drug prescriptions during hospitalisations. A causality analysis between those variables was impossible given our retrospective data collection method, our inability to calculate the time between drug intake and readmission, and the potential drug changes between hospitalisation sequences. We conducted a bivariate analysis relating the independent variables to 30-day readmission after discharge home from 2015–2018. In a second stage, a series of multilevel binary logistic regression models were computed to estimate how sets of predictors influenced the probability of 30-day hospital readmission. The first level concerned hospital LOS, and the second level included individuals' characteristics and health conditions. The model projected each

BMJ Open

2 3		
4	194	predictor's impact, other things being equal, by estimating its net impact, controlling for other factors
5 6	195	(adjusted ORs). The model also considered correlations between each subject's different variables, which
7	196	were generally not independent (50). The model's random intercept design allowed each individual's
8	197	intercept to vary, assuming that some unmeasured traits remained stable over time and allowing a better
9 10	198	estimation of the model's parameters. The other estimated parameters, on the other hand, had the same
11	199	effect on every subject. This regression analysis dichotomised the probabilities of future readmissions
12 13	200	within 30 days ($0 = no$, $1 = yes$) of discharge home. Since the data were based on a whole population, not
15 14	200	a sample, the ORs' confidence intervals and statistical tests were used to indicate the robustness of
15	201	relationships (they usually only make sense for statistical inference).
16 17	202	relationships (they usually only make sense for statistical inference).
18		Definite and multiplication of
19 20	204	Patients and public involvement
20	205	Patients were not involved in the development of the research questions, study design, outcome measures
22	206	and conduct of the study.
23 24	207	
25	208	Results
26 27	209	Associations between Thirty-day Hospital Readmission and Sociodemographic Characteristics and
27	210	Medical Conditions
29	211	The prevalence of 30-day hospital readmission for older patients discharged home was 7.8%. Bivariate
30 31	212	associations showed significant differences between participants' sociodemographic characteristics and
32	213	medical conditions (Table 2). Men showed a slightly higher proportion of 30-day hospital readmissions
33 34	214	than women (8.2% vs 7.3%). However, age did not significantly affect the probability of 30-day
35	215	readmission. More readmissions were also seen among older patients with a circulatory disease (8.2% vs
36	216	6.5%), those not affected by trauma (8.0% vs 5.8%), and especially those with a tumour (15.1% vs 6.9%).
37 38	217	Multimorbidity also increased the prevalence of 30-day hospital readmissions-from 1.5% for older
39	218	patients with a single ICD-10 condition to 8.8% for those with five.
40 41	219	[Insert Table 2]
42	220	[Insert Table 2] Associations between Thirty-day Hospital Readmission and Drugs
43	221	Associations between Thirty-day Hospital Readmission and Drugs
44 45	222	On average, older patients readmitted within 30 days had more prescribed drugs than those who were not
46	223	readmitted (9.95 drugs vs 8.87). We found a linear relationship between the 30-day readmission rate and
47 48	224	the average number of prescribed drugs ($p > 0.001$), which supported the absence of a cut-off point in this
49	225	relationship (Figure 1).
50	226	[Insert Figure 1]
51 52	227	
53	228	Among the most robust statistical associations with 30-day hospital readmissions involved the classes of
54 55	229	drugs including antineoplasics and immunomodulators (12.6% vs 7.6% for those not treated with them)
56	230	and taking antiemetics and antinauseants (27.7% vs 7.7%). There was also a high prevalence of 30-day
57	231	hospital readmission among participants taking drugs for functional gastrointestinal disorders (13.4% vs
58 59	232	7.4%) and antihypertensives (14.1% vs 7.7%) (Table 3).
60	-32	

1	
2	
3 4	
5	
6 7	
8	
9 10	
11	
12 12	
14	
15 16	
17	
18 10	
20	
21 22	
23	
24 25	
26	
27 28	
29	
30 31	
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 36 37 37 37 37 37 37 37 37 37 37	
33 34	
35	
30 37	
38 39	
40	
41 42	
43	
44 45	
46	
47 48	
49 50	
51	
52 53	
54	
55 56	
57	
58 59	
59	

233

234

[Insert Table 3]

235	Baseline Multivariate Model
236	A baseline, multivariate logistic regression model including older patients' sociodemographic and clinical
237	variables, but not their prescribed drugs at discharge, was computed to predict 30-day hospital
238	readmission after discharge home (Table 4). Neither sex nor age had a significant impact. On the
239	contrary, LOS had a significant impact (OR = 1.014 for each additional day; 95% CI: 1.006–1.021), as
240	did mobility (OR = 1.218 for older patients with an impaired mobility status; 95% CI: $1.039-1.427$).
241	Dependence in the activities of daily living and mental health status showed no influence. Concerning
242	diagnoses measured in the ICD-10, we found that older patients with a tumoural disease ($OR = 2.538$;
243	95% CI: 2.089–3.082) were much more susceptible to 30-day hospital readmission. Patients with
244	circulatory pathologies showed no difference from the reference category (OR = 0.938; 95% CI: 0.783-
245	1.124), and nor did those with respiratory problems (OR = 1.100 ; 95% CI: 0.875– 1.382), trauma
246	(OR = 0.847; 95% CI: 0.633–1.134) or infection-related problems (OR = 1.381; 95% CI: 0.964–1.977;
247	p = 0.078). Having several pathologies predicted a higher probability of readmission (OR = 1.419 per
248	additional ICD-10 condition; 95% CI: 1.282-1.572), whereas the number of surgical procedures had no
249	noticeable impact (OR = 0.978; 95% CI: 0.938-1.020). The year of hospital stay did have an impact,
250	however, as the earlier the hospitalisation during the four years under review, the higher the probability of
251	readmission (OR = 0.933 per additional year; 95% CI: 0.880–0.990).
252	[Insert Table 4]
253	
254	Prediction of 30-day Hospital Readmission and Drug Prescriptions
255	Table 5 presents the baseline logistic regression model completed with the drugs prescribed to older
256	patients at discharge home that were significantly associated ($p = < 0.05$) with 30-day hospital
257	readmission. It was impossible to introduce the total number of drugs prescribed jointly in this model
258	because of their collinearity with other drug variables. Non-significant drugs and other variables have
259	been omitted from Table 3 in order to simplify the presentation. The probabilities of 30-day hospital
260	readmission are presented in descending order of discharged older patients' ORs for each additional unit
261	of the drugs in question. Intake of antiemetics and antinauseants was very strongly linked to 30-day
262	readmission (OR = 3.216 for each additional drug unit taken; 95% CI: $1.842-5.617$), as were those of
263	antihypertensives (OR = 1.771; 95%CI: 1.287–2.438), gastrointestinal drugs (OR = 1.424; 95% CI:
264	1.166–1.739), systemic hormonal preparations (OR = 1.207 ; 95% CI: $1.052-1.385$) and vitamins
265	(OR = 1.201; 95% CI: 1.049-1.374). On the contrary, the intake of lipid-modifying agents was associated
266	with a decrease in 30-day hospital readmissions ($OR = 0.841$ for each drug from this class prescribed;
267	95% CI: 0.732–0.967).
268	[Insert Table 5]
269	
270	Drug Interactions and 30-day Hospital Readmissions

1	
2 3	
4	
5	
6	
7	
8 9	
10	
11	
12	
13 14	
14 15	
16	
17	
18 19	
19 20	
21	
22	
23 24	
25	
26	
27 20	
28 29	
30	
31	
32	
33 34	
35	
36	
37 38	
30 39	
40	
41	
42 43	
44	
45	
46	
47 48	
49	
50	
51 52	
52 53	
54	
55	
56 57	
57 58	
59	
60	

271	For statistical purposes, drug-drug interactions between different ATC drug classes (49) were
272	operationalised as dichotomised variables ($0 = no$ simultaneous use of drugs from both classes,
273	1 = simultaneous use of drugs from both classes) and added to the previous model. Drug class interactions
274	were selected based on a literature review, significant ORs, and expert opinions (51). The model
275	considered drug class interactions for the: 1) cardiovascular system * central nervous system,
276	gastrointestinal system, and metabolism * cardiovascular system; 2) gastrointestinal system and
277	metabolism * central nervous system; 3) cardiovascular system * anti-infectives; and 4) central nervous
278	system * anti-infectives. The analysis was carried out controlling for the basic model's variables (Table
279	4), and the table reports the ORs for each additional unit of the statistically significant drugs in question,
280	as well as for significant drug interactions. Antiemetics and antinauseants were very strongly associated
281	with 30-day readmission (OR = 3.222 ; 95% CI: $1.844-5.630$), as were drugs regulating the
282	gastrointestinal tract (OR = 1.428; 95% CI: 1.169–1.744) and systemic hormones (OR = 1.210; 95% CI:
283	1.054–1.390). The joint intake of beta-blocking agents and drugs for acid-related disorders was
284	significantly associated with 30-day hospital readmission (OR = 1.367; 95% CI: 1.046–1.788); this is the
285	only significant drug interaction in Table 4. On the contrary, lipid-modifying agents were associated with
286	lower 30-day hospital readmission ($OR = 0.838$), as were substances acting on the renin–angiotensin
287	system (OR = 0.892; 95% CI: 0.796–0.999) (Table 6).
288	[Insert Table 6]
289	

290 Discussion

The present study examined the records of 20,422 separate hospitalisations involving polymedicated 291 292 home-dwelling older patients, eventually discharged home, for the prevalence of 30-day hospital 293 readmission. These records were held in four years of an exhaustive hospital register. The 13,802 294 individual older patients identified showed a 30-day hospital readmission rate of almost 8%, 295 corroborating previously published all-cause hospital readmission rates among home-dwelling older 296 patients (9, 27). However, Jencks et al. (2009) found a much higher 30-day readmission prevalence, 297 reaching almost 20% among discharged older patients who had been hospitalised in acute medicine and 298 surgery wards (3). As a bivariate association, multimorbid men were at a significantly higher risk of 299 readmission than multimorbid women; however, in the adjusted multivariate analysis that significance 300 disappeared. Medical conditions, PP and multiple classes of prescribed drugs were all associated with 301 higher 30-day readmission rates, in line with previous studies (27, 52-54). 302 Our study found no significant differences in the risks of 30-day hospital readmission for men and 303 women. However, some previous research found that men were more likely to forget to take their drugs 304 or to not apply the changed drug dosages prescribed by their family physician, consequently increasing 305 their risk of hospital readmission for drug-related problems (55). Opposite results were found in a 306 population-based study by Manteufel et al. (56), with women being less likely than men to properly 307 adhere to their drug prescriptions. These differences may indicate a need for more personalised drug

- 308 prescription and drug management to improve clinical outcomes. Further research should explore
- 309 associations between different types of drugs and sex (56, 57), but this topic was beyond the present

3		
4 5	310	study's scope. Another interesting issue regarding sex differences in hospital readmission rates is the
6	311	study window. Some studies found higher rates among men than among women below three-month
7	312	readmissions. More extended time windows (e.g. one year) revealed no significant sex differences (52,
8 9	313	58). An analysis of our dataset using a more extended readmission window might clarify this point and
10	314	provide complementary knowledge about sex-associated hospital readmissions.
11 12	315	Our results indicated that ageing was not a risk factor for increased 30-day hospital readmission, in line
13	316	with some previous publications (53, 59). However, other research findings demonstrated that age was
14 15	317	only positively associated with the likelihood of readmission up to 74 years old; above that, there no
16	318	longer appeared to be any significant relationship between age and readmission (60, 61). These
17	319	contrasting results may be explained by the studies' designs, country settings, the ages of their research
18 19	320	populations or the medical conditions included (53, 60, 62).
20	321	Longer hospital stays were also associated with a higher risk of hospital readmission, in line with a cohort
21 22	322	study by Sud et al. concluding that an extended hospital LOS was associated with increased rates of all
23	323	types of readmission, except for hospitalisation after heart failure, where a short LOS was associated with
24 25	324	increased rates of readmission for cardiovascular disease and heart failure (63).
25	325	Our results indicated a significant positive association between the number of a patient's medical
27	326	conditions and the 30-day hospital readmission rate, confirming other recent retrospective hospital
28 29	327	register studies (64, 65). More specifically, older patients with impaired mobility showed an increased
30	328	risk of hospital readmission. This result was not surprising, bearing in mind that although these older
31 32	329	patients were discharged home-and not to a nursing home-after their hospital stay, their health status
33	330	might nevertheless require future readmission. Indeed, this corroborated publications about older patients
34 35	331	discharged after orthopaedic treatment or who had been initially admitted for heart failure, myocardial
36	332	infarction or pneumonia, but also presented with impaired mobility (66, 67).
37	333	Cognitive impairment was not associated with increased 30-day hospital readmission rates, in line with
38 39	334	findings from the systematic review by Pickens et al., which pointed out that dementia had a modest
40	335	impact on readmission rates (68). It was no surprise that inpatients hospitalised for cancer faced a high
41 42	336	risk of readmission, corroborating prior studies by Buhenn et al., Chang et al. and Butcher (69-71).
43	337	PP significantly increased the 30-day hospital readmission rate, but this result was based on the average
44 45	338	number of drugs prescribed to the sample of readmitted patients versus those not readmitted. Although PP
46	339	was confirmed as a strong determinant of 30-day hospital readmission in publications by Leendertse et al.
47 48	340	(72, 73), our results showed a progressive linear relationship between PP and readmission rate, and this
40 49	341	should be interpreted with caution. Despite our results and other publications and research underlining the
50	342	challenge of PP among multimorbid older patients, there is no overall consensus about the best way to
51 52	343	deal with the broad general relationship between PP and hospital readmission (74).
53	344	Our advanced statistical analysis demonstrated that some specific drugs and the concomitant use of
54 55	345	specific drug combinations were significantly associated with 30-day readmission risk, although this was
56	346	not unexpected and has been confirmed in previous publications (37, 75). Mostly in line with the research
57 58	347	findings of Zhang et al., drugs including hormones, antineoplastics, immunosuppressors, neoplastic
58 59 60	348	antibiotics and bacterial vaccines were substantial risk factors for hospital readmission (7).

2	
2 3	
4	
5 6 7 8	
6	
7	
8	
9	
9 10	
10	
11	
12 13	
13	
14	
15	
15 16 17 18	
17	
10	
10	
19	
20 21	
21	
22	
23	
24	
25	
25 26	
20	
27	
28	
29	
30	
31	
32	
34	
34 35 36	
27	
37 38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
40 49	
50	
51	
52	
53	
54	
55	
56	
50 57	
5/	
58	
59	

364

349 In summary, extended hospital LOS, functional impairments, medical conditions and drugs have been 350 demonstrated to be determinants of 30-day hospital readmission, although not all of them have clinically 351 or pharmacologically relevant interpretations or explanations. Further research involving large samples is 352 needed, notably to explore the drug-drug interactions with the highest risk of hospital readmissions. 353 Statistical predictions of potential drug-drug interactions provide important information for modeling 354 drug combinations and identifying pairs of drugs whose combination creates an exaggerated response (9). 355 As the association between the number of drugs and the prevalence of hospital readmission was linear, 356 more advanced inferential statistics would be needed to clarify a cut-off point for the mean number of 357 drugs that would significantly increase the readmission rate. In addition, problems involving adherence to 358 prescriptions, social support networks, and stronger or weaker primary health-care structures can all 359 influence hospital readmission rates (39). According to some publications, nearly 70% of people aged 360 over 65 make mistakes with their drugs (76, 77). Information about drug adherence, drug underuse and 361 overuse, drug changes and deprescription by family physicians, as well as medication management at 362 home would contribute to a more comprehensive understanding of disease- and drug-related 30-day 363 hospital readmissions.

365 Strengths and Limitations

366 This study's main strength was its use of comprehensive and recorded data from an exhaustive register.
367 We consider this retrospective study useful for clinical practice and future research because a whole series
368 of sociodemographic and clinical parameters, medical conditions and prescribed drugs were used to
369 predict the probability of hospital readmission. Using both bivariate and multivariate analyses enabled an
370 evaluation of the data's longitudinal nature.

371 Our study had several limitations, nevertheless. The design did not allow us to identify hospitalisations 372 and readmissions lost-to-follow-up and to adjust our data for death. We were also unable to identify 373 unnecessary hospitalisations or any bias towards hospitalisation rather than another health-care solution 374 among participants. Our dataset could not inform us about whether older inpatients had been first admitted to another hospital or were subsequently readmitted elsewhere during the study period. Another 375 376 limitation was the study's lack of formal screening methods to explain ADEs in detail, and it was 377 impossible to distinguish between elective and urgent hospitalisations. Although the study considered 378 statistical associations between drugs and rehospitalisations, it did not use clinically diagnosed drug-drug 379 interactions. Finally, we were unable to consider any potential causality between PP and hospital 380 readmission.

381

60

382 Conclusions

Hospital length of stay, medical conditions, functional impairments and prescribed drugs were all critical
factors in predicting hospital readmissions, thus affirming our hypotheses. Readmission patterns are
complex and poorly understood because older patients often present with multiple chronic conditions,
functional impairments and complex drug prescriptions. Hospital readmission is an under-investigated

2		
3 4	387	topic deserving of additional, well-conducted, predictive research exploiting accurate longitudinal data
5	388	from large samples.
6 7	389	nom large samples.
8	390	A also availad amonta
9 10		Acknowledgments
11	391 202	The authors thank the partner hospital, including the hospital's data warehouse, for its valuable
12	392	contributions. This research was developed, in part, using grants from the Swiss National Science
13 14	393	Foundation and the School of Health Sciences of the University of Applied Sciences and Arts Western
15	394 205	Switzerland (HES-SO) Valais/Wallis. The funders had no role in the design and conduct of the study, the
16 17	395	collection, management, analysis and interpretation of the data, the preparation, review or approval of the
18	396	manuscript, or the decision to submit the manuscript for publication.
19 20	397	Authors Contributions
21	398	All the authors contributed to data analysis or interpretation, to drafting or revising the article, gave final
22	399	approval to the version to be published and agree to be accountable for all aspects of the work.
23 24	400	Funding
25	401	This study was supported by the Swiss National Science Foundation via grant number 407440_183434/1.
26 27	402	Competing interest
28	403	The authors report no conflicts of interest surrounding this work.
29 30	404	Ethics approval and patient consent
31	405	Ethical approval was obtained from the Human Research Ethics Committee of the Canton of Vaud (CER-
32 33	406	VD, 2018-02196), thus permitting our partner hospital's data warehouse to provide the appropriate
34	407	dataset. Given the retrospective data source, obtaining consent from the patients concerned was
35	408	impossible or posed disproportionate difficulties. The present study respects the legal requirements for
36 37	409	research projects involving data re-use without consent, as set out in Art. 34 from the Swiss Human
38	410	Research Act (HTA).
39 40	411	Data sharing statement
41	412	As part of the Data Use Agreement, authors are not allowed to provide raw data. Upon a reasonable
42 43	413	request, the corresponding author will provide statistical programming code used to generate results.
44	414	Word Count: 4,158
45 46	415	
47	116	Deferences
48 49	416	References
49 50	417	1. Rayan-Gharra N, Rn ES, Tadmor B, Flaks-Manov N, Balicer RD. Patients' ratings of the in-
51	418 419	hospital discharge briefing and post-discharge primary care follow-up: the association with 30-day readmissions. Patient Education and Counseling. 2019.
52 53	420	 Kabue S, Greene J, Kipnis P, Lawson B, Rinetti-Vargas G, Liu V, et al. The Impact of
54	421	Pharmacy-specific Predictors on the Performance of 30-Day Readmission Risk Prediction Models. Med
55	422 423	 Care. 2019;57(4):295-9. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among Patients in the Medicare Fee-
56	423	for-Service Program. New England Journal of Medicine. 2009;360(14):1418-28.
57 58		
58 59		
60		

BMJ Open

3		
4	425	4. Covinsky KE, Palmer RM, Fortinsky RH, Counsell SR, Stewart AL, Kresevic DM. Loss of
5	426	independence in activities of daily living in older adults hospitalised with medical illness: increased
6	427	vulnerability with age. JAGS. 2003;51.
7	428	5. Hansen LO, Young RS, Hinami K, Leung A, Williams MV. Interventions to reduce 30-day
8	429	rehospitalization: a systematic review. Ann Intern Med. 2011;155(8):520-8.
9	430	6. Davies EC, Green CF, Mottram DR, Rowe PH, Pirmohamed M. Emergency re-admissions to
10	431	hospital due to adverse drug reactions within 1 year of the index admission. British Journal of Clinical
11	432	Pharmacology. 2010;70(5):749-55.
12	433	7. Zhang M, Holman CDAJ, Price SD, Sanfilippo FM, Preen DB, Bulsara MK. Comorbidity and
13	434	repeat admission to hospital for adverse drug reactions in older adults: retrospective cohort study. BMJ.
14	435	2009;338:a2752.
15	436	8. Bonnet-Zamponi D, d'Arailh L, Konrat C, Delpierre S, Lieberherr D, Lemaire A, et al. Drug-
16	437	Related Readmissions to Medical Units of Older Adults Discharged from Acute Geriatric Units: Results
17	438	of the Optimization of Medication in AGEd Multicenter Randomized Controlled Trial. Journal of the
18	439	American Geriatrics Society. 2013;61(1):113-21.
19	440	9. Blanc A-L, Fumeaux T, Stirnemann J, Dupuis Lozeron E, Ourhamoune A, Desmeules J, et al.
20	441	Development of a predictive score for potentially avoidable hospital readmissions for general internal
21	442	medicine patients. PLOS ONE. 2019;14(7):e0219348.
22	443	10. Stevenson JM, Davies JG, Martin F, Ali K, Rajkumar C, Schiff R. Is medication related harm as
23	444	a cause of readmission associated with the indicators of frailty? Age and Ageing. 2018;47:ii19.
24	445	11. Brunner-La Rocca H-P, Peden CJ, Soong J, Holman PA, Bogdanovskaya M, Barclay L. Reasons
25	446	for readmission after hospital discharge in patients with chronic diseases—Information from an
26	447	international dataset. PloS one. 2020;15(6):e0233457.
20	448	12. Dharmarajan K, Hsieh AF, Lin Z, Bueno H, Ross JS, Horwitz LI, et al. Hospital readmission
28	449	performance and patterns of readmission: retrospective cohort study of Medicare admissions. Bmj.
20 29	450	2013;347.
30	451	13. Arora S, Patel P, Lahewala S, Patel N, Patel NJ, Thakore K, et al. Etiologies, trends, and
31	452	predictors of 30-day readmission in patients with heart failure. The American journal of cardiology.
	453	2017;119(5):760-9.
32	454	14. Shams I, Ajorlou S, Yang K. A predictive analytics approach to reducing 30-day avoidable
33	455	readmissions among patients with heart failure, acute myocardial infarction, pneumonia, or COPD.
34	456	Health care management science. 2015;18(1):19-34.
35	457 458	15. Krumholz HM, Wang K, Lin Z, Dharmarajan K, Horwitz LI, Ross JS, et al. Hospital-
36	458 459	readmission risk—isolating hospital effects from patient effects. New England Journal of Medicine. 2017;377(11):1055-64.
37	439	16. Gruneir A, Fung K, Fischer HD, Bronskill SE, Panjwani D, Bell CM, et al. Care setting and 30-
38	461	day hospital readmissions among older adults: a population-based cohort study. CMAJ.
39	462	2018;190(38):E1124-E33.
40	463	17. Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, Garmen A, et al. Aging with
41	464	multimorbidity: A systematic review of the literature. Ageing Research Reviews. 2011;10:430-9.
42	465	18. Valderas JM, Starfield B, Sibbald B, Salisbury C, Rloand M. Defining comorbidity: implications
43	466	for understanding health and health services. Annals Of Family Medicine. 2009;7:357-63.
44	467	19. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. Expert
45	468	Opinion on Drug Safety. 2014;13:57-65.
46	469	20. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic
47	470	review of definitions. BMC Geriatrics. 2017;17:1-10.
48	471	21. Wastesson JW, Morin L, Tan ECK, Johnell K. An update on the clinical consequences of
49	472	polypharmacy in older adults: a narrative review. Expert Opin Drug Saf. 2018;17(12):1185-96.
50	473	22. Rieckert A, Trampisch US, Klaaßen-Mielke R, Drewelow E, Esmail A, Johansson T, et al.
51	474	Polypharmacy in older patients with chronic diseases: a cross-sectional analysis of factors associated with
52	475	excessive polypharmacy. BMC Family Practice. 2018;19(1):113.
53	476	23. Magill SS, Edwards JR, Bamberg W, Beldavs ZG, Dumyati G, Kainer MA, et al. Multistate
54	477	point-prevalence survey of health care-associated infections. N Engl J Med. 2014;370(13):1198-208.
55	478	24. Coleman EA, Smith JD, Raha D, Min SJ. Posthospital medication discrepancies: prevalence and
56	479	contributing factors. Arch Intern Med. 2005;165(16):1842-7.
57	480	25. Ferreri SP, Hughes TD, Snyder ME. Medication Therapy Management: Current Challenges.
58	481	Integr Pharm Res Pract. 2020;9:71-81.
59		
60		

1 2

3 4 482 Roux P, Verloo H, Santiago-Delefosse M, Pereira F. The spatial dimensions of medication 26. 5 483 management by home-dwelling older adults after hospital discharge. Health & Place. 2019;60:102230. 6 484 El Morabet N, Uitvlugt EB, van den Bemt BJF, van den Bemt P, Janssen MJA, Karapinar-Çarkit 27. 7 485 F. Prevalence and Preventability of Drug-Related Hospital Readmissions: A Systematic Review. J Am 8 486 Geriatr Soc. 2018;66(3):602-8. 9 487 Forster AJ, Murff HJ, Peterson JF, Gandhi TK, Bates DW. The incidence and severity of adverse 28. 10 488 events affecting patients after discharge from the hospital. Ann Intern Med. 2003;138(3):161-7. 489 Yeo I, Cheung JW, Feldman DN, Amin N, Chae J, Wong SC, et al. Assessment of Hospital 11 29. 490 Readmission Rates, Risk Factors, and Causes After Cardiac Arrest: Analysis of the US Nationwide 12 491 Readmissions Database. JAMA Network Open. 2019;2(9):e1912208-e. 13 492 Hauviller L, Eyvrard F, Garnault V, Rousseau V, Molinier L, Montastruc JL, et al. Hospital re-30. 14 493 admission associated with adverse drug reactions in patients over the age of 65 years. European Journal of 15 494 Clinical Pharmacology. 2016;72(5):631-9. 16 495 Davies EC, Green CF, Mottram DR, Rowe PH, M P. Emergency re-admissions to hospital due to 31. 17 496 adverse drug reactions within 1 year of the index admission. Br J Clin Pharmacol. 2010;70:749–55. 18 Samoy LJ, Zed PJ, Wilbur K, Balen RM, Abu-Laban RB, Roberts M. Drug-related 497 32. 19 498 hospitalizations in a tertiary care internal medicine service of a Canadian hospital: a prospective study. 20 499 Pharmacotherapy. 2006;26(11):1578-86. 21 Teymoorian SS, Dutcher D, Woods M. ASSOCIATION BETWEEN POSTDISCHARGE 500 33. 22 501 ADVERSE DRUG REACTIONS AND 30-DAY HOSPITAL READMISSION IN PATIENTS AGED 80 23 502 AND OLDER. Journal of the American Geriatrics Society. 2011;59(5):948-9. 24 WHO. ADHERENCE TO LONG-TERM THERAPIES: Evidence for action. Geneva: World 503 34. 25 504 Health Organisation; 2003. 26 505 35. Brahma DK, Wahlang JB, Marak MD, Ch Sangma M. Adverse drug reactions in the elderly. J 27 506 Pharmacol Pharmacother. 2013;4(2):91-4. 28 507 Davies EA, O'Mahony MS. Adverse drug reactions in special populations - the elderly. Br J Clin 36. 29 508 Pharmacol. 2015;80(4):796-807. 30 509 Moura CS, Tavares LS, Acurcio Fde A. [Hospital readmissions related to drug interactions: a 37. 31 510 retrospective study in a hospital setting]. Rev Saude Publica. 2012;46(6):1082-9. 32 Spinks JM, Kalisch Ellett LM, Spurling G, Theodoros T, Williamson D, Wheeler AJ. Adaptation 511 38. 33 512 of potentially preventable medication-related hospitalisation indicators for indigenous populations in 34 513 Australia using a modified Delphi technique. BMJ Open. 2019;9(11):e031369. 514 Rosen OZ, Fridman R, Rosen BT, Shane R, Pevnick JM. Medication adherence as a predictor of 35 39. 515 30-day hospital readmissions. Patient Prefer Adherence. 2017;11:801-10. 36 516 Pellegrin KL, Lee E, Uyeno R, Ayson C, Goo R. Potentially preventable medication-related 40. 37 hospitalizations: A clinical pharmacist approach to assessment, categorization, and quality improvement. 517 38 518 Journal of the American Pharmacists Association. 2017;57(6):711-6. 39 519 41. Pereira F, Roux P, Santiago-Delefosse M, von Gunten A, Wernli B, Martins MM, et al. 40 520 Optimising medication management for polymedicated home-dwelling older adults with multiple chronic 41 521 conditions: a mixed-methods study protocol. BMJ Open. 2019;9(10):e030030. 42 522 Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, et al. The REporting of 42. 43 523 studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. PLOS 44 524 Medicine. 2015;12(10):e1001885. 45 Strasberg HR, Geiger G, Tudiver F. Moving towards an electronic patient record: A survey to 525 43. 46 assess the needs of an academic family practice unit. Waegemann CP, editor. Newton: Medical Records 526 47 527 Institute; 1998. A434-A43 p. 48 528 Surgical interventions clasification S. Swiss classification of surgical interventions (CHOP). 44. 49 529 2016. 50 530 Parker S, Prince A, Thomas L, Song H, Milosevic D, Harris MF. Electronic, mobile and 45. 51 telehealth tools for vulnerable patients with chronic disease: a systematic review and realist synthesis. 531 52 532 BMJ Open. 2018;8(8). 53 533 Olsen J. Register-based research: some methodological considerations. Scandinavian journal of 46. 54 534 public health. 2011;39(3):225-9. 55 535 Taushanov Z, Verloo H, Wernli B, Di Giovanni S, von Gunten A, F P. Transforming a patient 47. 56 536 registry into a customised dataset for the advanced statistical analysis of health risk factors and for 537 medication-related hospitalisation research: a retrospective hospital patient registry study. JMIR Medical 57 538 Informatics, 2021. 58 539 Andrade C. Age as a variable: Continuous or categorical? Indian J Psychiatry. 2017;59(4):524-5. 59 48. 60

BMJ Open

2 3		
5 4		
5	540	49. WHO. The Anatomical Therapeutic Chemical Classification System with Defined Daily Doses
6	541	(ATC/DDD) Geneva: World Health Organization; 2014 [24 March 2020]. Available from:
7	542	http://www.who.int/classifications/atcddd/en/.
8	543	50. Goldstein H. Nonlinear Multilevel Models, with an Application to Discrete Response Data.
9	544 545	Biometrika. 1991;78(1):45-51. 51. Haider SI, Johnell K, Thorslund M, Fastbom J. Trends in polypharmacy and potential drug-drug
10	545 546	interactions across educational groups in elderly patients in Sweden for the period 1992 - 2002. Int J Clin
11	547	Pharmacol Ther. 2007;45(12):643-53.
12	548	52. Linkens AEMJH, Milosevic V, van der Kuy PHM, Damen-Hendriks VH, Mestres Gonzalvo C,
13	549	Hurkens KPGM. Medication-related hospital admissions and readmissions in older patients: an overview
14	550	of literature. International Journal of Clinical Pharmacy. 2020.
15	551	53. Berry JG, Gay JC, Joynt Maddox K, Coleman EA, Bucholz EM, O'Neill MR, et al. Age trends in
16	552	30 day hospital readmissions: US national retrospective analysis. BMJ. 2018;360:k497.
17	553	54. Kongkaew C, Hann M, Mandal J, Williams SD, Metcalfe D, Noyce PR, et al. Risk factors for
18	554	hospital admissions associated with adverse drug events. Pharmacotherapy. 2013;33(8):827-37.
19	555	55. Thunander Sundbom L, Bingefors K. Women and men report different behaviours in, and
20	556	reasons for medication non-adherence: a nationwide Swedish survey. Pharmacy practice. 2012;10(4):207-
21	557	21.
22	558	56. Manteuffel M, Williams S, Chen W, Verbrugge RR, Pittman DG, Steinkellner A. Influence of
23	559	patient sex and gender on medication use, adherence, and prescribing alignment with guidelines. J
24	560	Womens Health (Larchmt). 2014;23(2):112-9.
25	561	57. Thunander Sundbom L, Hedborg K. Association between prescribed antidepressants and other
26	562	prescribed drugs differ by gender: a nationwide register-based study in Sweden. Nord J Psychiatry.
27	563	2019;73(1):73-9.
28	564 565	58. Silverstein MD, Qin H, Mercer SQ, Fong J, Haydar Z. Risk Factors for 30-Day Hospital
29	565	Readmission in Patients ≥65 Years of Age. Baylor University Medical Center Proceedings. 2008;21(4):363-72.
30	567	59. Schwab C, Hindlet P, Sabatier B, Fernandez C, Korb-Savoldelli V. Risk scores identifying
31	568	elderly inpatients at risk of 30-day unplanned readmission and accident and emergency department visit:
32	569	a systematic review. BMJ Open. 2019;9(7):e028302.
33	570	60. Jain S, Khera R, Mortensen EM, Weissler JC. Readmissions of adults within three age groups
34	571	following hospitalization for pneumonia: Analysis from the Nationwide Readmissions Database. PLOS
35	572	ONE. 2018;13(9):e0203375.
36	573	61. Hasegawa K, Gibo K, Tsugawa Y, Shimada YJ, Camargo CA, Jr. Age-Related Differences in
37	574	the Rate, Timing, and Diagnosis of 30-Day Readmissions in Hospitalized Adults With Asthma
38	575	Exacerbation. Chest. 2016;149(4):1021-9.
39	576	62. Shebeshi DS, Dolja-Gore X, Byles J. Unplanned Readmission within 28 Days of Hospital
40	577	Discharge in a Longitudinal Population-Based Cohort of Older Australian Women. International Journal
41	578	of Environmental Research and Public Health. 2020;17(9):3136.
42	579	63. Sud M, Yu B, Wijeysundera HC, Austin PC, Ko DT, Braga J, et al. Associations Between Short
43	580	or Long Length of Stay and 30-Day Readmission and Mortality in Hospitalized Patients With
44	581	Heart Failure. JACC: Heart Failure. 2017;5(8):578-88.
45	582	64. Donzé J, Lipsitz S, Bates DW, Schnipper JL. Causes and patterns of readmissions in patients
46	583	with common comorbidities: retrospective cohort study. Bmj. 2013;347:f7171.
47	584	65. Hijazi HH, Alyahya MS, Hammouri HM, Alshraideh HA. Risk assessment of comorbidities on
48	585 586	30-day avoidable hospital readmissions among internal medicine patients. J Eval Clin Pract. 2017;23(2):391-401.
49	587	66. Falvey JR, Bade MJ, Hogan C, Forster JE, Stevens-Lapsley JE. Preoperative Activities of Daily
50	588	Living Dependency is Associated With Higher 30-Day Readmission Risk for Older Adults After Total
51	589	Joint Arthroplasty. Clin Orthop Relat Res. 2020;478(2):231-7.
52	590	67. Greysen SR, Stijacic Cenzer I, Auerbach AD, Covinsky KE. Functional impairment and hospital
53	591	readmission in Medicare seniors. JAMA Intern Med. 2015;175(4):559-65.
54	592	68. Pickens S, Naik AD, Catic A, Kunik ME. Dementia and Hospital Readmission Rates: A
55	593	Systematic Review. Dementia and Geriatric Cognitive Disorders Extra. 2017;7(3):346-53.
56	594	69. Chiang LY, Liu J, Flood KL, Carroll MB, Piccirillo JF, Stark S, et al. Geriatric assessment as
57	595	predictors of hospital readmission in older adults with cancer. J Geriatr Oncol. 2015;6(4):254-61.
58	596	70. Butcher L. Oncologists Seek to Understand, Address Hospital Readmissions. Oncology Times.
59	597	2016;38(6):1,9-10.
60		

Burhenn P, Sun C-L, Scher KS, Hsu J, Pandya P, Chui C-Y, et al. Predictors of hospital 71. readmission among older adults with cancer. J Geriatr Oncol. 2020;11(7):1108-14. Leendertse AJ, Egberts ACG, Stoker LJ, van den Bemt PMLA, Group HS. Frequency of and 72. Risk Factors for Preventable Medication-Related Hospital Admissions in the Netherlands. Archives of Internal Medicine. 2008;168(17):1890-6. Leendertse AJ, Van Den Bemt PM, Poolman JB, Stoker LJ, Egberts AC, Postma MJ. 73. Preventable hospital admissions related to medication (HARM): cost analysis of the HARM study. Value Health. 2011;14(1):34-40. Garfinkel D, Bilek A. Inappropriate medication use and polypharmacy in older people. BMJ. 74. 2020;369:m2023. 75. Tesfaye WH, Peterson GM, Castelino RL, McKercher C, Jose MD, Wimmer BC, et al. Medication Regimen Complexity and Hospital Readmission in Older Adults With Chronic Kidney Disease. Annals of Pharmacotherapy. 2019;53(1):28-34. Fialová D, Onder G. Medication errors in elderly people: contributing factors and future 76. perspectives. British journal of clinical pharmacology. 2009;67(6):641-5. Lavan AH, Gallagher PF, O'Mahony D. Methods to reduce prescribing errors in elderly patients 77. with multimorbidity. Clinical interventions in aging. 2016;11:857-66. Relationship between 30-day readmission rate and the number of prescribed drugs at discharge 16.0% 14.0% 12.0% **30-day readmission** 10.0% 8.0% 6.0% 4.0% 2.0% 0.0% 4 to 6 7 to 9 Number of prescribed drugs Figure 1. Relationship between 30-day readmission rate and the number of prescribed drugs at discharge. Table 1. Descriptive statistics of drugs prescribed per patient (N = 13,802) at discharge based on the ATC Classification System.

Drug classes based on the ATC Classification System	Min-Max	Mean (SD)		
First level, anatomical main group				
Blood and blood forming organs (B)	0-5	1.15 (0.86)		
Dermatologicals (D)	0–3	0.04 (0.21)		
Genitourinary system and sex hormones (G)	0-4	0.21 (0.47)		
Systemic hormonal preparations, excl. sex hormones and insulins (H)	0-4	0.20 (0.46)		

10 to 12

13 to 15

16 and more

3			
4	Anti-infectives for systemic use (J)	0-4	0.24 (0.47)
5	Antineoplastic and immunomodulating agents (L)	0-5	0.05 (0.23)
6	Musculo-skeletal system (M)	0–3	0.15 (0.39)
7	Antiparasitic products, insecticides and repellents (P)	0-2	0.02 (0.13)
8	Respiratory system (R)	0-7	0.28 (0.72)
9	Sensory organs (S)	0–6	0.10 (0.39)
10 11	Second level, therapeutic subgroup	•	
12	Stomatological preparations (A01)	0-1	0.00 (0.06)
12	Drugs for acid-related disorders (A02)	0-3	0.56 (0.52)
14	Drugs for functional gastrointestinal disorders (A03)	0-3	0.07 (0.28)
15	Antiemetics and antinauseants (A04)	0-1	0.01 (0.08)
16	Bile and liver therapy (A05)	0-1	0.00 (0.05)
17	Drugs for constipation (A06)	0-3	0.15 (0.40)
18	Antidiarrhoeals, intestinal anti-inflammatory/anti-infective agents (A07)	0-2	0.03 (0.18)
19	Digestives, incl. Enzymes (A09)	0-2	0.02 (0.13)
20	Drugs used in diabetes (A10)	0-5	0.26 (0.63)
21	Vitamins (A11)	0-4	0.15 (0.44)
22	Mineral supplements (A12)	0-3	0.29 (0.51)
23	Other alimentary tract and metabolism products (A16)	0-1	0.00 (0.05)
24	Cardiac therapy drugs (C01)	0-4	0.14 (0.42)
25	Antihypertensives (C02)	0-2	0.02 (0.17)
26	Diuretics (C03)	0-3	0.27 (0.53)
27	Peripheral vasodilators (C04)	0-1	0.00 (0.06)
28	Vasoprotectives (C05)	0-3	0.02 (0.14)
29	Beta-blocking agents (C07)	0-2	0.46 (0.51)
30	Calcium channel blockers (C08)	0-2	0.16 (0.37)
31	Agents acting on the renin-angiotensin system (C09)	0-3	0.64 (0.62)
32	Lipid modifying agents (C10)	0-3	0.43 (0.52)
33	Anaesthetics (N01)	0-1	0.00 (0.05)
34	Analgaesics (N02)	0-7	1.02 (0.91)
35	Antiepileptics (N03)	0-5	0.11 (0.35)
36	Drugs for Parkinson's disease (N04)	0-5	0.04 (0.24)
37	Psycholeptics (N05)	0-6	0.53 (0.73)
38	Psychoanaleptics (N06)	0-3	0.20 (0.44)
39 40	Other nervous system drugs(N07)	0-3	0.03 (0.19)
40 41	Total number of drugs	5-30	8.95 (3.24)
41 42 620			

Table 2. Prevalence of hospital 30-day readmissions at different periods for different age groups

(N = 13,802).

Variables	30-day hospital readmission	<i>p</i> -value
Complete sample	7.8%	
Sex		*
Women vs men	7.3% vs 8.2%	
Year-end age, in years		NS
65–69	7.5%	
70–79	7.6%	
80–89	8.4%	
\geq 90	6.4%	
Mobility cluster:		NS
Preserved mobility vs impaired mobility	7.6% vs 8.5%	

1	
2	
3	
4	
5	
6	
6 7	
8	
a	
8 9 10 11	
10	
11	
12	
12 13	
14	
15	
16	
13 14 15 16 17	
18	
18 19 20 21	
20	
∠∪ ว1	
21	
22 23	
24 25	
25	
26	
26 27	
28	
29	
30	
31	
32	
33	
34 35 36 37	
35	
36	
37	
38	
39	
40	
40 41	
42	
43	
44	
45	
46	
47	
48	
49	
50	
51	
51 52	
53	
54	
55	
56	
57	
58	
59	

Activities in daily living (ADL):		NS
Full ADL ability vs impaired ADL	7.8% vs 7.2%	
Cognitive status:		NS
Preserved cognitive status vs cognitive impairment	7.8% vs 7.9%	
ICD-10 diagnosis: circulatory problems		*>
No vs Yes	8.2% vs 6.5%	
ICD-10 diagnosis: infection		NS
No vs Yes	7.7% vs 9.9%	
ICD-10 diagnosis: respiratory problems		NS
No vs Yes	7.8% vs 8.0%	
ICD-10 diagnosis: trauma		*
No vs Yes	8.0% vs 5.8%	
ICD-10 diagnosis: tumour		**
No vs Yes	6.9% vs 15.1%	
Number of ICD-10 conditions		**
	1.5%	
2	4.9%	
3	3.6%	
4	4.8%	
5	8.8%	
Number of surgical procedures (CHOP)		
0	7.7%	
	7.8%	
	7.0%	
3	7.3%	
4	7.1%	
5	9.7%	
Year: 2015–2018		Ν
2015	8.3%	
2016	8.0%	
2017	8.0%	
$\frac{2018}{\text{Note. } * = p < 0.05; ** = p < 0.01; *** = p < 0.001; \text{NS} = 1}$	6.8%	

624

625 Table 3. Prevalence of readmission for different classes of drugs based on the ATC (N = 13,802).

Drug class	30-day readmission with NO drugs in this class	30-day readmission with drugs in this class	<i>p</i> - value
First level, anatomical main group)		
Blood and blood-forming organ drugs (B)	7.1%	8.0%	NS
Dermatologicals (D)	7.7%	9.4%	NS
Genitourinary system and sex hormones (G)	7.7%	8.3%	NS
Systemic hormonal preparations, excluding sex hormones and insulins (H)	7.4%	9.5%	***
Anti-infectives for systemic use (J)	8.0%	7.2%	NS
Antineoplastic and immunomodulating agents (L)	7.6%	12.6%	***
Drugs for the musculo-skeletal system (M)	8.0%	6.5%	*
Antiparasitic products, insecticides, and repellents (P)	7.8%	6.6%	***
Respiratory system drugs (R)	7.4%	9.9%	***
Sensory organ drugs (S)	7.8%	8.4%	NS

Second level, therapeutic subgroup			
Stomatological preparations (A01)	7.8%	12.2%	NS
Drugs for acid-related disorders (A02)	7.0%	8.5%	**
Drugs for functional gastrointestinal disorders (A03)	7.4%	13.4%	**
Antiemetics and antinauseants (A04)	7.7%	27.7%	**
Bile and liver therapy drugs (A05)	7.8%	14.3%	NS
Drugs for constipation (A06)	7.3%	10.8%	**
Antidiarrhoeals, intestinal anti-inflammatory/anti-infective agents (A07)	7.7%	12.9%	**
Digestives, including enzymes (A09)	7.8%	10.0%	N
Drugs used in diabetes (A10)	7.4%	9.5%	**
Vitamins (A11)	7.5%	9.9%	**
Mineral supplements (A12)	7.4%	8.8%	**
Other alimentary tract and metabolism products (A16)	7.8%	6.3%	N
Cardiac therapy (C01)	7.6%	8.9%	N
Antihypertensives (C02)	7.7%	14.1%	**
Diuretics (C03)	7.2%	9.8%	**
Peripheral vasodilators (C04)	7.8%	15.2%	N
Vasoprotective drugs (C05)	7.8%	9.8%	N
Beta-blocking agents (C07)	7.1%	8.6%	**
Calcium channel blockers (C08)	7.7%	8.6%	N
Agents acting on the renin-angiotensin system (C09)	8.7%	7.1%	**
Lipid-modifying agents (C10)	8.3%	7.1%	*:
Anaesthetics (N01)	7.8%	18.8%	*
Analgaesics (N02)	7.8%	7.8%	N
Antiepileptics (N03)	7.7%	9.0%	N
Drugs for Parkinson's disease (N04)	7.8%	6.9%	N
Psycholeptics (N05)	6.8%	9.3%	**
Psychoanaleptics (N06)	7.8%	7.7%	N
Other nervous system drugs (N07)	7.9%	5.1%	N

626 Note. * = p < 0.05; ** = p < 0.01; *** = p < 0.001; NS = non-significant

628 Table 4. Baseline, multilevel, logistic regression model using 30-day readmission (0 = no; 1 = yes) as the

629 dependent variable associated with independent sociodemographic, LOS, and clinical variables

(N = 13,802 observations for 8,878 different participants).

Variables	Odds Ratio ³	<i>P</i> > z	95% CI ⁴
Sex	1.079	0.285	0.938-1.242
Year-end age, in years	0.999	0.878	0.990-1.009
Hospital length of stay (LOS), in days	1.014	0.000	1.006-1.021
Mobility cluster ¹	1.218	0.015	1.039-1.427
Dependency in the activities of daily living ¹	0.794	0.248	0.537-1.174
Mental health status ¹	0.992	0.966	0.687-1.433
CIM 1 diagnosis: circulatory problems ²	0.938	0.491	0.783-1.124
CIM 1 diagnosis: infection ²	1.381	0.078	0.964–1.977
CIM 1 diagnosis: respiratory problems ²	1.100	0.414	0.875-1.382
CIM 1 diagnosis: trauma ²	0.847	0.265	0.633-1.134
CIM 1 diagnosis: tumour ²	2.538	0.000	2.089-3.082
Number of CIM	1.419	0.000	1.282-1.572

2	
3	
4 5	
6	
7	
8	
9	
10	
11	
12	
13	
14 15	
16	
16 17	
18	
19	
20	
21	
22 23	
23 24	
25	
26	
27	
28	
29	
30	
31 32	
33	
34	
35	
36 37	
37	
38	
39	
40 41	
41	
43	
44	
45	
46	
47	
48	
49 50	
50	
52	
53	
54	
55	
56	
57	
58	

Number of CHOP	0.978	0.304	0.938-1.020
Number of drugs	1.043	0.000	1.028-1.058
Year: 2015 to 2018	0.933	0.022	0.880-0.990
Intercept		0.027	

Note. 1: 0 = good state, 1 = impairment; 2: 0 = no, 1 = yes; 3: adjusted Odds ratio; 4:

Table 5. Multilevel logistic regression model results for the drugs prescribed to older patients at discharge
home that had significant predictive values (odds ratios) for 30-day hospital readmission (controlled for
variables in the baseline model: Table 4) (N = 13,802 observations for 8,878 different participants).

Variables	Odds ratio ¹	p > z	95% CI ²
First level, anatomical main group			
Blood and blood-forming organs drugs (B)	1.089	0.041	1.003-1.18
Systemic hormonal preparations, excluding sex hormones and insulins	1.207	0.007	1.052-1.38
(H)			
Respiratory system drugs (R)	1.146	0.003	1.046-1.25
Second level, therapeutic subgroup)		
Drugs for functional gastrointestinal disorders (A03)	1.424	0.001	1.166–1.739
Antiemetics and antinauseants (A04)	3.216	0.000	1.842-5.617
Drugs for constipation (A06)	1.195	0.018	1.031-1.386
Drugs used in diabetes (A10)	1.125	0.021	1.018-1.243
Vitamins (A11)	1.201	0.008	1.049-1.374
Antihypertensives (C02)	1.771	0.000	1.287-2.438
Diuretics (C03)	1.149	0.024	1.018-1.296
Beta-blocking agents (C07)	1.156	0.040	1.007-1.327
Lipid-modifying agents (C10)	0.841	0.015	0.732-0.967
Psycholeptics (N05)	1.130	0.009	1.031-1.238

 Table 6. Drugs and drugs interactions from ATC classes A and B with a significant risk of 30-day

643 hospital readmission (controlled for variables in the baseline model: Table 4) (N = 13,802 observations

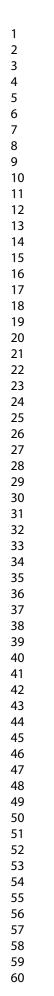
644 for 8,878 different participants).

Variables	Odds ratio ¹	p > z	95% CI ²		
First level, anatomical main grou	p				
Blood and blood-forming organ drugs (B)	1.089	0.040	1.004–1.182		
Systemic hormonal preparations, excluding sex hormones and insulins (H)	1.210	0.007	1.054–1.390		
Respiratory system drugs (R)	1.149	0.003	1.049-1.258		
Second level, therapeutic subgroup					
Antiemetics and antinauseants (A04)	3.222	0.000	1.844-5.630		

1.428	0.000	1.169–1744
1.367	0.022	1.046-1.788
1.199	0.017	1.033-1.392
0.892	0.049	0.796-0.999
0.838	0.013	0.729-0.964
	1.367 1.199 0.892	1.367 0.022 1.199 0.017 0.892 0.049

645 Note. 1: adjusted odds ratio; 2: CI = Confidence Interval

For beer terien only



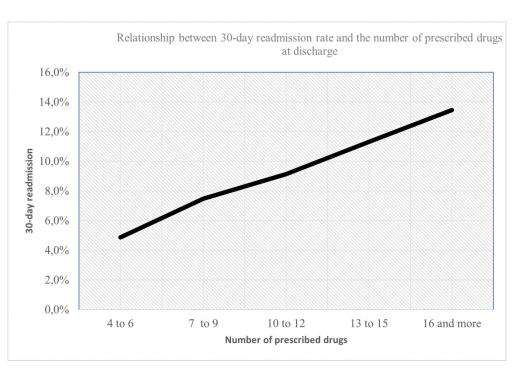


Figure 1. Relationship between 30-day readmission rate and the number of prescribed drugs at discharge.

688x467mm (72 x 72 DPI)

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 To cite: Pereira F. Roux P. 17 Santiago-Delefosse M, 18 et al. Optimising medication management for polymedicated 19 home-dwelling older adults 20 with multiple chronic 21 conditions: a mixed-methods 22 study protocol. BMJ Open 23 2019;9:e030030. doi:10.1136/ bmjopen-2019-030030 24 25 Prepublication history and 26 additional material for this 27 paper are available online. To view these files, please visit 28 the journal online (http://dx.doi. 29 org/10.1136/bmjopen-2019-30 030030). 31 Received 23 February 2019 32 Revised 17 August 2019 33 Accepted 03 October 2019 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 C Author(s) (or their employer(s)) 2019. Re-use 50 permitted under CC BY-NC. No 51 commercial re-use. See rights 52 and permissions. Published by 53 BMJ. 54 For numbered affiliations see end of article. 55 56 **Correspondence to** 57

Open access **BMJ Open** Optimising medication management for polymedicated home-dwelling older adults with multiple chronic conditions: a mixed-methods study protocol

Filipa Pereira ,^{1,2} Pauline Roux,³ Marie Santiago-Delefosse,³ Armin von Gunten,⁴ Boris Wernli,⁵ Maria Manuela Martins,^{2,6} Henk Verloo^{1,4}

ABSTRACT

Introduction Optimal medication management is one of the basic conditions necessary for home-dwelling older adults living with multiple chronic conditions (OAMCC) to be able to remain at home and preserve their quality of life. Currently, the reasons for such high numbers of emergency department visits and the very significant rate of hospitalisations for OAMCC, due to medication-related problems (MRPs), is poorly explored. This study aims to reveal the current state of the medication management practices of polymedicated, home-dwelling OAMCC and to make proposals for improving clinical and medication pathways through an innovative and integrated model for supporting medication management and preventing adverse health outcomes.

Methods and analysis A mixed-methods study will address the medication management of polymedicated, home-dwelling OAMCC. Its explanatory sequential design will involve two major phases conducted sequentially over time. The quantitative phase will consist of retrospectively exploiting the last 5 years of electronic patient records from a local hospital (N \approx 50 000) in order to identify the different profiles-made up of patient-related, medication-related and environment-related factors-of the polymedicated. home-dwelling OAMCC at risk of hospitalisation, emergency department visits, hospital readmission (notably for MRPs), institutionalisation or early death. The gualitative study will involve: (a) obtaining and understanding the medication management practices and experiences of the identified profiles extracted from the hospital data of OAMCC who will be interviewed at home (N \approx 30); (b) collecting and analysing the perspectives of the formal and informal caregivers involved in medication management at home in order to cross-reference perspectives about this important dimension of care at home. Finally, the mixed-methods findings will enable the development of an innovative, integrated model of medication management based on the Agency for Clinical Innovation framework and Bodenheimer and Sinsky's quadruple aim.

Ethics and dissemination Ethical approval has been obtained from the Human Research Ethics Committee of the Canton Vaud (2018-02196). Findings will be disseminated in peer-reviewed journals, professional conferences and other knowledge transfer activities with primary healthcare providers, hospital care units, informal caregivers' and patients' associations.

Strengths and limitations of this study

- This mixed methodology will rely on a closely coordinated combination of methods and on the utilisation of valuable existing data underexploited to date (patients' electronic hospital records and Resident Assessment Instrument-Home Care (RAI-HC) data).
- The investigation draws on an interprofessional and interdisciplinary approach, which associates general practitioners, community healthcare nurses, pharmacists and researchers in health psychology, old age psychiatry, nursing and survey methodology.
- Our findings will contribute to the development of an evidence-based and innovative, cooperative model of medication management for polymedicated, home-dwelling older adults with multiple chronic conditions.
- Although patients' electronic hospital records and RAI-HC data provide a broad range of patient-related, medication-related and environment-related information, they rarely highlight factors that may influence the occurrence of medication-related problems.

INTRODUCTION

The number of older adults living at home with multiple chronic conditions (OAMCC) rises considerably around the world and has been estimated to affect 25.2% of people aged from 65 to 79% and 41.3% of those aged 80 and over.¹ Multiple chronic conditions is a comprehensive concept used to properly cover the diverse definitions of multimorbidity^{2 3} and therefore the complexity of older adults' health statuses. The concept encompasses the simultaneous presence of an individual's diseases and their chronic physical, mental or behavioural health problems requiring ongoing management over years or decades.⁴

These long-term health conditions require taking multiple medications,⁵ known as polypharmacy (PP) when the daily intake

58

59 60 Filipa Pereira:

filipa.pereira@hevs.ch

Check for updates

Open access

1

2

3

4

5

6

7

8

9

6

corresponds to five or more medicines.⁶ PP places older adults at higher risk of medication-related problems (MRPs), including adverse medication reactions, medication errors and potentially inappropriate medications.⁷⁸ Potentially inappropriate medications are the intake of medicines for which the associated risks outweigh the potential benefits, particularly when more effective alternatives are available.⁹ Consequently, MRPs can lead to a degradation of the patient's clinical condition, phys-10 ical and cognitive decline, an exacerbation of chronic medical conditions and avoidable health costs.¹⁰¹¹ More-11 over, up to 25% of emergency department visits by home-12 dwelling OAMCC are due to MRPs.¹⁰ However, 60% of 13 14 MRPs in patients visiting the emergency department with 15 non-specific complaints (such as weakness) may go undiagnosed, whereas 83% of those MRPs may be responsible 16 for acute morbidity.¹⁰ MRPs are also a frequent cause 17 18 of readmission, and they were the most frequent cause 19 in one study that followed older patients for 6 months after hospital discharge.¹² Care-coordination problems, 20 21 associated with low or suboptimal medication manage-22 ment, are all the more evident in the sensitive period of 23 discharge home from hospital.^{11 13} The complexity of 24 OAMCC's care needs leads them to be significant users 25 of health services and to consult many different health-26 care professionals.¹⁴ The number of healthcare profes-27 sionals consulted by home-dwelling OAMCC has been 28 directly associated with fragmented and uncoordinated 29 care.¹³ Moreover, different healthcare professionals may 30 have different treatment preferences. Failure to coordi-31 nate care among home-dwelling OAMCC contributes to 32 MRPs.¹³ In addition to the role of healthcare professionals in

33 34 medication management, informal caregivers play a vital 35 role in ensuring safe and appropriate medication use by home-dwelling OAMCC, especially among those who may also have cognitive impairment.^{15–17} Despite the important 36 37 38 role of informal caregivers in medication management, 39 several complications to do with their activities have been 40 documented in relation to the time spent, anxiety making 41 a mistake and the uncooperative behaviour of the home-42 dwelling OAMCC.¹⁸ They are also confronted with diffi-43 culties in maintaining continuous supplies of medication, 44 assisting with administration, making clinical judgements 45 (eg, in response to side effects and about over-the-counter 46 medication), and solving conflictual communications or 47 disagreements with the older adult,¹⁸ or even with health-48 care professionals, with regard to ineffective and addic-49 tive medication practices.¹⁵¹⁸

Nonetheless, many MRPs are preventable.^{8 10 19} Studies 50 51 about medicine-related hospitalisations suggest that up to 52 58% may be preventable with appropriate primary care.⁸ 53 An essential strategy for medicine-related hospitalisations 54 prevention and medication safety is medication reconcil-55 iation—the process of creating and maintaining a single 56 list of the patient's current list of medications.²⁰ This 57 process allows a systematic and comprehensive review 58 of all the medications the patient is taking, reducing

medication errors by a consistent communication across transitions of care.²¹

Therefore, optimising medication management among home-dwelling OAMCC requires regular monitoring of MRPs, interprofessional collaboration across different health and social care providers, organisations and departments¹³ and medication reconciliation at every transition of care including changes in the clinical setting, practitioner or level of care.²²

Aim and objectives

This study's aim is to document the current state of medication management practices of polymedicated, homedwelling OAMCC and to make proposals for improving evidence-based clinical and medication pathways through an innovative, integrated model intended to support medication management and to prevent adverse health outcomes related to MRPs (recurrent hospitalisation, emergency department visits, institutionalisation in nursing homes and early death). To achieve this aim, three main objectives will guide this project:

The first objective is to carry out a retrospective analysis of patients' hospital records, their medication and environment-related factors in order to identify those that increase the risk of hospitalisation, emergency department visits, hospital readmission (notably due to MRPs), institutionalisation or early death, among home-dwelling polymedicated OAMCC-factors that prevent OAMCC from staying at home.

The second objective is to use a prospective qualitative study to explore and better understand the medication experiences and practices of home-dwelling OAMCC with different profiles. We seek to identify the skills and strategies developed by them to manage polymedication within their social contexts and health trajectories despite possible cognitive impairment and particularly after a recent hospitalisation.

The third objective is to better understand the roles and coordination of the different caregivers involved in the medication management of home-dwelling OAMCC. We seek to investigate the perspectives of both professional caregivers (community healthcare nurses, pharmacists, general practitioners or specialist physicians) and non-professional/informal caregivers (family members, friends or neighbours).

METHODS

Study design

To enable us to meet our objectives, a mixed-methods study will address the medication management of polymedicated, home-dwelling OAMCC.²³ Two major phases will be conducted sequentially from February 2019 to January 2022: a quantitative data collection phase followed by a qualitative phase. The reasons for using an explanatory sequential design are, first, that existing data in electronic patient records from a local hospital will enable us to identify profiles affected by similar

59

6

BMJ Open: first published as 10.1136/bmjopen-2019-030030 on 28 October 2019. Downloaded from http://bmjopen.bmj.com/ on November 12, 2019 at HES-SO Valais-Wallis - Fili?re Soins Infirmiers. Protected by copyright.

patient-related, medication-related and environment-re-2 lated factors among the polymedicated, home-dwelling 3 OAMCC at risk of hospitalisation, emergency depart-4 ment visits, hospital readmission (notably due to MRPs), 5 institutionalisation or early death. Second, the identi-6 fied profiles extracted from the hospital data will allow 7 proceeding to a purposive sampling-of those polymed-8 icated, home-dwelling OAMCC who present with more 9 risk factors-for the qualitative data collection focused 10 on medication management at home. Thus, the anal-11 ysis of the results from the retrospective quantitative 12 phase will be integrated with the data collected from the 13 prospective qualitative phase. Finally, phase 3 will develop 14 a Medication Management Model based on interpreting 15 the quantitative and qualitative findings. 16

17 Phase 1: retrospective quantitative analysis

18 To fulfil the first objective, the purpose of the quantita-19 tive phase is to identify the different profiles-made up of 20 patient-related, medication-related and environment-re-21 lated factors-of the polymedicated, home-dwelling 22 OAMCC at risk of hospitalisation, emergency department 23 visits, hospital readmission (notably for MRPs), institu-24 tionalisation in nursing homes or early death (before the 25 average age of death described by the Organisation for 26 Economic Cooperation and Development in 2018).²⁴ A 27 systematic, retrospective chart analysis of the electronic 28 patient records from a local hospital over the last 4 years 29 using the evidence-based methodology developed by 30 Vassar and Holzmann will provide substantial clinical information.²⁵ Motheral *et al*'s standardised extraction 31 32 sheets will be adapted to explore and assess the data of 33 older inpatients or emergency department-visiting home-34 dwelling older adults.²⁶ The 4-year analysis was selected 35 based on the availability of systematic, well-coded patient 36 data using the Swiss-Diagnostic Related Groups²⁷ and the 37 Swiss Classification of Surgical Interventions (CHOP).²⁸ 38

Research population

39

53

54

60

40 All home-dwelling OAMCC with somatic and/or mental 41 health disorders who were hospitalised, rehospitalised 42 or who consulted the emergency department (for MRPs 43 or other reasons) at the partner hospital between 2015 44 and 2018 (estimated n=50 000) will be included. The esti-45 mated sample of 50 000 older adults' electronic inpatient 46 charts are part of the 40 000 yearly adult inpatients in 47 acute care units and more than 40 000 adult emergency 48 department consultations yearly at the partner hospital. 49 To explore generalisability, we will compare their sociode-50 mographic and health status characteristics with those of 51 the national sample of hospitalised older adults in Swiss 52 hospitals for the same period.

Data collection

55 Data from the hospitalisation and emergency admissions 56 databases will be collected on patient-related, medica-57 tion-related and environment-related factors that could 58 have influenced the occurrence of MRPs that resulted in 59

hospitalisation, rehospitalisation or emergency department admission.

Patient-related factors comprise sociodemographic characteristics, the International Classification of Diseases 10th version (ICD-10) diagnostics (main diagnosis and comorbidities), the Swiss Classification of Surgical Interventions (CHOP) category and the reason for hospitalisation, rehospitalisation or emergency department admission. Supplementary filters will be added to discriminate polymedication, multimorbidity (secondary ICD-10 diagnosis), physical and cognitive impairment documented in the clinical data files (Function Independence Measure, Mini-Mental State Examination and Activities of Daily Living).

Medication-related factors include the number, types and changes in medication at admission, during hospitalisation and at discharge.

Environment-related factors include the presence of formal and/or informal caregivers, patient's provenance (rural or urban), hospital pathways (wards and eventual transfers), length of stay, readmissions (number of admissions in the previous year, 30-day readmission and unplanned readmission), discharge destination and, potentially, death during hospitalisation. A unique patient identification number will allow us to analyse rehospitalisations via the emergency department during the period from 2015 to 2018. Retrospective data collection began in April 2019.

Data analyses

The data set of polymedicated, home-dwelling OAMCC will be analysed using multivariate regression analysis, in order to identify the patient-related, medication-related and environment-related factors that can increase the risk of hospitalisation, emergency department visits, readmission (notably due to MRPs), institutionalisation or early death. Furthermore, the profiles of polymedicated, home-dwelling OAMCC hospitalised or visiting the emergency department due to MRPs, and identified via multicluster analysis, will serve to guide the qualitative study and lead to a purposive sampling of polymedicated, home-dwelling OAMCC presenting with more risk factors. A draft of the cluster analysis strategy is available as an online supplementary file.

Phase 2: prospective patient-centred qualitative analysis

To meet the second and third objectives, a qualitative investigation, based on purposive sampling, will draw on work done in a feasibility study.²⁹ This qualitative investigation will consist of collecting and understanding the medication practices and experiences of OAMCC presenting with the risk factors identified in the first phase. The focus will be on identified OAMCC who were recently hospitalised and are at risk of hospital readmission. The older adult will be interviewed at home on two separate occasions. This methodology is a way to analyse changes in their medication practises and their experiences following their recent hospitalisation. The data

2

3

4

5

6

7

8

9

22

23

24

25

26

27

28

29

30

31

32

33

collection tools include a walking-interview³⁰ based on a medication journal and household photographs of where medication is stored. This allows us to focus on the tangible practices of OAMCC and contextualises them within the private space of their daily lives.

To discriminate the older adults' health profile, we will use the Resident Assessment Instrument-Home Care (RAI-HC) introduced by the Swiss Association for Home Care Services for all home care services in 2004. Based on 10 a comprehensive geriatric assessment, the RAI-HC both 11 allows for the establishment of an individualised care 12 plan and generates quality indicators, plans resource use, 13 optimises the medication management process by moni-14 toring and documenting the number and types of medi-15 cation and the persons involved in preparing medication, 16 and regularly assesses adherence to the medication 17 prescribed.³¹ This instrument will provide information 18 on the patient-related, medication-related and environ-19 ment-related factors which may influence the occurrence 20 of MRPs, and it will be used to recruit OAMCC at risk of 21 or already presenting with MRPs.

Furthermore, we will also collect and analyse the perspectives of the formal and informal caregivers involved in medication management at home to cross-reference perspectives about this important dimension of care at home.

Research population

The profiles of the polymedicated OAMCC hospitalised/ rehospitalised or consulting the emergency department, as identified in the retrospective investigation, will be used to select participants for the qualitative investigation. A theoretical, purposive sampling will be carried out. Based on Guest et al, the principal investigator will

recruit about 30 polymedicated OAMCC (until saturation of data), all recently hospitalised (within the last 90 days) and at risk of hospital readmission.³² For each OAMCC participant, an informal caregiver will also be integrated into the investigation. We defined informal caregivers as any family member, neighbour or friend assisting a dependent older adult with certain activities in their daily life. That assistance, help, care or physical presence must be given on a regular basis, for at least two basic activities or instrumental activities of daily living or to ensure patient safety, and for 6 months or more.³³ The informal caregiver will be included in the study if the recruited older adult identifies that person as being significant in their medication management and if they give informed written consent to participate.

Furthermore, a formal caregiver will be integrated into the investigation for each participant. Professional caregivers are those employed to provide professional healthcare services (ie, nurses, nursing assistants, general practitioners, pharmacists and social workers). They will be included in the study if the recruited OAMCC identifies them as the professional most involved in their medication management.

Table 1 presents the specific inclusion/exclusion criteria for each group of participants.

Participant recruitment

Polymedicated, home-dwelling OAMCC will be recruited via two paths so that all of the participants meet the eligibility criteria and fit corresponding profiles established in the quantitative phase. Some OAMCC will be receivers of care from Community Healthcare Centres and others will be functioning without that day-to-day support.

Participants	Inclusion criteria	Exclusion criteria
OAMCC	 Aged 65 or above Man or woman Hospitalised within the last 90 days Managing at least five different medications (prescribed and over-the- counter medications explored during recruitment) Suffering from multiple chronic conditions⁴ Living alone or in a couple, in a rural or urban area With or without support from a Community Healthcare Centre 	Not able to speak and understand French
Informal caregiver	 Designated by the OAMCC as the most significant informal caregiver involved in medication management Aged 18 or above 	 Not able to speak and understan French
Professional caregiver	 Designated by the OAMCC as having a key role in medication management 	A StudentApprentice

2

3

4

5

22

- ► For OAMCC who do not receive support from a Community Healthcare Centre, recruitment will be based on variables in their patient files and carried out in collaboration with different nursing departments from the partner hospital.
- For OAMCC who do receive support from a Community Healthcare Centre, recruitment will be based on the clinical and health data documented in the RAI-HC and carried out in collaboration with community healthcare nurses from Sion Community Healthcare Centre.

12 Research nurses partnering the project, from a hospital 13 or a Community Healthcare Centre, will briefly explain 14 the study to the patient. Potential participants will be 15 asked for permission to give their name to the researchers. 16 The principal investigator will contact the older adult by 17 telephone during the week following hospital discharge 18 and ask for their agreement to participate in the study. 19 In case of agreement, a first meeting will be organised at 20 the older adult's home in the next few days. Participant 21 recruitment will start in October 2019.

23 Data collection from OAMCC

24 During the first home meeting with the OAMCC, the 25 principal investigator will provide all the study details and 26 will suggest two semistructured interviews, each lasting 27 about an hour, starting on the first meeting and spaced 28 2-3 weeks apart. According to participants' levels of tired-29 ness, it may be necessary to subdivide the interviews. The 30 older adult will be invited to sign the informed written 31 consent form, allowing the researcher to collect sociode-32 mographic and health data (RAI-HC and the patient's 33 hospital records). Eligible home-dwelling OAMCC from 34 both recruitment paths will be screened using the RAI-HC 35 Minimal Data Set (MDS), which includes information on 36 polymedication (section P), multiple chronic conditions 37 (sections J and K) and recent hospitalisation (section Ac). 38 Research team members trained on the RAI-HC will also 39 carry out this evaluation for participants who do not have 40 an RAI-HC. The following multidimensional clinical data 41 will be retrieved from the RAI-HC MDS: cognitive status, 42 hearing, vision, mood status, functional and physical 43 status, continence, healthcare problems and nutritional 44 state. The MDS will aid interviews with OAMCC and the 45 exploration of the facilitators and barriers to daily medi-46 cation management.

47 The first semistructured interview will collect the 48 perspectives of OAMCC with regard to their medi-49 cation management, the return home, information 50 received about their treatment and its possible modifi-51 cations, whether their opinions and preferences were 52 taken into account in the prescription of medications, 53 and the informal and professional caregivers involved. 54 OAMCCs will be interviewed alone or with an informal 55 caregiver, if necessary. The principal investigator will 56 then ask the participant to complete a week-long medi-57 cation journal,^{34 35} either alone or with the help from 58 informal or professional caregivers, emphasising that any

information on daily medication routines is helpful, even if the OAMCC feels unable to complete the journal for the full 7 days. The instructions will mention the importance of noting all the medicines taken—those prescribed by general practitioners or specialist physicians, but also any others taken at their own initiative (over-the-counter medications). Participants will be asked to note their perceptions of and satisfaction with their treatment in a week-long medication journal. This will provide information on the daily routines associated with the participant's medication and will form the basis of the second interview.

The second interview will be based on the participant's medication journal and will take the form of a walking-interview³⁶ using household photographs.³⁵ The principal investigator will ask the participant to explain their medication practises while pointing out the locations within their home where drugs are stored, prepared and taken. The hypothesis underlying this methodology is that the physical presence of drugs promotes discussion.^{37 38} We will identify and photograph, with the participants' agreement, the places where medication, contact details for medical professionals and other information are stored as well as the locations of any other objects involved in daily care practises. The collection and analysis of photographs provide a better understanding of the complexity of medication management in home settings. They help to capture the interviewee's concerns or strategies when they are pointed out to the interviewer. The interview guide will also investigate the issue of self-medication in order to reveal the extent and influence of this practice.

Data collection from informal caregivers

Sociodemographic data and information related to medication management will be collected. When possible and appropriate, a joint third interview³⁹ with the OAMCC and their principal informal caregiver³⁴ will be organised at the older adult's home 1–2 weeks after the walking interview. This type of interview provides access to the interactions between OAMCC and their informal caregivers with regard to medication management. We hypothesise that the main informal caregiver is deeply involved in the older adult's experience of medication management, but the caregiver's ideas about this may be similar to, overlapping with or different from those of an OAMCC.

Data collection from professional caregivers

A semistructured interview of about 1 hour will be conducted with a professional caregiver in order to explore their point of view on the OAMCC's medication management and other issues associated with the return home after hospitalisation. In agreement with the project's field partners and stakeholders, these interviews will take place in professionals' workplaces (Community Healthcare Centre, medical practice office or pharmacy), during working hours, 1–2 weeks after the interview with the OAMCC and their informal caregiver.

Qualitative data analyses

1 2

3

4

5

6

7

8

9

A database will be prepared using the RedCap software platform to record and store the participants' sociodemographic, health and interview data. Information on their health statuses will be collected using the RAI-HC data and will be analysed using the IBM-Statistical Package for Social Sciences V.25.0.

Data collected via the interviews will be examined according to an analytical plan that integrates and 10 compares two different methods. First, thematic content analysis,40 41 using NVivo V.12 software, will be used to 11 12 identify the themes emerging from the data, and this will 13 provide a rich, detailed account of the data set. Themes 14 will be compared by different members of the analysis 15 team until a consensus is reached. Second, lexicometric 16 analysis, using Iramuteg software—a technique derived 17 from the Alceste method⁴²—will allow a very fine explo-18 ration, both within each interview and across the whole 19 corpus of interviews, of the structures underlying the 20 discourse. Each older adult's medication journal will be 21 analysed and categorised according to the same prin-22 ciples as the interviews. The data collected from these 23 documents will be put into perspective by the analysis 24 of the interviews. In the final data analysis, links will be 25 made between the interviews, the medication journal, the 26 older adult's RAI-HC data and the photos of the medi-27 cines' locations. 28

29 Phase 3: development of a medication management model

30 Connecting retrospective and prospective findings, 31 using an explanatory sequential design and participants' 32 different perspectives, will contribute to a deep under-33 standing of the current state of medication management 34 practices of polymedicated, home-dwelling OAMCC. This 35 mixed-methods study corresponds to the 'diagnostic' 36 phase of the process of developing a Model of Care, as 37 presented by the Agency for Clinical Innovation (ACI).⁴³ 38 It will guide the 'solution design' phase-the next step 39 in the creation of an innovative, integrated model for 40 supporting medication management and preventing 41 adverse health outcomes. In addition to the ACI's 42 framework, the development of a proposed Medication 43 Management Model will consider the quadruple aim of 44 enhancing the patient's experience, improving popula-45 tion health, reducing costs and improving the working 46 lives of healthcare providers.⁴⁴

47 Finally, our mixed-methods research findings will be 48 completed with those of an ongoing systematic review of 49 Medication Management Models.⁴⁵ 50

The study phase outcomes are summarised in table 2.

Patient and public involvement

53 This study and the feasibility study on which it is based 54 were developed in collaboration with representatives from 55 a Community Healthcare Centre, a regional hospital, 56 medical and pharmacy associations and an informal care-57 givers association. They shared their expertise on the 58 study's relevance and the feasibility of data collection with 59

Table 2 C	Outcomes for each study phase
Phase 1 outcomes	Patient-related, medication-related and environment-related factors which can increase the risk of hospitalisation, emergency department visits, hospital readmission (notably due to MRPs), institutionalisation or early death. Profiles of polymedicated, home-dwelling OAMCC hospitalised or visiting the emergency department due to MRPs based on the previously identified patient-related, medication-related and environment-related factors.
Phase 2 outcomes	 For OAMCC participants: Patient-related, medication-related and environment-related factors for MRPs (defined by phase 1's outcomes) extracted from the RAI-HC MDS and the patient's electronic hospital records (number and types of medication, multiple chronic conditions, recent hospitalisations, cognitive status, hearing, vision, mood status, functional and physical status, continence, healthcare problems and nutritional state). Medication practices and experiences of OAMCC following their recent hospitalisation, facilitators/barriers to medication management, informal and professional caregivers involved. For informal caregivers: Sociodemographic profiles. Practices and experiences related to medication management. For professional caregivers: Sociodemographic and professional profiles. Role and perspectives on OAMCC medication management. Coordination activities related to returning home after hospitalisation.
Phase 3 outcomes	 Three first steps in the process of developing a Model of Care⁴³: 'Project initiation'. 'Diagnostic'. 'Solution design' considering the quadruple aim. Proposals for the Medication Management Model's 'Implementation' and 'Sustainability' steps⁴³ to support medication management and to prevent adverse health outcomes related to MRPs. mal Data Set; MRPs, medication-related problems;

MDS, Minimal Data Set; MRPs, medication-related problems: OAMCC, older adults living with multiple chronic conditions; RAI-HC, Resident Assessment Instrument-Home Care.

the research team. Patients' priorities, experiences and preferences, collected during the feasibility study, were the drivers for the development of the research question and outcome measures.

A steering committee will involve these different actors at various stages in the project, both to contribute to data collection and to provide their expertise to the coconstruction of a Medication Management Model and its future implementation. As regards data collection, the hospital's medical informatics department will provide the appropriate data based on a data extraction protocol (phase 1) and the Community Healthcare

51

52

2

3

4

5

6

7 8

9

Centre will help with OAMCC recruitment and access to participants' RAI-HC and professional caregivers (phase 2).

Results will be disseminated to study participants through presentations to associations of patients and informal caregivers and at professional training sessions.

10 ETHICS AND DISSEMINATION

11 With the approval, the medical informatics department 12 of partner hospital will provide the appropriate data 13 for the retrospective phase based on a data extraction 14 protocol. Extracted data will be delivered and stored in 15 the ReDCap data platform via a secure coded data file. In 16 coherence with the Data Management Plan submitted to 17 the Swiss National Science Foundation, the collected data 18 will be securely stored for future research.

19 The autonomy of the participants will be respected. 20 Participation in the prospective phase in this research is 21 free. It will be possible for participants to refuse to record 22 the interview or to request the deletion of the recorded 23 data. Participating in a structured effort to understand 24 medication practises and the posthospital return home 25 experience can contribute to improvements in health 26 management in the community at large, and particularly 27 in the area of home support.

Findings will be disseminated in peer-reviewed journals, professional conferences and other knowledge transfer activities with primary healthcare providers, hospital care units, informal caregiver and patient associations.

Author affiliations

34

60

- 35 ¹School of Health Sciences, HES-SO Valais-Wallis, Sion, Switzerland
- 36 ²Institute of Biomedical Sciences Abel Salazar, University of Porto, Porto, Portugal
- ³Research Center for Psychology of Health, Aging and Sport Examination, University of Lausanne, Lausanne, Switzerland
- 38 ⁴Service of Old Age Psychiatry, Lausanne University Hospital, Lausanne, Switzerland
- ⁵Swiss Centre of Expertise in the Social Sciences, University of Lausanne, FORS,
 Lausanne, Switzerland
- 40
 Lausanne, Switzerland

 41
 ⁶Higher School of Nursing of Porto, Porto, Portugal
- 42 Twitter Maria Manuela Martins @mmmartins1956
- 43
 44
 44
 45
 46
 46
 47
 48
 48
 49
 49
 49
 49
 49
 40
 40
 40
 41
 41
 42
 43
 44
 44
 45
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 47
 47
 48
 48
 49
 49
 49
 49
 40
 40
 41
 41
 44
 44
 44
 45
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 47
 47
 48
 48
 49
 49
 49
 40
 40
 41
 41
 41
 42
 44
 44
 45
 46
 46
 46
 46
 46
 46
 46
 46
 47
 47
 48
 48
 49
 49
 49
 49
 40
 40
 41
 41
 41
 44
 44
 44
 44
 44
 45
 46
 46
 46
 46
 47
 47
 48
 48
 49
 49
 49
 49
 49
 40
 40
 40
 40
 41
 41
 41
 44
 44
 44
 44
 44
 45
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 46
 <
- 47 Funding This work is supported by the Swiss National Science Foundation grant
 48 number 407440_183434/1.
- 49 **Competing interests** None declared.
- 50 Patient consent for publication Not required.
- 51
 52 Ethics approval Ethical approval has been obtained from the Human Research Ethics Committee of the Canton Vaud (2018-02196).
- 53 Provenance and peer review Not commissioned; externally peer reviewed.
- 54 Data availability statement Data are available upon reasonable request.
- Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is

properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD

Filipa Pereira http://orcid.org/0000-0001-9207-4856

REFERENCES

- 1 Bachmann N, Burla L, Kohler D, et al. La santé en Suisse-Le point sur les maladies chroniques: Rapport national sur la santé 2015. Retrieved from Berne: & Older people's experiences of medicine changes on leaving hospital. Research in Social and Administrative Pharmacy 2015;10:791-800.
- 2 Marengoni A, Angleman S, Melis R, et al. Aging with multimorbidity: a systematic review of the literature. Ageing Res Rev 2011;10:430–9.
- 3 Valderas JM, Starfield B, Sibbald B, et al. Defining comorbidity: implications for understanding health and health services. Ann Fam Med 2009;7:357–63.
- 4 WHO. Innovative care for chronic conditions: building blocks for action: global report. Geneva: World Health Organization, 2002.
- 5 Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. *Expert Opin Drug Saf* 2014;13:57–65.
- 6 Masnoon N, Shakib S, Kalisch-Ellett L, et al. What is polypharmacy? A systematic review of definitions. *BMC Geriatr* 2017;17:1–10.
- 7 Monégat M, Rococo E. Polypharmacy: definitions, measurement and stakes involved. Review of the literature and measurement tests, 2014.
- 8 Al Hamid A, Ghaleb M, Aljadhey H, *et al*. A systematic review of hospitalization resulting from medicine-related problems in adult patients. *Br J Clin Pharmacol* 2014;78:202–17.
- 9 Renom-Guiteras A, Meyer G, Thürmann PA. The EU(7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries. *Eur J Clin Pharmacol* 2015;71:861–75.
- 10 Nickel CH, Ruedinger JM, Messmer AS, et al. Drug related emergency department visits by elderly patients presenting with nonspecific complaints. Scand J Trauma Resusc Emerg Med 2013;21:15.
- 11 Fallis BA, Dhalla IA, Klemensberg J, *et al.* Primary medication nonadherence after discharge from a general internal medicine service. *PLoS One* 2013;8:e61735.
- 12 Bonnet-Zamponi D, d'Arailh L, Konrat C, *et al.* Drug-Related readmissions to medical units of older adults discharged from acute geriatric units: results of the optimization of medication in aged multicenter randomized controlled trial. *J Am Geriatr Soc* 2013;61:113–21.
- 13 Gilbert A, Roughead L, McDermott R, et al. Multiple Chronic Health Conditions in Older People: Implications for Health Policy Planning, Practitioners and Patients. University of South Australia 2013 [Ageing well ageing productively: people living with multiple chronic health conditions [1-48]. Available: https://www.unisa.edu.au/siteasets/ episerver-6-files/global/health/sansom/documents/qumprc/multiplechronic-health-conditions.pdf
- 14 Roughead EE, Vitry AI, Caughey GE, *et al*. Multimorbidity, care complexity and prescribing for the elderly. *Aging Health* 2011;7:695–705.
- 15 O'Quin KE, Semalulu T, Orom H. Elder and caregiver solutions to improve medication adherence. *Health Educ Res* 2015;30:323–35.
- 16 Gillespie R, Mullan J, Harrison L. Managing medications: the role of informal caregivers of older adults and people living with dementia. A review of the literature. *J Clin Nurs* 2014;23:3296–308.
- 17 Look KA, Stone JA. Medication management activities performed by informal caregivers of older adults. *Res Social Adm Pharm* 2018;14:418–26.
- 18 Reinhard SC, Levine C, Samis S. Home alone: family caregivers providing complex chronic care. BMJ 2012;41.
- 19 Pellegrin KL, Lee E, Uyeno R, et al. Potentially preventable medication-related hospitalizations: a clinical pharmacist approach to assessment, categorization, and quality improvement. J Am Pharm Assoc 2017;57:711–6.
- 20 Almanasreh E, Moles R, Chen TF. The medication reconciliation process and classification of discrepancies: a systematic review. Br J Clin Pharmacol 2016;82:645–58.
- 21 IHI. How-to guide: prevent adverse drug events by implementing medication reconciliation. Cambridge, Massachusetts, USA: Institute for Healthcare Improvement, 2011.
- 22 Barnsteiner JH, Reconciliation M. Medication reconciliation. In: Hughes RG, ed. *Patient safety and quality: an evidence-based Handbook for nurses*. Rockville (MD), 2008.

Open access

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

- 23 Creswell JW, Plano Clark VL. Improving medication management in home care: issues and solutions, 2011.
- 24 OECD. Health Status : Life expectancy, 2018. Available: https://stats. oecd.org/index.aspx?gueryid=30114 [Accessed 1 Aug 2019].
- 25 Vassar M, Holzmann M. The retrospective chart review: important methodological considerations. J Educ Eval Health Prof 2013;10:12.
- 26 Motheral B, Brooks J, Clark MA, et al. A checklist for retrospective database studies--report of the ISPOR Task Force on Retrospective Databases. Value Health 2003;6:90-7.
- 27 Holzer B. SwissDRG - L'essentiel en bref. Bulletin des médecins suisses 2012:93:1079-81.
- 28 OFS. Classification Suisse des interventions Chirurgicales (CHOP). Office fédéral de la statistique, 2018.
- 29 Roux P. Pereira F. Santiago-Delefosse M. et al. Medication practices and experiences of older adults discharged home from Hospital: a feasibility study protocol. Patient Prefer Adherence 2018;12:1055-63.
- 30 Evans J, Jones P. The walking interview: methodology, mobility and place. Applied Geography 2011;31:849-58.
- Monod S, Büla C, Hongler T, et al. Le Resident Assessment 31 Instrument-Home-Care (RAI-Domicile) : ce que le médecin de premier recours doit savoir. Revue Médicale Suisse 2011;7:2176-83.
- Guest G, Bunce A, Johnson L. How many interviews are enough? 32 Field methods 2006;18:59-82.
- 33 ÉD V. Commission consultative du soutien aux proches aidants. État de Vaud 2018.
- Knight DA, Thompson D, Mathie E, et al. 'Seamless care? Just a list 34 would have helped!' older people and their carer's experiences of support with medication on discharge home from hospital. Health Expect 2013;16:277-91.

- Dew K, Chamberlain K, Hodgetts D, et al. Home as a hybrid centre of 35 medication practice. Sociol Health Illn 2014;36:28-43.
- Carpiano RM. Come take a walk with me: the "go-along" interview as a novel method for studying the implications of place for health and well-being. Health Place 2009:15:263-72.
- 37 Fainzang S. Les médicaments dans l'espace privé. Anthropologie et Sociétés 2003;27.
- 38 Haxaire C. « Calmer les nerfs » : automédication, observance et dépendance à l'égard des médicaments psychotropes. Sciences sociales et santé 2002;20:63-88.
- Polak L, Green J. Using joint interviews to add analytic value. Qual 39 Health Res 2016:26:1638-48.
- 40 Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006;3:77-101.
- Elo S, Kyngäs H. The qualitative content analysis process. J Adv 41 Nurs 2008:62:107-15.
- 42 Ratinaud P, Déjean S. IRaMuTeQ: implémentation de la méthode ALCESTE d'analyse de texte dans un logiciel libre. Modélisation Appliquée aux Sciences Humaines et Sociales 2009:8-9.
- ACI. Understanding the process to develop a model of care: an ACI framework. Chatswood: Agency for Clinical Innovation, 2013.
- Bodenheimer T, Sinsky C. From triple to quadruple aim: care of the 44 patient requires care of the provider. Ann Fam Med 2014;12:573-6.
- Janu. So Just a lis. So Just A Health Pereira F, Roux P, Rosselet Amoussou J, et al. Medication management models for Polymedicated home-dwelling older adults with multiple chronic conditions: protocol of a systematic review.

Page 32 of 38

6

Page 33 of 38

BMJ Open

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items ar reported
Title and abstra	ct				-
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b)Provide in the abstract an informative and balanced		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included.	Title Abstract (lines 2 8)
		summary of what was done and what was found	Pr	RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract.	Line 6 Lines 118-121
			· e/;e	RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Not applicable, only one hospit register
Introduction		1	1		1
Background rationale	2	Explain the scientific background and rationale for the investigation being reported		5/1	Lines 39-101
Objectives	3	State specific objectives, including any prespecified hypotheses			Lines 101-107
Methods			1		
Study Design	4	Present key elements of study design early in the paper			Lines 110-114
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			Lines 117-133

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using

Participants	6	(a) Cohort study - Give the	RECORD 6.1: The methods of study	in press/
1		eligibility criteria, and the	population selection (such as codes or	forthcoming
		sources and methods of selection	algorithms used to identify subjects)	JMIR article:
		of participants. Describe	should be listed in detail. If this is not	https://www.ncl
		methods of follow-up	possible, an explanation should be	nlm.nih.gov/pul
		<i>Case-control study</i> - Give the	provided.	ed/management
		eligibility criteria, and the	1	alidator/909A44
		sources and methods of case	RECORD 6.2: Any validation studies	74F70/citations
		ascertainment and control	of the codes or algorithms used to	tart=0
		selection. Give the rationale for	select the population should be	
		the choice of cases and controls	referenced. If validation was conducted	
		<i>Cross-sectional study</i> - Give the	for this study and not published	
		eligibility criteria, and the	elsewhere, detailed methods and results	
		sources and methods of selection	should be provided.	
		of participants	1	
			RECORD 6.3: If the study involved	
		(b) Cohort study - For matched	linkage of databases, consider use of a	Not applicable,
		studies, give matching criteria	flow diagram or other graphical display	only one hospit
		and number of exposed and	to demonstrate the data linkage	register
		unexposed	process, including the number of	C
		<i>Case-control study</i> - For	individuals with linked data at each	
		matched studies, give matching	stage.	
		criteria and the number of		
		controls per case		
Variables	7	Clearly define all outcomes,	RECORD 7.1: A complete list of codes	Lines 152-177
		exposures, predictors, potential	and algorithms used to classify	and
		confounders, and effect	exposures, outcomes, confounders, and	in press/
		modifiers. Give diagnostic	effect modifiers should be provided. If	forthcoming
		criteria, if applicable.	these cannot be reported, an	JMIR article:
			explanation should be provided.	https://www.nc
				<u>nlm.nih.gov/pu</u>
				ed/managemen
				alidator/909A4
				74F70/citations
				<u>tart=0</u>
Data sources/	8	For each variable of interest,		Lines 122-128
measurement		give sources of data and details		and

		of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group			in press/ forthcoming JMIR article: <u>https://www.n</u> nlm.nih.gov/p ed/management alidator/909Ad 74F70/citation tart=0
Bias	9	Describe any efforts to address potential sources of bias	or revio		Lines 180-200 and in press/ forthcoming JMIR article: <u>https://www.n</u> nlm.nih.gov/p ed/manageme alidator/909A 74F70/citation tart=0
Study size	10	Explain how the study size was arrived at	C.	2	Lines 141-144
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why		- 7/2	Lines 139-150 and in press/ forthcoming JMIR article: <u>https://www.n</u> nlm.nih.gov/p ed/management alidator/909Aa 74F70/citation tart=0

Statistical methods	12	 (a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> - If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> - If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses 			Lines 180-200
Data access and cleaning methods			2	RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Lines 118-122 and in press/ forthcoming JMIR article: https://www.ncbi. nlm.nih.gov/pubm ed/management/v alidator/909A44E 74F70/citations/?s tart=0
Linkage				RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of	in press/ forthcoming JMIR article: <u>https://www.ncbi.</u> <u>nlm.nih.gov/pubm</u>

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

				linkage quality evaluation should be provided.	ed/manageme alidator/909A 74F70/citation tart=0
Results					
Participants	13	 (a) Report the numbers of individuals at each stage of the study (<i>e.g.</i>, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non- participation at each stage. (c) Consider use of a flow diagram 	2	RECORD 13.1: Describe in detail the selection of the persons included in the study (<i>i.e.</i> , study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Lines 142-143
Descriptive data	14	 (a) Give characteristics of study participants (<i>e.g.</i>, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) <i>Cohort study</i> - summarise follow-up time (<i>e.g.</i>, average and total amount) 	revie	201/2	Lines 152-177
Outcome data	15	Cohort study - Report numbersof outcome events or summarymeasures over timeCase-control study - Reportnumbers in each exposurecategory, or summary measuresof exposureCross-sectional study - Reportnumbers of outcome events orsummary measures			Lines 142-144

Page 3	38 of	38
--------	-------	----

Main results	16	 (a) Give unadjusted estimates and, if applicable, confounder- adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period 			Lines 207-285
Other analyses	17	Report other analyses done— e.g., analyses of subgroups and interactions, and sensitivity analyses			Lines 207-285
Discussion					
Key results	18	Summarise key results with reference to study objectives			Lines 289-294
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	2	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Lines 369-378
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			Lines 294-361

Generalisability	21	Discuss the generalisability		Lines 349-355
		(external validity) of the study		
		results		
Other Information	on			
Funding	22	Give the source of funding and		Line 399
		the role of the funders for the		
		present study and, if applicable,		
		for the original study on which		
		the present article is based		
Accessibility of		🔨	RECORD 22.1: Authors should	in press/
protocol, raw			provide information on how to access	forthcoming
data, and			any supplemental information such as	JMIR article:
programming			the study protocol, raw data, or	https://www.ncbi
code			programming code.	nlm.nih.gov/pubi
				ed/management/v
				alidator/909A441
				74F70/citations/?
				tart=0

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. PLoS Medicine 2015; in press.

*Checklist is protected under Creative Commons Attribution (CC BY) license.

BMJ Open

Risks of 30-day hospital readmission associated with medical conditions and drug regimens of polymedicated, older inpatients discharged home: a registry-based cohort study

Journal:	BMJ Open
Manuscript ID	bmjopen-2021-052755.R1
Article Type:	Original research
Date Submitted by the Author:	19-Jun-2021
Complete List of Authors:	Pereira, Filipa; University of Porto, Institute of Biomedical Sciences Abel Salazar; HES-SO University of Applied Sciences and Arts Western Switzerland, School of Health Sciences Verloo, Henk; HES-SO University of Applied Sciences and Arts Western Switzerland, School of Health Sciences; Lausanne University Hospital, Service of Old Age Psychiatry Zhivko, Taushanov; University of Geneva Di Giovanni, Saviana; HES-SO University of Applied Sciences and Arts Western Switzerland, School of Health Sciences; Pharmacy Benu Tavil- Chatton Meyer-Massetti, Carla; University of Bern, Institute for Primary Health Care Von-Gunten, Armin; Lausanne University Hospital, Service of Old Age Psychiatry Martins, Maria Manuela; Porto Higher School of Nursing; University of Porto, Institute of Biomedical Sciences Abel Salazar Wernli, Boris; University of Lausanne, FORS, Swiss Centre of Expertise in the Social Sciences
Primary Subject Heading :	Geriatric medicine
Secondary Subject Heading:	Epidemiology, Health informatics
Keywords:	GERIATRIC MEDICINE, CLINICAL PHARMACOLOGY, EPIDEMIOLOGY

SCHOLARONE[™] Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our <u>licence</u>.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which <u>Creative Commons</u> licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

reziez onz

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Risks of 30-day hospital readmission associated with medical conditions and drug regimens of polymedicated, older inpatients discharged home: a registry-based cohort study

Pereira Filipa¹, Verloo Henk², Taushanov Zhivko³, Di Giovanni Saviana⁴, Meyer-Massetti Carla⁵, von Gunten Armin⁶, Martins Maria Manuela⁷, Wernli Boris⁸

¹Institute of Biomedical Sciences Abel Salazar, University of Porto
Rua de Jorge Viterbo Ferreira, 228 4050-313 Porto, Portugal
School of Health Sciences, HES-SO University of Applied Sciences and Arts Western Switzerland
5, Chemin de l'Agasse, CH-1950 Sion, Switzerland
Email: <u>filipa.pereira@hevs.ch</u>; Phone: +41 78 666 17 00; Fax: +41 27 606 84 00
ORCID: https://orcid.org/0000-0001-9207-4856

² School of Health Sciences, HES-SO University of Applied Sciences and Arts Western Switzerland
5, Chemin de l'Agasse, CH-1950 Sion, Switzerland
Service of Old Age Psychiatry, Lausanne University Hospital
Email: <u>henk.verloo@hevs.ch</u>; Phone: +41 27 606 84 34
ORCID: <u>http://orcid.org/0000-0002-5375-3255</u>

³University of Geneva CH-1205 Geneva, Switzerland Email: <u>zhivko.taushanov@unige.ch</u> ORCID: https://orcid.org/0000-0002-3798-757X

⁴ School of Health Sciences, HES-SO University of Applied Sciences and Arts Western Switzerland 5, Chemin de l'Agasse, CH-1950 Sion, Switzerland Pharmacy Benu Tavil-Chatton Grand rue 11, CH-1110 Morges, Switzerland Email: saviana.digiovanni@gmail.com

⁵Institute for Primary Health Care, University of Bern Mittelstrasse 43, CH-3012 Bern, Switzerland Email: <u>carla.meyer-massetti@biham.unibe.ch</u> ORCID: https://orcid.org/0000-0002-3523-5729

⁶ Service of Old Age Psychiatry,

f 32	BMJ Open
	Lausanne University Hospital
	Route de Cery 60, 1008 Prilly, Switzerland Email: <u>armin.von-gunten@chuv.ch;</u> Phone: +41 21 314 52 67
	ORCID: <u>https://orcid.org/0000-0001-7852-3803</u>
	⁷ Higher School of Nursing of Porto
	Institute of Biomedical Sciences Abel Salazar, University of Porto
	Rua Dr. António Bernardino de Almeida
	4200-072 Porto, Portugal
	Email: mmartins@esenf.pt; Phone: +351 22 507 35 00
	ORCID: https://orcid.org/0000-0003-1527-9940
	⁸ FORS, Swiss Centre of Expertise in the Social Sciences, University of Lausanne
	Géopolis, CH-1015 Lausanne, Switzerland
	Email: boris.wernli@fors.unil.ch; Phone: +41 21 692 37 23
	ORCID: https://orcid.org/0000-0002-5567-1317
	Corresponding author: Pereira F
	Institute of Biomedical Sciences Abel Salazar, University of Porto
	Rua de Jorge Viterbo Ferreira, 228 4050-313 Porto, Portugal
	School of Health Sciences, HES-SO University of Applied Sciences and Arts Western Switzerland
	5, Chemin de l'Agasse, CH-1950 Sion, Switzerland
	Email: <u>filipa.pereira@hevs.ch;</u> Phone: +41 78 666 17 00; Fax: +41 27 606 84 00
	ORCID: https://orcid.org/0000-0001-9207-4856

3		
4 5	1	Abstract
6	2	Objectives: The present study analysed four years of a hospital register (2015–2018) to determine the
7	3	risks of 30-day hospital readmission associated with the medical conditions and drug regimens of
8 9	4	polymedicated, older inpatients discharged home.
10	5	Design: Registry-based cohort study.
11 12	6	Setting: Valais Hospital—a public general hospital centre in the French-speaking part of Switzerland.
13	7	Participants: We explored the electronic records of 20,422 inpatient stays by polymedicated, home-
14 15	8	dwelling older adults held in the hospital's patient register. We identified 13,802 hospital readmissions
16	9	involving 8,878 separate patients over 64 years old.
17	10	Outcome measures: Sociodemographic characteristics, medical conditions and drug regimen data
18 19	11	associated with the risk of readmission within 30 days of discharge.
20	12	Results: The overall 30-day hospital readmission rate was 7.8%. Adjusted multivariate analyses revealed
21 22	13	increased risks of hospital readmission for patients with longer hospital lengths of stay (OR = 1.014 per
23	14	additional day; 95% CI: 1.006–1.021), impaired mobility (OR = 1.218 ; 95% CI: 1.039–1.427),
24 25	15	multimorbidity (OR = 1.419 per additional ICD-10 condition; 95% CI: 1.282–1.572), tumoural disease
26	16	(OR = 2.538; 95% CI: 2.089–3.082), polypharmacy (OR = 1.043 per additional drug prescribed; 95% CI:
27 28	17	1.028–1.058), and certain specific drugs, including antiemetics and antinauseants (OR = 3.216 per
28 29	18	additional drug unit taken; 95% CI: 1.842–5.617), antihypertensives (OR = 1.771; 95% CI: 1.287–2.438),
30	19	drugs for functional gastrointestinal disorders (OR = 1.424; 95% CI: 1.166–1.739), systemic hormonal
31 32	20	preparations (OR = 1.207; 95% CI: 1.052–1.385), and vitamins (OR = 1.201; 95% CI: 1.049–1.374), as
33	21	well as the concurrent use of beta-blocking agents and drugs for acid-related disorders (OR = 1.367;
34 35	22	95% CI: 1.046–1.788). Conclusions: Thirty-day hospital readmission risks were associated with longer
36	23	hospital length of stay, health disorders, polypharmacy and drug regimens. The drug regimen patterns
37 38	24	increasing the risk of hospital readmission were very heterogeneous. Further research is needed to explore
39	25	hospital readmissions caused solely by specific drugs and drug-drug interactions.
40	26	
41 42	27	Keywords: polypharmacy; odds ratio; logistic regression; hospital register; ATC Classification System;
43	28	adverse-drug events; hospital readmission.
44 45	29	
46	30	Strengths and limitations of this study:
47 48	31	• The records of 20,422 hospitalisations involving 8,878 different polymedicated home-dwelling
49	32	older patients readmitted to hospital at least once were studied to determine the risks of 30-day
50 51	33	hospital readmission.
52	34	• The study included four years' data from a comprehensive hospital register (2015–2018).
53	35	• A whole series of sociodemographic and clinical parameters, medical conditions and prescribed
54 55	36	drugs were used to predict the probability of hospital readmission.
56	37	Analyses were correlational and causality was not explored.
57 58		
59		
60		

39

40 41

51

1

BMJ Open

2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16 17	
17	
18 10	
19 20	
20 21	
∠ I 22	
22 23	
24	
24 25	
26	
20	
28	
29	
30	
31	
32	
33	
34	
35	
36 37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	
51	
52	
53	
54	
55 56	
56	
57	
58 50	
59 60	
nU	

Although the study considered statistical associations between drugs and hospital readmissions, it did not consider clinically diagnosed drug-drug interactions.

42 Introduction

43 Longitudinal studies have demonstrated that approximately 20% of the home-dwelling older adults 44 supported by home health-care services experienced hospital readmission within 30 days of their 45 discharge (1-3). For many older adults, readmission to an acute hospital is associated with a functional 46 decline that has not always recovered by the time they are discharged (4). However, the systematic review 47 by Hansen et al. revealed wide-ranging estimates (5%-79%) of how many hospital readmissions were 48 preventable (5). The period between hospital discharge and readmission has not always been clearly 49 stated in the literature, ranging from 30 days to 3 years. However, 30 days is the most frequently used in 50 public health policy when measuring health-care system performance (6-8).

52 Numerous determinants have been identified and associated with hospital readmissions, e.g. 53 sociodemographic and individual characteristics, multimorbidity and medical events (9, 10). A substantial 54 risk of 30-day hospital readmission has been associated with older inpatients treated for different diseases 55 and surgical interventions involving hip fracture, cancer, bypass, acute cardiovascular events or complex 56 surgery (11). The reasons for hospital readmission after a surgical intervention are often not directly 57 related to the surgery itself but rather to underlying chronic health conditions (12). Thus, chronic diseases 58 may play an important role in readmission risk, independently of the reason for the initial hospitalisation 59 (13, 14). Older adults' chronic diseases are not isolated health conditions; they can influence each other, 60 and treatment for one disease may adversely affect another (15). For all these reasons, patterns of 30-day 61 hospital readmissions may be very complex (16).

62

63 Multimorbidity, in the case of two or more diseases (17, 18), may require taking multiple medicines (19), 64 known as polypharmacy (PP) when daily intake involves five or more drugs (20). Increasing incidences 65 of multimorbidity with age, and consequently PP, add to the complexity of managing older inpatients' 66 drug prescriptions, particularly at hospital discharge (21, 22). PP and inadequate drug management are 67 significant risk factors for adverse drug events (ADEs)—the most common post-discharge 68 complications—alongside hospital-acquired infections and procedural complications (23, 24). ADEs 69 resulting from inappropriate drug prescribing, discrepancies between prescribed and current regimens, 70 poor adherence and the inadequate surveillance of adverse effects frequently lead to hospital admissions, 71 readmissions (8) and other undesirable consequences such as increased morbidity, decreased autonomy, 72 institutionalisation and even early death (25, 26). A systematic review by Morabet et al. indicated ADE 73 rates of 18%-38% after hospital discharge and 4.5%-24% hospital readmission rates due to those ADEs 74 (27). Because older adults use more drugs, they are at a greater risk of drug-related readmission. 75 Numerous studies have found that nearly 30% of older inpatients experienced ADEs within three weeks

76 of hospital discharge, almost three-quarters of which could have been prevented or lessened (10, 28, 29).

77	
78	Despite the significant overall impact of ADEs on hospital readmission rates, little is known about
79	hospital readmission risk's associations with medical conditions and drug regimens (30, 31). Morabet en
80	al. revealed the high prevalence of antibiotics, diuretics, vitamin K antagonists, opioids, antidiabetics,
81	anti-cancer drugs, antihypertensives, digitalis glycosides, corticosteroids and psychotropic drugs in drug
82	related hospital readmissions (27). Samoy <i>et al.</i> reported that anticoagulants, hypoglycaemics, beta-
83	blocking agents, antidepressants, calcium channel blockers and lenograstim were associated with high
84	risks of hospital readmission (32). A retrospective patient record study by Teymoorian et al. reported the
85	anticoagulants and antiplatelet agents, diuretics and antihypertensives, and opioids were associated with
86	high risk of persons aged 80 years old or more being readmitted to hospital within 30 days (33). Blanc
87	<i>al.</i> reported the readmission scores of different drugs in a large sample of 10,374 adult hospital
88	admissions in general medicine. Taking beta-blocking agents, calcium channel blockers, diuretics,
89	hypoglycaemic drugs or opioids was a significant risk for 30-day readmission (9).
90	
91	Besides higher risks of drug-related hospital readmission, some studies have also investigated
92	associations between combining drugs—a common practice when treating complex diseases or co-
93	existing medical conditions—and drug-related hospital readmissions. Although using multiple drugs m
94	be good clinical practice and compliant with guidelines for treating certain diseases, one significant
95	consequence of combining drugs is that patients face much higher risks of ADEs, which can be caused
96	drug-drug interactions (34-36). ADEs can emerge because a drug's pharmacokinetics and
97	pharmacodynamics change if taken with another drug (36). Moura <i>et al.</i> found that participants with
98	potential drug-drug interactions on their prescription list had a 2.4 times higher adjusted odds ratio (OI
99	of being readmitted (37).
100	
101	Even though some studies have reported high numbers of readmissions among home-dwelling older
102	patients for a variety of drugs (38), this health issue was mostly investigated using prospective or cross
103	sectional studies with small samples. More insight is needed into patterns of drug-related hospital
104	readmissions and risk factors in order to design better interventions for addressing ADEs (39, 40). As p
105	of a broader project (41), the present study's goal was to use hospital register data to prioritise risk fact
106	for hospital readmission. We hypothesised that sociodemographic characteristics, medical conditions
107	(defined using the WHO's International Classification of Diseases, tenth revision: ICD-10, and the Swi
108	Classification of Surgical Interventions: CHOP), and drug prescriptions (based on the WHO's Anatom
109	Therapeutic Chemical (ATC) Classification System) were significant risk factors for 30-day hospital
110	readmission for discharged older adults.
111	Material and Methods
112	Study Design
113	This longitudinal study (2015–2018) used data on a population cohort taken from a hospital registry
111	

114 composed of 140 variables. These were used to investigate the associations between the risks of 30-day

hospital readmission and the medical conditions and drug regimens of polymedicated older inpatients

Page 7 of 32

1

1 2		
3 4	116	discharged home. The study was performed with close regard to the REporting of studies Conducted
5 6	117	using Observational Routinely collected health Data (RECORD) statement (42).
7	118	Population and Data Collection
8	119	Our custom, four-year, registry-based dataset included polymedicated inpatients (five or more drugs
9 10	120	prescribed at hospital discharge), aged 65 years old or more, living in their own homes and hospitalised at
11	121	least once at the Valais Hospital (a public general hospital in the French-speaking part of Switzerland).
12 13	122	This specific population was selected because of its increased risk of hospital readmission (10, 28, 29).
14	123	Older inpatients hospitalised once only or who died during hospitalisation were excluded, as were those
15 16	124	hospitalised for fewer than 24 hours (the criterion to count as "hospitalised" in Switzerland). Valais
16 17	125	Hospital's register contains a comprehensive electronic health record composed of 140 variables routinely
18	126	collected during hospital stays. However, no electronic patient records were available for adult psychiatry
19 20	127	for 2015–2018. The extracted patient data contained sociodemographic characteristics, medical and
21	128	surgical diagnoses, routinely assessed clinical data (such as gait, falls risk or hearing) from hospitalised
22 23	129	patients with at least five prescribed drugs at discharge. Medical and surgical diagnoses were coded based
24	130	on the ICD-10 and CHOP (43). Drug classification was based on the WHO's ATC Classification System
25 26	131	(44).
20	132	The strategy for transforming and synthesising the data extracted from the register's multiple dataset
28	133	sources was based on Olsen's register-based methodological considerations (45) and has been
29 30	134	documented elsewhere (46). Our dataset was composed of 20,422 hospital admission records running
31	135	from January 2015 to December 2018, with similar numbers of annual hospital admissions: 5134, 5095,
32 33	136	
34	137	5125, and 5068, respectively. Dataset Customisation for Predictive Analysis
35 36	138	
37	139	Dataset Customisation for Predictive Analysis
38	140	The dataset was recoded and customised to identify the frequency of older patients' hospital admissions.
39 40	141	Each subject's unique identifier was used to distinguish their different hospital stays from 2015–2018.
41	142	The dataset included 13,802 readmissions involving 8,878 different older inpatients discharged home,
42 43	143	readmitted to hospital within 30 days and whose data were complete (no missing values).
44	144	Sociodemographic and clinical data were considered independent variables and used to compute the
45 46	145	predictive models. Readmission following discharge home was defined as the dependent variable of
47	146	interest and was dichotomised ($0 = n_0$, $1 = yes$) based on 30-day readmission between 2015 and 2018.
48 49	147	Furthermore, the custom dataset was composed of six clinical clusters based on agglomerative
50	148	hierarchical clustering methods for identifying clinically relevant characteristics and representing older
51 52	149	inpatients' health status. Medical status and drugs data were recoded and copied to an exploitable
52 53	150	population database (46).
54	151	
55 56	152	Sociodemographic Variables and Length of Stay
57	153	The sociodemographic data set—almost exclusively composed of ordinal variables—included two
58 59	154	categorical variables (sex and place of discharge from hospital) and three continuous variables (age and
60		
		6

admission and discharge dates). Sex and age were included in the analysis as sociodemographic control
variables. Age was considered a continuous variable as its progressive impact has been proven in
preliminary investigations and previous studies (47).

159 Health Variables

Numerous variables were used to describe older patients' health status during each hospital stay. The health dataset was composed of 23 categorical variables: 21 measured as ordinal variables (mobility, changing position, falls in the last year, etc.) and two measured as nominal variables (altered gait and chronic pain). A cleaner, better-structured dataset-composed of hierarchical clusters-was obtained in a previous study combining empirical and best-practice statistical approaches (46). Three of six preliminarily computed hierarchical clusters were included in the modeling analysis as confounding variables: the mobility cluster, the dependency in the activities of daily living cluster and the mental state cluster (46). These three clusters were selected because of their significant contributions to hospital readmissions (48-50). The dataset of medical information was composed of patients' principal medical diagnosis and four secondary medical diagnoses, based on the ICD-10. Finally, the year of hospitalisation was introduced as a control variable, based on the fact that earlier admission to hospital during this period led to a higher probability of unplanned readmissions during the entire period covered.

173 Included Drugs

The hospital dataset showed that discharged patients had been prescribed 2,370 different drugs. Drug prescriptions were considered continuous, classified according to the WHO's ATC Classification System (51) and then included in the predictive model as independent variables. To ensure robust statistical results, the model only included drug categories prescribed to at least 30 inpatients who were readmitted within 30 days. Supplementary File 1 presents the prescribed ATC classified drugs included in the predictive model as independent variables. For statistical purposes, drug-drug interactions between different ATC drug classes (51) were operationalised as dichotomised variables (0 = no simultaneous use of drugs from both classes, 1 = simultaneous use of drugs from both classes) and added to the previous model. Drug class interactions were selected based on a literature review, significant ORs and expert opinions (52). Data analysis strategy Data were extracted into a Microsoft Excel spreadsheet (Microsoft, Redmond, Washington, United States) and then imported into SPSS software, version 26.0 (IBM Corp, Armonk, New York, United States). We examined statistical associations between hospital readmissions and patient age and sex, LOS, principal and related ICD-10 diagnoses, CHOP interventions and drug prescriptions during hospitalisations. A causality analysis between those variables was impossible given our retrospective data collection method, our inability to calculate the time between drug intake and readmission, and the potential drug changes between hospitalisation sequences. We conducted a bivariate analysis relating the independent variables to 30-day readmission after discharge home from 2015–2018. Next, we calculated a series of multilevel logistic regression models for binary outcomes explaining the readmissions, within

2 3		
4	194	30 days, of patients discharged home ($0 = no$, $1 = yes$). These hierarchical models included two levels: the
5 6	195	first level concerned hospital stays themselves, nested in the second level, that of individuals. Firstly, we
7	196	computed a baseline multilevel binary logistic regression model to estimate how sets of predictors
8 9	197	influenced the probability of 30-day hospital readmission, which included individuals' characteristics,
9 10	198	health conditions and hospital LOS. Secondly, we completed this baseline model with the drugs
11	199	prescribed to older inpatients on their discharge home. Finally, to that baseline model completed with
12 13	200	prescribed drugs, we added the known drug–drug interactions between different ATC drug classes, based
14	201	on a literature review and expert opinions. The model computed each predictor's impact, other things
15 16	202	being equal, by estimating its net impact, controlling for other factors (adjusted ORs). The model also
17	203	considered correlations between each subject's different variables, which were generally not independent
18 19	204	(53). The model's random intercept design allowed each individual's intercept to vary, assuming that
20	205	some unmeasured traits remained stable over time and allowing a better estimation of the model's
21 22	206	parameters. The estimated parameters, on the other hand, had the same effect on every subject. Since the
23	207	data were based on the whole population-not a sample-of polymedicated older inpatients discharged
24	208	home from the Valais Hospital, the ORs' confidence intervals and statistical tests were used to indicate
25 26	209	the robustness of relationships (they usually only make sense for statistical inference).
27	210	In a second stage,
28 29	211	In a second stage,
30	211	
31 32	212	
33 34	213	Patients and public involvement
35	215	Patients were not involved in the development of the research questions, study design, outcome measures
36	216	
37 38	217	and conduct of the study.
39 40	218	Results
40	219	Descriptive results
42	220	The electronic records of 20,422 inpatient stays by polymedicated, home-dwelling older adults included
43 44	221	the 13,802 hospital readmissions of 8,878 different older inpatients previously discharged home—an
45	222	average of 1.55 inpatient hospital readmissions. The total sample's mean age was 77.77 years old
46 47	223	(SD = 7.48), and 57% were men (Table 1). The average hospital LOS was 8.44 days (SD = 7.58). At
48	224	discharge, 25% of the sample had impaired mobility, 4% were impaired in their activities of daily living
49 50	225	and 4% showed mental impairment. Our sample population averaged 4.58 (SD = 0.92) ICD-10 diagnoses
51	226	and 1.83 (SD = 1.76) surgical interventions (CHOP) performed during hospitalisation. The selected
52 53	227	medical diagnoses distinguished patients affected by circulatory (24%), infectious (3%) and respiratory
54	228	diseases (11%), as well as trauma (8%) and tumours (11%). On average, 8.95 (SD = 3.24) drugs were
55 56	229	prescribed per patient at hospital discharge.
57	230	[Insert Table 1]
58 59	231	
60		

3		
4 5	232	Associations between Thirty-day Hospital Readmission Risk and Sociodemographic Characteristics
6	233	and Medical Conditions
7	234	The rate of 30-day hospital readmission for older patients discharged home was 7.8%. Bivariate
8 9	235	associations with chi-square tests showed significant differences between older inpatients'
10	236	sociodemographic characteristics and medical conditions (Table 2). Men showed a slightly higher
11 12	237	proportion of 30-day hospital readmissions than women (8.2% vs 7.3%). However, age did not
13	238	significantly affect the probability of 30-day readmission. More readmissions were also seen among older
14 15	239	patients with a circulatory disease (8.2% vs 6.5%), those not affected by trauma (8.0% vs 5.8%), and
16	240	especially those with a tumour (15.1% vs 6.9%). Multimorbidity also increased the risk of 30-day hospital
17	241	readmissions—from 1.5% for older patients with a single ICD-10 condition to 8.8% for those with five.
18 19	242	[Insert Table 2]
20	243	
21 22	244	Associations between Thirty-day Hospital Readmission Risk and Drugs
23	245	On average, older patients readmitted within 30 days had more prescribed drugs than those who were not
24 25	246	readmitted (9.95 drugs vs 8.87). We found a linear relationship between the 30-day readmission rate and
25 26	247	the average number of prescribed drugs ($p > 0.001$), which supported the absence of a cut-off point in this
27	248	relationship (Figure 1).
28 29	249	[Insert Figure 1]
30	250	
31 32	251	Among the most robust statistical associations (chi-square tests) with 30-day hospital readmissions
33	252	involved the classes of drugs including antineoplasics and immunomodulators (12.6% vs 7.6% for those
34 35	253	not treated with them) and taking antiemetics and antinauseants (27.7% vs 7.7%). There was also a higher
36	254	risk of 30-day hospital readmission among older inpatients taking drugs for functional gastrointestinal
37	255	disorders (13.4% vs 7.4%) and antihypertensives (14.1% vs 7.7%) (Table 3).
38 39	256	[Insert Table 3]
40	257	
41 42	258	Baseline Multivariate Model
43	259	A baseline, multivariate logistic regression model including older patients' sociodemographic and clinical
44 45	260	variables, but not their prescribed drugs at discharge, was computed to predict 30-day hospital
46	261	readmission after discharge home (Table 4). Neither sex nor age had a significant impact. On the
47	262	contrary, LOS had a significant impact (OR = 1.014 for each additional day; 95% CI: 1.006–1.021), as
48 49	263	did mobility ($OR = 1.218$ for older patients with an impaired mobility status; 95% CI: 1.039–1.427).
50	264	Dependence in the activities of daily living and mental health status showed no influence. Concerning
51 52	265	diagnoses measured in the ICD-10, we found that older patients with a tumoural disease ($OR = 2.538$;
53	266	95% CI: 2.089-3.082) were much more susceptible to 30-day hospital readmission. Patients with
54 55	267	circulatory pathologies showed no difference from the reference category ($OR = 0.938$; 95% CI: 0.783–
56	268	1.124), and nor did those with respiratory problems ($OR = 1.100$; 95% CI: 0.875–1.382), trauma
57 58	269	(OR = 0.847; 95% CI: 0.633–1.134) or infection-related problems (OR = 1.381; 95% CI: 0.964–1.977;
58 59	270	p = 0.078). Multimorbidity predicted a higher probability of readmission (OR = 1.419 per additional ICD-
60		

2 3		
4	271	10 condition; 95% CI: 1.282–1.572), whereas the number of surgical procedures had no noticeable impact
5 6	272	(OR = 0.978; 95% CI: 0.938-1.020). The year of hospital stay did have an impact, however, as the earlier
7	273	the hospitalisation during the four years under review, the higher the probability of readmission
8 9	274	(OR = 0.933 per additional year; 95% CI: 0.880–0.990).
9 10	275	Some variables that were non-significant in bivariate analyses became significant in multivariate
11	276	analyses. This was because the results of multivariate analyses were controlled by all the other parameters
12 13	277	and interpretations were made with "other things being equal". Also, the composition of subgroups could
14	278	be very different in some bivariate analyses.
15 16	279	[Insert Table 4]
17	280	
18 19	281	Prediction of 30-day Hospital Readmission and Drug Prescriptions
20	282	Table 5 presents the baseline logistic regression model completed with the drugs prescribed to older
21 22	283	patients at discharge home that were significantly associated ($p = < 0.05$) with 30-day hospital
22	284	readmission. It was not possible to introduce the total number of drugs prescribed jointly in this model
24	285	because of their collinearity with other drug variables. Non-significant drugs and other variables have
25 26	286	been omitted from Table 3 in order to simplify the presentation. The probabilities of 30-day hospital
27	287	readmission are presented in descending order of discharged older patients' ORs for each additional unit
28 29	288	of the drugs in question. Intake of antiemetics and antinauseants was very strongly linked to 30-day
30	289	readmission (OR = 3.216 for each additional drug unit taken; 95% CI: 1.842–5.617), as were those of
31 32	290	antihypertensives (OR = 1.771; 95%CI: 1.287–2.438), gastrointestinal drugs (OR = 1.424; 95% CI:
33	291	1.166–1.739), systemic hormonal preparations (OR = 1.207; 95% CI: 1.052–1.385) and vitamins
34 35	292	(OR = 1.201; 95% CI: 1.049–1.374). On the contrary, the intake of lipid-modifying agents was associated
36	293	with a decrease in 30-day hospital readmissions ($OR = 0.841$ for each drug from this class prescribed;
37	294	95% CI: 0.732–0.967).
38 39	295	[Insert Table 5]
40	296	
41 42	297	Drug Interactions and 30-day Hospital Readmissions
43	298	The model considered drug class interactions for the: 1) cardiovascular system * central nervous system,
44 45	299	gastrointestinal system, and metabolism * cardiovascular system; 2) gastrointestinal system and
46	300	metabolism * central nervous system; 3) cardiovascular system * anti-infectives; and 4) central nervous
47 48	301	system * anti-infectives. The analysis was carried out controlling for the basic model's variables (Table
49	302	4), and the table reports the ORs for each additional unit of the statistically significant drugs in question,
50 51	303	as well as for significant drug interactions. Antiemetics and antinauseants were very strongly associated
52	304	with 30-day readmission ($OR = 3.222$; 95% CI: 1.844–5.630), as were drugs regulating the
53	305	gastrointestinal tract (OR = 1.428; 95% CI: 1.169–1.744) and systemic hormones (OR = 1.210; 95% CI:
54 55	306	1.054–1.390). The joint intake of beta-blocking agents and drugs for acid-related disorders was
56	307	significantly associated with 30-day hospital readmission (OR = 1.367 ; 95% CI: $1.046-1.788$); this is the
57 58	308	only significant drug interaction in Table 4. On the contrary, lipid-modifying agents were associated with
59		
60		

lower 30-day hospital readmission (OR = 0.838), as were substances acting on the renin–angiotensin
system (OR = 0.892; 95% CI: 0.796–0.999) (Table 6).

311 [Insert Table 6]312

313 Discussion

The present study examined the records of 20,422 hospitalisations involving polymedicated home-dwelling older patients, eventually discharged home, for the risk of 30-day hospital readmission. These records were held in four years of a comprehensive hospital register. The 8,878 individual older patients readmitted to the Valais Hospital showed a 30-day hospital readmission rate of almost 8%, corroborating previously published all-cause hospital readmission rates among home-dwelling older patients (9, 27). However, Jencks et al. (2009) found a much higher 30-day readmission rate, reaching almost 20% among discharged older patients who had been hospitalised in acute medicine and surgery wards (3). As a bivariate association, multimorbid men were at a significantly higher risk of readmission than multimorbid women; however, in the adjusted multivariate analysis, that significance disappeared. Medical conditions, PP and multiple classes of prescribed drugs were all associated with higher 30-day readmission rates, in line with previous studies (27, 54-56). Our study found no significant differences in the risks of 30-day hospital readmission for men and women. However, some previous research found that men were more likely to forget to take their drugs or to not apply the changed drug dosages prescribed by their family physician, consequently increasing their risk of hospital readmission for drug-related problems (57). Opposite results were found in a population-based study by Manteufel et al. (58), with women being less likely than men to properly adhere to their drug prescriptions. These differences may indicate a need for more personalised drug prescription and drug management to improve clinical outcomes. Further research should explore

- 37
 38
 39
 33
 33
 33
 33
 33
 34
 35
 36
 37
 37
 38
 39
 39
 30
 31
 31
 32
 33
 33
 33
 33
 33
 33
 33
 33
 33
 34
 35
 36
 37
 37
 38
 39
 31
 31
 32
 33
 33
 34
 35
 36
 37
 37
 38
 39
 31
 31
 32
 33
 33
 34
 35
 35
 36
 37
 37
 38
 38
 39
 31
 31
 32
 33
 33
 34
 35
 36
 37
 37
 38
 38
 39
 39
 30
 30
 31
 31
 32
 32
 33
 34
 35
 36
 37
 37
 38
 38
 39
 39
 30
 31
 32
 33
 34
 35
 36
 37
 37
 38
 38
 39
 39
 30
 31
 32
 32
 34
 34
 35
 36
 37
 37
 38
 38
 39
 30
 31
 32
 34
 34
 35
 36
 37
 37
 38
 38
 38
 39
 39
 30
 31
 32
 33
 34
 34
 34
 35
 36
 37
 37
 38
 38
 38
 39
 39
 30
 30
 30
 31
 31
 32
 32
 34
 34
 34
 34
 34
 34
 34
 34
 34
 34
 34
 34
 34
 34
 34
 <
- 40
 41
 42
 334 study window. Some studies found higher rates among men than among women below three-month
 42
 43
 43
 43
 44
 45
 46
 47
 48
 49
 49
 40
 41
 41
 42
 43
 43
 44
 44
 45
 46
 47
 48
 49
 49
 40
 41
 41
 41
 42
 43
 44
 44
 45
 46
 47
 48
 49
 49
 40
 41
 41
 41
 41
 41
 42
 43
 44
 44
 44
 44
 44
 45
 46
 47
 48
 49
 49
 40
 41
 41
 41
 42
 43
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44
 44</l
- 336 60). An analysis of our dataset using a more extended readmission window might clarify this point and
 337 provide complementary knowledge about sex-associated hospital readmissions.
- Our results indicated that ageing was not a risk factor for increased 30-day hospital readmission, in line with some previous publications (55, 61). However, other research findings demonstrated that age was only positively associated with the likelihood of readmission up to 74 years old; above that, there no longer appeared to be any significant relationship between age and readmission (62, 63). These contrasting results may be explained by the studies' designs, country settings, the ages of their research
- ⁵³ 343 populations or the medical conditions included (55, 62, 64).

Longer hospital stays were also associated with a higher risk of hospital readmission, in line with a cohort
study by Sud *et al.* concluding that an extended hospital LOS was associated with increased rates of all
types of readmission, except for hospitalisation after heart failure, where a short LOS was associated with
increased rates of readmission for cardiovascular disease and heart failure (65).

2 3		
4	348	Our results indicated a significant positive association between the number of a patient's medical
5 6	349	conditions and the 30-day hospital readmission rate, confirming other recent retrospective hospital
7	350	register studies (66, 67). More specifically, older patients with impaired mobility showed an increased
8 9	351	risk of hospital readmission. This result was not surprising, bearing in mind that although these older
9 10	352	patients were discharged home—and not to a nursing home—after their hospital stay, their health status
11	353	might nevertheless require future readmission. Indeed, this corroborated publications about older patients
12 13	354	discharged after orthopaedic treatment or who had been initially admitted for heart failure, myocardial
14	355	infarction or pneumonia, but also presented with impaired mobility (68, 69).
15 16	356	Cognitive impairment was not associated with increased 30-day hospital readmission rates, in line with
17	357	findings from the systematic review by Pickens <i>et al.</i> , which pointed out that dementia had a modest
18 19	358	impact on readmission rates (70). It was no surprise that inpatients hospitalised for cancer faced a high
20	359	risk of readmission, corroborating prior studies by Buhenn <i>et al.</i> , Chang <i>et al.</i> and Butcher (71-73).
21	360	PP significantly increased the 30-day hospital readmission rate, but this result was based on the average
22 23	361	number of drugs prescribed to the sample of readmitted patients versus those not readmitted. Although PP
24	362	was confirmed as a strong determinant of 30-day hospital readmission in publications by Leendertse <i>et al.</i>
25 26	363	(74, 75), our results showed a progressive linear relationship between PP and readmission rate, and this
27	364	should be interpreted with caution. Despite our results and other publications and research underlining the
28 29	365	challenge of PP among multimorbid older patients, there is no overall consensus about the best way to
30	366	deal with the broad general relationship between PP and hospital readmission (76).
31	367	Our advanced statistical analysis demonstrated that some specific drugs and the concomitant use of
32 33	368	specific drug combinations were significantly associated with 30-day readmission risk, although this was
34	369	not unexpected and has been confirmed in previous publications (37, 77). Mostly in line with the research
35 36	370	findings of Zhang <i>et al.</i> , drugs including hormones, antineoplastics, immunosuppressors, neoplastic
37	371	antibiotics and bacterial vaccines were substantial risk factors for hospital readmission (7).
38 39	372	In summary, extended hospital LOS, functional impairments, medical conditions and drugs have been
40	373	demonstrated to be determinants of 30-day hospital readmission, although not all of them have clinically
41	374	or pharmacologically relevant interpretations or explanations. Further research involving large samples is
42 43	375	needed, notably to explore the drug-drug interactions with the highest risk of hospital readmissions.
44	376	Statistical predictions of potential drug–drug interactions provide important information for modeling
45 46	377	drug combinations and identifying pairs of drugs whose combination creates an exaggerated response (9).
47	378	As the association between the number of drugs and the risk of hospital readmission was linear, more
48 49	379	advanced inferential statistics would be needed to clarify a cut-off point for the mean number of drugs
50	380	that would significantly increase the readmission rate. In addition, problems involving adherence to
51 52	381	prescriptions, social support networks, and stronger or weaker primary health-care structures can all
52 53	382	influence hospital readmission rates (39). According to some publications, nearly 70% of people aged
54	383	over 65 make mistakes with their drugs (78, 79). Information about drug adherence, drug underuse and
55 56	384	overuse, drug changes and deprescription by family physicians, as well as medication management at
57	385	home, would contribute to a more comprehensive understanding of disease- and drug-related 30-day
58 59	386	hospital readmissions.
60	500	noopraal readinitionolis.

Finally, it would be interesting to explore the risks of readmission according to different hospital wards. As psychiatric conditions are a frequent cause of rehospitalisation (80), it would be relevant for future research to explore registries from adult psychiatry departments and investigate the hospital readmission risks faced by their inpatients. **Strengths and Limitations** This study's main strength was its use of data recorded in a comprehensive register. We consider this retrospective study useful for clinical practice and future research because a whole series of sociodemographic and clinical parameters, medical conditions and prescribed drugs were used to predict the probability of hospital readmission. Using both bivariate and multivariate analyses enabled an evaluation of the data's longitudinal nature. Our study had several limitations, nevertheless. The design did not allow us to identify hospitalisations and readmissions lost-to-follow-up and to adjust our data for death outside the hospital. We were also unable to identify unnecessary hospitalisations or any bias towards hospitalisation rather than another health-care solution for older inpatients. Our dataset could not inform us about whether older inpatients had been first admitted to another hospital or were subsequently readmitted elsewhere during the study period. Because the reasons for hospital admission are not chosen from a list but are entered into the register as free descriptive text, these factors were not part of our dataset, and the study was unable to explore the reasons for an admission's impact on 30-day rehospitalisation. Another limitation was the study's lack of formal screening methods to explain ADEs in detail, and it was impossible to distinguish between elective and urgent hospitalisations. Although the study considered statistical associations between drugs and rehospitalisations, it did not use clinically diagnosed drug-drug interactions. Finally, we were unable to consider any potential causality between PP and hospital readmission. Conclusions Hospital length of stay, medical conditions, functional impairments and prescribed drugs were all critical factors in predicting hospital readmissions, thus affirming our hypotheses. Readmission patterns are complex and poorly understood because older patients often present with multiple chronic conditions, functional impairments and complex drug prescriptions. Hospital readmission is an under-investigated topic deserving of additional, well-conducted, predictive research exploiting accurate longitudinal data from large samples. Acknowledgments The authors thank the partner hospital, including the hospital's data warehouse, for its valuable contributions. This research was developed, in part, using grants from the Swiss National Science Foundation and the School of Health Sciences of the University of Applied Sciences and Arts Western Switzerland (HES-SO) Valais/Wallis. The funders had no role in the design and conduct of the study, the

- collection, management, analysis and interpretation of the data, the preparation, review or approval of the
 collection, management, analysis and interpretation of the data, the preparation, review or approval of the
- 58 424 manuscript, or the decision to submit the manuscript for publication.
- 425 Authors Contributions
 60

1		
2		
3 4	420	
5	426	BW, FP, and HV had the original idea. BW, ZT, SdG, MMM and HV provided conceptual and
6	427	methodological expertise to the study design and BW, FP, ZT, SdG, CMM, AvG and HV to data analysis
7	428	and interpretation. BW, FP, and HV were major contributors to writing the manuscript. All authors read,
8 9	429	edited, and approved the final manuscript.
10	430	
11 12	431	Funding
13	432	This study was supported by the Swiss National Science Foundation via grant number 407440_183434/1.
14 15	433	Competing interest
16	434	The authors report no conflicts of interest surrounding this work.
17 18	435	Ethics approval and patient consent
19	436	Ethical approval was obtained from the Human Research Ethics Committee of the Canton of Vaud (CER-
20	437	VD, 2018-02196), thus permitting our partner hospital's data warehouse to provide the appropriate
21 22	438	dataset. Given the retrospective data source, obtaining consent from the patients concerned was
23	439	impossible or posed disproportionate difficulties. The present study respects the legal requirements for
24	440	research projects involving data re-use without consent, as set out in Art. 34 from the Swiss Human
25 26		
27	441	Research Act (HTA).
28	442	Data sharing statement
29 30	443	As part of the Data Use Agreement, authors are not allowed to provide raw data. Upon a reasonable
31	444	request, the corresponding author will provide statistical programming code used to generate results.
32	445	Word Count: 4,158
33 34	446	
35	447	Figure 1. Relationship between 30-day readmission rate and the number of prescribed drugs at discharge.
36		
37	448	
38 39	440	Defenered
40	449	References
41	450	1. Rayan-Gharra N, Rn ES, Tadmor B, Flaks-Manov N, Balicer RD. Patients' ratings of the
42 43	451	in-hospital discharge briefing and post-discharge primary care follow-up: the association with
44	452	30-day readmissions. Patient Education and Counseling. 2019.
45	453	2. Kabue S, Greene J, Kipnis P, Lawson B, Rinetti-Vargas G, Liu V, et al. The Impact of
46	454	Pharmacy-specific Predictors on the Performance of 30-Day Readmission Risk Prediction
47	455	Models. Med Care. 2019;57(4):295-9.
48	456	3. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among Patients in the
49	457	Medicare Fee-for-Service Program. New England Journal of Medicine. 2009;360(14):1418-28.
50 51	458	4. Covinsky KE, Palmer RM, Fortinsky RH, Counsell SR, Stewart AL, Kresevic DM. Loss of
51 52	459	independence in activities of daily living in older adults hospitalised with medical illness:
53	460	increased vulnerability with age. JAGS. 2003;51.
54	461	5. Hansen LO, Young RS, Hinami K, Leung A, Williams MV. Interventions to reduce 30-day
55	462	rehospitalization: a systematic review. Ann Intern Med. 2011;155(8):520-8.
56	463	6. Davies EC, Green CF, Mottram DR, Rowe PH, Pirmohamed M. Emergency re-admissions
57	464	to hospital due to adverse drug reactions within 1 year of the index admission. British Journal
58	465	of Clinical Pharmacology. 2010;70(5):749-55.
59 60		

1		
2		
3		
4	466	7 Zhana M. Halman CDAL Drive CD. Canfiling a FM. Dream DD. Dulaans MIK Companyidite
5	466	7. Zhang M, Holman CDAJ, Price SD, Sanfilippo FM, Preen DB, Bulsara MK. Comorbidity
6	467	and repeat admission to hospital for adverse drug reactions in older adults: retrospective
7	468	cohort study. BMJ. 2009;338:a2752.
8	469	8. Bonnet-Zamponi D, d'Arailh L, Konrat C, Delpierre S, Lieberherr D, Lemaire A, et al.
9	470	Drug-Related Readmissions to Medical Units of Older Adults Discharged from Acute Geriatric
10	471	Units: Results of the Optimization of Medication in AGEd Multicenter Randomized Controlled
11	472	Trial. Journal of the American Geriatrics Society. 2013;61(1):113-21.
12 13	473	9. Blanc A-L, Fumeaux T, Stirnemann J, Dupuis Lozeron E, Ourhamoune A, Desmeules J, et
14	474	al. Development of a predictive score for potentially avoidable hospital readmissions for
15	475	general internal medicine patients. PLOS ONE. 2019;14(7):e0219348.
16	476	10. Stevenson JM, Davies JG, Martin F, Ali K, Rajkumar C, Schiff R. Is medication related
17	477	harm as a cause of readmission associated with the indicators of frailty? Age and Ageing.
18	478	2018;47:ii19.
19	479	11. Brunner-La Rocca H-P, Peden CJ, Soong J, Holman PA, Bogdanovskaya M, Barclay L.
20	480	Reasons for readmission after hospital discharge in patients with chronic diseases—
21	481	Information from an international dataset. PloS one. 2020;15(6):e0233457.
22	482	12. Dharmarajan K, Hsieh AF, Lin Z, Bueno H, Ross JS, Horwitz LI, et al. Hospital
23	483	readmission performance and patterns of readmission: retrospective cohort study of Medicare
24 25	484	admissions. Bmj. 2013;347.
25	485	13. Arora S, Patel P, Lahewala S, Patel N, Patel NJ, Thakore K, et al. Etiologies, trends, and
27	486	predictors of 30-day readmission in patients with heart failure. The American journal of
28	487	cardiology. 2017;119(5):760-9.
29	488	14. Shams I, Ajorlou S, Yang K. A predictive analytics approach to reducing 30-day
30	489	avoidable readmissions among patients with heart failure, acute myocardial infarction,
31	490	pneumonia, or COPD. Health care management science. 2015;18(1):19-34.
32	491	15. Krumholz HM, Wang K, Lin Z, Dharmarajan K, Horwitz LI, Ross JS, et al. Hospital-
33	492	readmission risk—isolating hospital effects from patient effects. New England Journal of
34	493	Medicine. 2017;377(11):1055-64.
35 36	494	16. Gruneir A, Fung K, Fischer HD, Bronskill SE, Panjwani D, Bell CM, et al. Care setting and
30 37	495	30-day hospital readmissions among older adults: a population-based cohort study. CMAJ.
38	496	2018;190(38):E1124-E33.
39	497	17. Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, Garmen A, et al. Aging
40	498	with multimorbidity: A systematic review of the literature. Ageing Research Reviews.
41	499	2011;10:430-9.
42	500	18. Valderas JM, Starfield B, Sibbald B, Salisbury C, Rloand M. Defining comorbidity:
43	500 501	implications for understanding health and health services. Annals Of Family Medicine.
44	501	2009;7:357-63.
45	502	19. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly.
46	505 504	Expert Opinion on Drug Safety. 2014;13:57-65.
47 48	504 505	20. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A
48 49		
50	506	systematic review of definitions. BMC Geriatrics. 2017;17:1-10.
51	507	21. Wastesson JW, Morin L, Tan ECK, Johnell K. An update on the clinical consequences of
52	508	polypharmacy in older adults: a narrative review. Expert Opin Drug Saf. 2018;17(12):1185-96.
53	509	22. Rieckert A, Trampisch US, Klaaßen-Mielke R, Drewelow E, Esmail A, Johansson T, et al.
54	510	Polypharmacy in older patients with chronic diseases: a cross-sectional analysis of factors
55	511	associated with excessive polypharmacy. BMC Family Practice. 2018;19(1):113.
56	512	23. Magill SS, Edwards JR, Bamberg W, Beldavs ZG, Dumyati G, Kainer MA, et al. Multistate
57	513	point-prevalence survey of health care-associated infections. N Engl J Med.
58 50	514	2014;370(13):1198-208.
59 60		
00		

1		
2		
3		
4	515	24. Coleman EA, Smith JD, Raha D, Min SJ. Posthospital medication discrepancies:
5	516	prevalence and contributing factors. Arch Intern Med. 2005;165(16):1842-7.
6 7	517	25. Ferreri SP, Hughes TD, Snyder ME. Medication Therapy Management: Current
8	518	Challenges. Integr Pharm Res Pract. 2020;9:71-81.
8 9	519	26. Roux P, Verloo H, Santiago-Delefosse M, Pereira F. The spatial dimensions of
10	520	medication management by home-dwelling older adults after hospital discharge. Health &
11	520	Place. 2019;60:102230.
12	521	
13		
14	523	Çarkit F. Prevalence and Preventability of Drug-Related Hospital Readmissions: A Systematic
15	524	Review. J Am Geriatr Soc. 2018;66(3):602-8.
16	525	28. Forster AJ, Murff HJ, Peterson JF, Gandhi TK, Bates DW. The incidence and severity of
17	526	adverse events affecting patients after discharge from the hospital. Ann Intern Med.
18	527	2003;138(3):161-7.
19	528	29. Yeo I, Cheung JW, Feldman DN, Amin N, Chae J, Wong SC, et al. Assessment of Hospital
20	529	Readmission Rates, Risk Factors, and Causes After Cardiac Arrest: Analysis of the US
21	530	Nationwide Readmissions Database. JAMA Network Open. 2019;2(9):e1912208-e.
22	531	30. Hauviller L, Eyvrard F, Garnault V, Rousseau V, Molinier L, Montastruc JL, et al. Hospital
23	532	re-admission associated with adverse drug reactions in patients over the age of 65 years.
24	533	European Journal of Clinical Pharmacology. 2016;72(5):631-9.
25 26	534	31. Davies EC, Green CF, Mottram DR, Rowe PH, M P. Emergency re-admissions to hospital
26 27	535	due to adverse drug reactions within 1 year of the index admission. Br J Clin Pharmacol.
27	536	2010;70:749–55.
20	537	32. Samoy LJ, Zed PJ, Wilbur K, Balen RM, Abu-Laban RB, Roberts M. Drug-related
30	538	hospitalizations in a tertiary care internal medicine service of a Canadian hospital: a
31	539	
32		prospective study. Pharmacotherapy. 2006;26(11):1578-86.
33	540	33. Teymoorian SS, Dutcher D, Woods M. ASSOCIATION BETWEEN POSTDISCHARGE
34	541	ADVERSE DRUG REACTIONS AND 30-DAY HOSPITAL READMISSION IN PATIENTS AGED 80 AND
35	542	OLDER. Journal of the American Geriatrics Society. 2011;59(5):948-9.
36	543	34. WHO. ADHERENCE TO LONG-TERM THERAPIES: Evidence for action. Geneva: World
37	544	Health Organisation; 2003.
38	545	35. Brahma DK, Wahlang JB, Marak MD, Ch Sangma M. Adverse drug reactions in the
39	546	elderly. J Pharmacol Pharmacother. 2013;4(2):91-4.
40	547	36. Davies EA, O'Mahony MS. Adverse drug reactions in special populations - the elderly.
41	548	Br J Clin Pharmacol. 2015;80(4):796-807.
42	549	37. Moura CS, Tavares LS, Acurcio Fde A. [Hospital readmissions related to drug
43 44	550	interactions: a retrospective study in a hospital setting]. Rev Saude Publica. 2012;46(6):1082-9.
44 45	551	38. Spinks JM, Kalisch Ellett LM, Spurling G, Theodoros T, Williamson D, Wheeler AJ.
45 46	552	Adaptation of potentially preventable medication-related hospitalisation indicators for
40 47	553	indigenous populations in Australia using a modified Delphi technique. BMJ Open.
48	554	2019;9(11):e031369.
49	555	39. Rosen OZ, Fridman R, Rosen BT, Shane R, Pevnick JM. Medication adherence as a
50	556	predictor of 30-day hospital readmissions. Patient Prefer Adherence. 2017;11:801-10.
51	557	40. Pellegrin KL, Lee E, Uyeno R, Ayson C, Goo R. Potentially preventable medication-
52	558	
53		related hospitalizations: A clinical pharmacist approach to assessment, categorization, and
54	559	quality improvement. Journal of the American Pharmacists Association. 2017;57(6):711-6.
55	560	41. Pereira F, Roux P, Santiago-Delefosse M, von Gunten A, Wernli B, Martins MM, et al.
56	561	Optimising medication management for polymedicated home-dwelling older adults with
57	562	multiple chronic conditions: a mixed-methods study protocol. BMJ Open. 2019;9(10):e030030.
58		
59 60		
00		

42. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. PLOS Medicine. 2015;12(10):e1001885. Surgical interventions clasification S. Swiss classification of surgical interventions 43. (CHOP). 2016. 44. Parker S, Prince A, Thomas L, Song H, Milosevic D, Harris MF. Electronic, mobile and telehealth tools for vulnerable patients with chronic disease: a systematic review and realist synthesis. BMJ Open. 2018;8(8). Olsen J. Register-based research: some methodological considerations. Scandinavian 45. journal of public health. 2011;39(3):225-9. Taushanov Z, Verloo H, Wernli B, Di Giovanni S, von Gunten A, F P. Transforming a 46. patient registry into a customised dataset for the advanced statistical analysis of health risk factors and for medication-related hospitalisation research: a retrospective hospital patient registry study. JMIR Medical Informatics. 2021. Andrade C. Age as a variable: Continuous or categorical? Indian J Psychiatry. 47. 2017;59(4):524-5. 48. Gerka A LC, Pfingsthorn M, Eichelberg M, Muller S, Stolle C, Hein A, editor A Clustering-based Approach to Determine a Standardized Statistic for Daily Activities of Elderly Living Alone. . Proceedings of the 12th International Joint Conference on Biomedical Engineering Systems and Technologies; 2019: SCITEPRESS – Science and Technology Publications, Lda. 49. Trevithick L, Painter J, Keown P. Mental health clustering and diagnosis in psychiatric in-patients. BJPsych bulletin. 2015;39(3):119-23. Delil S, Çelik RN, San S, Dundar M. Clustering patient mobility patterns to assess 50. effectiveness of health-service delivery. BMC health services research. 2017;17(1):1-14. WHO. The Anatomical Therapeutic Chemical Classification System with Defined Daily 51. Doses (ATC/DDD) Geneva: World Health Organization; 2014 [24 March 2020]. Available from: http://www.who.int/classifications/atcddd/en/. 52. Haider SI, Johnell K, Thorslund M, Fastbom J. Trends in polypharmacy and potential drug-drug interactions across educational groups in elderly patients in Sweden for the period 1992 - 2002. Int J Clin Pharmacol Ther. 2007;45(12):643-53. Goldstein H. Nonlinear Multilevel Models, with an Application to Discrete Response 53. Data. Biometrika. 1991;78(1):45-51. 54. Linkens AEMJH, Milosevic V, van der Kuy PHM, Damen-Hendriks VH, Mestres Gonzalvo C, Hurkens KPGM. Medication-related hospital admissions and readmissions in older patients: an overview of literature. International Journal of Clinical Pharmacy. 2020. 55. Berry JG, Gay JC, Joynt Maddox K, Coleman EA, Bucholz EM, O'Neill MR, et al. Age trends in 30 day hospital readmissions: US national retrospective analysis. BMJ. 2018;360:k497. 56. Kongkaew C, Hann M, Mandal J, Williams SD, Metcalfe D, Noyce PR, et al. Risk factors for hospital admissions associated with adverse drug events. Pharmacotherapy. 2013;33(8):827-37. Thunander Sundbom L, Bingefors K. Women and men report different behaviours in, 57. and reasons for medication non-adherence: a nationwide Swedish survey. Pharmacy practice. 2012;10(4):207-21. Manteuffel M, Williams S, Chen W, Verbrugge RR, Pittman DG, Steinkellner A. 58. Influence of patient sex and gender on medication use, adherence, and prescribing alignment with guidelines. J Womens Health (Larchmt). 2014;23(2):112-9. Thunander Sundbom L, Hedborg K. Association between prescribed antidepressants 59. and other prescribed drugs differ by gender: a nationwide register-based study in Sweden. Nord J Psychiatry. 2019;73(1):73-9.

1 2		
3		
4 5	613	60. Silverstein MD, Qin H, Mercer SQ, Fong J, Haydar Z. Risk Factors for 30-Day Hospital
6	614	Readmission in Patients ≥65 Years of Age. Baylor University Medical Center Proceedings.
7	615	2008;21(4):363-72.
8	616	61. Schwab C, Hindlet P, Sabatier B, Fernandez C, Korb-Savoldelli V. Risk scores identifying
9	617	elderly inpatients at risk of 30-day unplanned readmission and accident and emergency
10	618	department visit: a systematic review. BMJ Open. 2019;9(7):e028302.
11	619	62. Jain S, Khera R, Mortensen EM, Weissler JC. Readmissions of adults within three age
12 13	620	groups following hospitalization for pneumonia: Analysis from the Nationwide Readmissions
13	621	Database. PLOS ONE. 2018;13(9):e0203375.
15	622	63. Hasegawa K, Gibo K, Tsugawa Y, Shimada YJ, Camargo CA, Jr. Age-Related Differences
16	623	in the Rate, Timing, and Diagnosis of 30-Day Readmissions in Hospitalized Adults With Asthma
17	624	Exacerbation. Chest. 2016;149(4):1021-9.
18	625	64. Shebeshi DS, Dolja-Gore X, Byles J. Unplanned Readmission within 28 Days of Hospital
19	626	Discharge in a Longitudinal Population-Based Cohort of Older Australian Women. International
20	627	Journal of Environmental Research and Public Health. 2020;17(9):3136.
21 22	628	65. Sud M, Yu B, Wijeysundera HC, Austin PC, Ko DT, Braga J, et al. Associations Between
22	629	Short or Long Length of Stay and 30-Day Readmission and Mortality in Hospitalized Patients
24	630	With Heart Failure. JACC: Heart Failure. 2017;5(8):578-88.
25	631	66. Donzé J, Lipsitz S, Bates DW, Schnipper JL. Causes and patterns of readmissions in
26	632	patients with common comorbidities: retrospective cohort study. Bmj. 2013;347:f7171.
27	633	67. Hijazi HH, Alyahya MS, Hammouri HM, Alshraideh HA. Risk assessment of
28	634	comorbidities on 30-day avoidable hospital readmissions among internal medicine patients. J
29 30	635	Eval Clin Pract. 2017;23(2):391-401.
30	636	68. Falvey JR, Bade MJ, Hogan C, Forster JE, Stevens-Lapsley JE. Preoperative Activities of
32	637	Daily Living Dependency is Associated With Higher 30-Day Readmission Risk for Older Adults
33	638 639	After Total Joint Arthroplasty. Clin Orthop Relat Res. 2020;478(2):231-7. 69. Greysen SR, Stijacic Cenzer I, Auerbach AD, Covinsky KE. Functional impairment and
34	639 640	hospital readmission in Medicare seniors. JAMA Intern Med. 2015;175(4):559-65.
35	641	70. Pickens S, Naik AD, Catic A, Kunik ME. Dementia and Hospital Readmission Rates: A
36	641 642	Systematic Review. Dementia and Geriatric Cognitive Disorders Extra. 2017;7(3):346-53.
37 38	643	71. Chiang LY, Liu J, Flood KL, Carroll MB, Piccirillo JF, Stark S, et al. Geriatric assessment as
39	644	predictors of hospital readmission in older adults with cancer. J Geriatr Oncol. 2015;6(4):254-
40	645	61.
41	646	72. Butcher L. Oncologists Seek to Understand, Address Hospital Readmissions. Oncology
42	647	Times. 2016;38(6):1,9-10.
43	648	73. Burhenn P, Sun C-L, Scher KS, Hsu J, Pandya P, Chui C-Y, et al. Predictors of hospital
44	649	readmission among older adults with cancer. J Geriatr Oncol. 2020;11(7):1108-14.
45 46	650	74. Leendertse AJ, Egberts ACG, Stoker LJ, van den Bemt PMLA, Group HS. Frequency of
40	651	and Risk Factors for Preventable Medication-Related Hospital Admissions in the Netherlands.
48	652	Archives of Internal Medicine. 2008;168(17):1890-6.
49	653	75. Leendertse AJ, Van Den Bemt PM, Poolman JB, Stoker LJ, Egberts AC, Postma MJ.
50	654	Preventable hospital admissions related to medication (HARM): cost analysis of the HARM
51	655	study. Value Health. 2011;14(1):34-40.
52	656	76. Garfinkel D, Bilek A. Inappropriate medication use and polypharmacy in older people.
53 54	657	BMJ. 2020;369:m2023.
55	658	77. Tesfaye WH, Peterson GM, Castelino RL, McKercher C, Jose MD, Wimmer BC, et al.
56	659	Medication Regimen Complexity and Hospital Readmission in Older Adults With Chronic
57	660	Kidney Disease. Annals of Pharmacotherapy. 2019;53(1):28-34.
58	661	78. Fialová D, Onder G. Medication errors in elderly people: contributing factors and
59	662	future perspectives. British journal of clinical pharmacology. 2009;67(6):641-5.
60		

1	
2	
3	
4	
5	
6	
6 7 8 9 10	
8	
q	
10	
10	
11	
12	
13	
14	
15	
16	
17	
12 13 14 15 16 17 18 19 20	
19	
20	
21	
 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 	
22	
23	
24	
25	
26	
27	
28	
29	
30	
31	
31 32	
33	
34	
34 35	
22 26	
36 37	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	
51	
52	
53	
54	
55	
56	
57	
58	
59	
59	

Kavan AH, Gallagher PF, O'Mahony D. Methods to reduce prescribing errors in elderly
patients with multimorbidity. Clinical interventions in aging. 2016;11:857-66.
Cook JA, Burke-Miller JK, Jonikas JA, Aranda F, Santos A. Factors associated with 30-day
readmissions following medical hospitalizations among Medicaid beneficiaries with
schizophrenia, bipolar disorder, and major depressive disorder. Psychiatry Research.
2020;291:113168.

669

670 Table 1. Sociodemographic and hospitalisation data for inpatient stays by polymedicated, home-dwelling671 adults aged 65 or more (n = 13,802)

$\begin{array}{c cccc} 2015 (\%) & 3,501 (25.4) \\ 2016 (\%) & 3,318 (24.0) \\ 2017 (\%) & 3,530 (25.6) \\ 2018 (\%) & 3,453 (25.0) \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$	Inpatient stays by polymedicated, home-dwelling adult aged 65 or more (n = 13,802)	
Stays by women (%) 5,968 (43.2) Age at discharge (years) Mean inpatient age at discharge (SD) Min-Max 77.77 (7.48) Med [IQR 25-75] 77.00 [68.00-80.00 65-69 (%) 2,226 (16.1) 70-79 (%) 5,811 (42.1) 80-89 (%) 4,845 (35.1) 90 and more (%) 920 (6.7) Year of discharge 2015 (%) 2017 (%) 3,530 (25.4) 2017 (%) 3,530 (25.6) 2018 (%) 3,453 (25.0) Length of stay (days) Mean (SD) Mean (SD) 8.44 (7.58) Min-Max 1-149 Med [IQR 25-75] 7 [4-11] Number of ICDs-10 Mean (SD) Min-Max 1-5 Med [IQR 25-75] 5 [5-5] Principal ICD-10 diagnosis Circulatory (%) Circulatory (%) 3,336 (24.2) Infectious (%) 404 (2.9) Respiratory (%) 1,444 (10.5) Trauma (%) 1,043 (7.6) Min-Max 0-5 Mean (SD) 1.83 (1.76) Min-Max		
Age at discharge (years) 77.77 (7.48) Mean inpatient age at discharge (SD) 77.77 (7.48) Min-Max 65-106 Med [IQR 25-75] 77.00 [68.00-80.00 65-69 (%) 2.226 (16.1) 70-79 (%) 5,811 (42.1) 80-89 (%) 4,845 (35.1) 90 and more (%) 920 (6.7) Year of discharge 2015 (%) 2016 (%) 3,531 (25.4) 2016 (%) 3,530 (25.6) 2017 (%) 3,530 (25.6) 2018 (%) 3,453 (25.0) Length of stay (days) Mean (SD) Min-Max 1-149 Med [IQR 25-75] 7 [4-11] Number of ICDs-10 Mean (SD) Min-Max 1-5 Med [IQR 25-75] 5 [5-5] Principal ICD-10 diagnosis Circulatory (%) Circulatory (%) 3,336 (24.2) Infectious (%) 404 (2.9) Respiratory (%) 1,444 (10.5) Trauma (%) 1,043 (7.6) Turnours (%) 1.605 (10.9) Number of CHOP surgical procedures		
Mean inpatient age at discharge (SD) $77.77 (7.48)$ Min-Max $65-106$ Med [IQR 25-75] $77.00 [68.00-80.00]$ $65-69 (\%)$ $2,226 (16.1)$ $70-79 (\%)$ $5,811 (42.1)$ $80-89 (\%)$ $4,845 (35.1)$ 90 and more (%) $920 (6.7)$ Year of discharge $2015 (\%)$ $2016 (\%)$ $3,501 (25.4)$ $2016 (\%)$ $3,530 (25.6)$ $2017 (\%)$ $3,530 (25.6)$ $2018 (\%)$ $3,453 (25.0)$ Length of stay (days) Mean (SD) Mede [IQR 25-75] $7[4-11]$ Number of ICDs-10 Mean (SD) Min-Max $1-149$ Med [IQR 25-75] $5 [5-5]$ Principal ICD-10 diagnosis Circulatory (%) Circulatory (%) $1,336 (24.2)$ Infectious (%) $404 (2.9)$ Respiratory (%) $1,444 (10.5)$ Trauma (%) $1,043 (7.6)$ Mean (SD) $1.83 (1.76)$ Mean (SD) $1.83 (1.76)$ Mean (SD) $1.83 (1.76)$		
Min-Max 65-106 Med [IQR 25-75] 77.00 [68.00-80.00 65-69 (%) 2,226 (16.1) 70-79 (%) 5,811 (42.1) 80-89 (%) 4,845 (35.1) 90 and more (%) 920 (6.7) Year of discharge 2015 (%) 2016 (%) 3,510 (25.4) 2016 (%) 3,318 (24.0) 2017 (%) 3,530 (25.6) 2018 (%) 3,453 (25.0) Length of stay (days) Mean (SD) Min-Max 1-149 Med [IQR 25-75] 7 [4-11] Number of ICDs-10 Mean (SD) Mean (SD) 4.58 (0.92) Min-Max 1-5 Med [IQR 25-75] 5 [5-5] Principal ICD-10 diagnosis Girculatory (%) Circulatory (%) 3,336 (24.2) Infectious (%) 404 (2.9) Respiratory (%) 1,444 (10.5) Trauma (%) 1,043 (7.6) Tumours (%) 1,505 (10.9) Number of CHOP surgical procedures Mean (SD) Mean (SD) 1.83 (1.76)		
Med [IQR 25-75] 77.00 [68.00-80.00 65-69 (%) 2,226 (16.1) 70-79 (%) 5,811 (42.1) 80-89 (%) 4,845 (35.1) 90 and more (%) 920 (6.7) Year of discharge 2015 (%) 2016 (%) 3,501 (25.4) 2016 (%) 3,318 (24.0) 2017 (%) 3,530 (25.6) 2018 (%) 3,453 (25.0) Length of stay (days) 8.44 (7.58) Min-Max 1-149 Med [IQR 25-75] 7 [4-11] Number of ICDs-10 4.58 (0.92) Min-Max 1-5 Med [IQR 25-75] 5 [5-5] Principal ICD-10 diagnosis 3,336 (24.2) Infectious (%) 4.04 (2.9) Respiratory (%) 1,444 (10.5) Trauma (%) 1,043 (7.6) Umber of CHOP surgical procedures 1.505 (10.9) Number of CHOP surgical procedures 0-5 Med [IQR 25-75] 1.60-3] Number of medicines prescribed at hospital discharge 0-5 Med [IQR 25-75] 1 [0-3]		
$\begin{array}{c cccc} 65-69 (\%) & 2,226 (16.1) \\ 70-79 (\%) & 5,811 (42.1) \\ 80-89 (\%) & 4,845 (35.1) \\ 90 and more (\%) & 920 (6.7) \\ \end{array}$ Year of discharge $\begin{array}{c ccccccccccccccccccccccccccccccccccc$		
$\begin{array}{c c} 70-79\ (\%) & 5,811\ (42.1) \\ 80-89\ (\%) & 4,845\ (35.1) \\ 90\ and\ more\ (\%) & 920\ (6.7) \\ \end{array}$	0]	
80-89 (%) 4,845 (35.1) 90 and more (%) 920 (6.7) Year of discharge 3,501 (25.4) 2015 (%) 3,501 (25.4) 2016 (%) 3,318 (24.0) 2017 (%) 3,530 (25.6) 2018 (%) 3,453 (25.0) Length of stay (days) 8.44 (7.58) Min-Max 1-149 Med [IQR 25-75] 7 [4-11] Number of ICDs-10 Mean (SD) Min-Max 1-5 Med [IQR 25-75] 5 [5-5] Principal ICD-10 diagnosis		
90 and more (%) 920 (6.7) Year of discharge 2015 (%) 3,501 (25.4) 2016 (%) 3,318 (24.0) 3,318 (24.0) 2017 (%) 3,530 (25.6) 2018 (%) 3,453 (25.0) Length of stay (days) 3,453 (25.0) Length of stay (days) 8.44 (7.58) Mean (SD) 8.44 (7.58) 1-149 Med [IQR 25-75] 7 [4-11] 1-149 Number of ICDs-10 Mean (SD) 4.58 (0.92) Min-Max 1-5 1458 (0.92) Min-Max 1-5 155] Principal ICD-10 diagnosis 3,336 (24.2) Infectious (%) 4.04 (2.9) 4.04 (2.9) Respiratory (%) 1,444 (10.5) 1,043 (7.6) Trauma (%) 1,043 (7.6) 1.043 (7.6) Number of CHOP surgical procedures Mean (SD) 1.83 (1.76) 0 Min-Max 0-5 0 0 Mean (SD) 1.83 (1.76) 0 0 Mumber of CHOP surgical procedures		
Year of discharge 2015 (%) $3,501 (25.4)$ 2016 (%) $3,318 (24.0)$ 2017 (%) $3,530 (25.6)$ 2018 (%) $3,453 (25.0)$ Length of stay (days) Mean (SD) Mean (SD) $8.44 (7.58)$ Min-Max $1-149$ Med [IQR 25-75] 7 [4-11] Number of ICDs-10 4.58 (0.92) Min-Max $1-5$ Med [IQR 25-75] 5 [5-5] Principal ICD-10 diagnosis $3,336 (24.2)$ Infectious (%) $4,333 (24.2)$ Infectious (%) $4.58 (0.92)$ Min-Max $1-5$ Med [IQR 25-75] 5 [5-5] Principal ICD-10 diagnosis $4.58 (0.92)$ Number of CHOP surgical procedures $4.04 (2.9)$ Number of CHOP surgical procedures $1,043 (7.6)$ Number of CHOP surgical procedures $1.83 (1.76)$ Min-Max $0-5$ Med [IQR 25-75] $1 [0-3]$ Number of medicines prescribed at hospital discharge $8.95 (3.24)$		
$\begin{array}{c cccc} 2015 (\%) & 3,501 (25.4) \\ 2016 (\%) & 3,318 (24.0) \\ 2017 (\%) & 3,530 (25.6) \\ 2018 (\%) & 3,453 (25.0) \\ \end{array}$ Length of stay (days) $\begin{array}{c ccccccccccccccccccccccccccccccccccc$		
$\begin{array}{c cccc} 2016 (\%) & 3,318 (24.0) \\ 2017 (\%) & 3,530 (25.6) \\ 2018 (\%) & 3,453 (25.0) \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$		
2017 (%) 3,530 (25.6) 2018 (%) 3,453 (25.0) Length of stay (days) Mean (SD) Mean (SD) 8.44 (7.58) Min-Max 1–149 Med [IQR 25-75] 7 [4–11] Number of ICDs-10 Mean (SD) Min-Max 1–5 Med [IQR 25-75] 5 [5–5] Principal ICD-10 diagnosis 5 [5–5] Circulatory (%) 3,336 (24.2) Infectious (%) 404 (2.9) Respiratory (%) 1,043 (7.6) Tumours (%) 1,505 (10.9) Number of CHOP surgical procedures Mean (SD) Mean (SD) 1.83 (1.76) Min-Max 0–5 Med [IQR 25–75] 1 [0–3] Number of medicines prescribed at hospital discharge Mean (SD) Mean (SD) 1.83 (1.76) Min-Max 0–5 Med [IQR 25–75] 1 [0–3]		
2018 (%) 3,453 (25.0) Length of stay (days) Mean (SD) Mean (SD) 8.44 (7.58) Min-Max 1–149 Med [IQR 25-75] 7 [4–11] Number of ICDs-10 Mean (SD) Min-Max 1–5 Med [IQR 25-75] 5 [5–5] Principal ICD-10 diagnosis 5 [5–5] Principal ICD-10 diagnosis 3,336 (24.2) Infectious (%) 404 (2.9) Respiratory (%) 1,444 (10.5) Trauma (%) 1,043 (7.6) Tumours (%) 1,505 (10.9) Number of CHOP surgical procedures Mean (SD) Mean (SD) 1.83 (1.76) Min-Max 0–5 Med [IQR 25-75] 1 [0–3] Number of medicines prescribed at hospital discharge Mean (SD) Mean (SD) 8.95 (3.24)		
Length of stay (days) Mean (SD) 8.44 (7.58) Min-Max 1–149 Med [IQR 25-75] 7 [4–11] Number of ICDs-10 Mean (SD) Min-Max 1–5 Med [IQR 25-75] 5 [5–5] Principal ICD-10 diagnosis 1–5 Principal ICD-10 diagnosis 3,336 (24.2) Infectious (%) 3,336 (24.2) Infectious (%) 4.044 (2.9) Respiratory (%) 1,444 (10.5) Trauma (%) 1,043 (7.6) Tumours (%) 1,505 (10.9) Number of CHOP surgical procedures 0–5 Mean (SD) 1.83 (1.76) Min-Max 0–5 Med [IQR 25–75] 1 [0–3] Number of medicines prescribed at hospital discharge Mean (SD) Mean (SD) 8.95 (3.24)		
Mean (SD) 8.44 (7.58) Min-Max 1-149 Med [IQR 25-75] 7 [4-11] Number of ICDs-10 Mean (SD) Mean (SD) 4.58 (0.92) Min-Max 1-5 Med [IQR 25-75] 5 [5-5] Principal ICD-10 diagnosis 5 [5-5] Principal ICD-10 diagnosis 3,336 (24.2) Infectious (%) 404 (2.9) Respiratory (%) 1,444 (10.5) Trauma (%) 1,043 (7.6) Tumours (%) 1,505 (10.9) Number of CHOP surgical procedures 0-5 Med [IQR 25-75] 1 [0-3] Number of medicines prescribed at hospital discharge Mean (SD) Mean (SD) 8.95 (3.24)		
Min-Max 1-149 Med [IQR 25-75] 7 [4-11] Number of ICDs-10 Mean (SD) Mean (SD) 4.58 (0.92) Min-Max 1-5 Med [IQR 25-75] 5 [5-5] Principal ICD-10 diagnosis 5 Circulatory (%) 3,336 (24.2) Infectious (%) 404 (2.9) Respiratory (%) 1,444 (10.5) Trauma (%) 1,043 (7.6) Tumours (%) 1,505 (10.9) Number of CHOP surgical procedures 0-5 Med [IQR 25-75] 1 [0-3] Number of medicines prescribed at hospital discharge Mean (SD) Mean (SD) 8.95 (3.24)		
Med [IQR 25-75] 7 [4-11] Number of ICDs-10 Mean (SD) Mean (SD) 4.58 (0.92) Min-Max 1-5 Med [IQR 25-75] 5 [5-5] Principal ICD-10 diagnosis		
Number of ICDs-10 Mean (SD) 4.58 (0.92) Min–Max 1–5 Med [IQR 25–75] 5 [5–5] Principal ICD-10 diagnosis 3,336 (24.2) Infectious (%) 404 (2.9) Infectious (%) 404 (2.9) Respiratory (%) 1,444 (10.5) Trauma (%) 1,043 (7.6) Tumours (%) 1,505 (10.9) Number of CHOP surgical procedures 9 Mean (SD) 1.83 (1.76) Min–Max 0–5 Med [IQR 25–75] 1 [0–3] Number of medicines prescribed at hospital discharge 8.95 (3.24)		
Mean (SD) 4,58 (0.92) Min-Max 1-5 Med [IQR 25-75] 5 [5-5] Principal ICD-10 diagnosis 3,336 (24.2) Infectious (%) 404 (2.9) Infectious (%) 404 (2.9) Respiratory (%) 1,444 (10.5) Trauma (%) 1,043 (7.6) Tumours (%) 1,505 (10.9) Number of CHOP surgical procedures 9 Mean (SD) 1.83 (1.76) Min-Max 0-5 Med [IQR 25-75] 1 [0-3] Number of medicines prescribed at hospital discharge 8.95 (3.24)		
Min–Max 1–5 Med [IQR 25–75] 5 [5–5] Principal ICD-10 diagnosis 3,336 (24.2) Infectious (%) 404 (2.9) Infectious (%) 404 (2.9) Respiratory (%) 1,444 (10.5) Trauma (%) 1,043 (7.6) Tumours (%) 1,505 (10.9) Number of CHOP surgical procedures 1 Mean (SD) 1.83 (1.76) Min–Max 0–5 Med [IQR 25–75] 1 [0–3] Number of medicines prescribed at hospital discharge 8.95 (3.24)		
Med [IQR 25–75] 5 [5–5] Principal ICD-10 diagnosis 3,336 (24.2) Circulatory (%) 3,336 (24.2) Infectious (%) 404 (2.9) Respiratory (%) 1,444 (10.5) Trauma (%) 1,043 (7.6) Tumours (%) 1,505 (10.9) Number of CHOP surgical procedures 1 Mean (SD) 1.83 (1.76) Min–Max 0–5 Med [IQR 25–75] 1 [0–3] Number of medicines prescribed at hospital discharge 8.95 (3.24)		
Principal ICD-10 diagnosis 3,336 (24.2) Circulatory (%) 3,336 (24.2) Infectious (%) 404 (2.9) Respiratory (%) 1,444 (10.5) Trauma (%) 1,043 (7.6) Tumours (%) 1,505 (10.9) Number of CHOP surgical procedures 1.83 (1.76) Mean (SD) 1.83 (1.76) Min–Max 0– 5 Med [IQR 25–75] 1 [0–3] Number of medicines prescribed at hospital discharge 8.95 (3.24)		
Circulatory (%) 3,336 (24.2) Infectious (%) 404 (2.9) Respiratory (%) 1,444 (10.5) Trauma (%) 1,043 (7.6) Tumours (%) 1,505 (10.9) Number of CHOP surgical procedures 1.83 (1.76) Mean (SD) 1.83 (1.76) Med [IQR 25–75] 1 [0–3] Number of medicines prescribed at hospital discharge 8.95 (3.24)		
Infectious (%) 404 (2.9) Respiratory (%) 1,444 (10.5) Trauma (%) 1,043 (7.6) Tumours (%) 1,505 (10.9) Number of CHOP surgical procedures 1.83 (1.76) Mean (SD) 1.83 (1.76) Min–Max 0– 5 Med [IQR 25–75] 1 [0–3] Number of medicines prescribed at hospital discharge 8.95 (3.24)		
Respiratory (%) 1,444 (10.5) Trauma (%) 1,043 (7.6) Tumours (%) 1,505 (10.9) Number of CHOP surgical procedures Mean (SD) 1.83 (1.76) Min–Max 0–5 Med [IQR 25–75] 1 [0–3] Number of medicines prescribed at hospital discharge Mean (SD) 8.95 (3.24)		
Trauma (%) 1,043 (7.6) Tumours (%) 1,505 (10.9) Number of CHOP surgical procedures Mean (SD) Mean (SD) 1.83 (1.76) Min–Max 0– 5 Med [IQR 25–75] 1 [0–3] Number of medicines prescribed at hospital discharge 8.95 (3.24)		
Tumours (%)1,505 (10.9)Number of CHOP surgical proceduresMean (SD)Mean (SD)1.83 (1.76)Min–Max0– 5Med [IQR 25–75]1 [0–3]Number of medicines prescribed at hospital discharge4Mean (SD)8.95 (3.24)		
Number of CHOP surgical procedures Mean (SD) Min–Max 0– 5 Med [IQR 25–75] 1 [0–3] Number of medicines prescribed at hospital discharge Mean (SD) Mean (SD) 8.95 (3.24)		
Mean (SD) 1.83 (1.76) Min–Max 0– 5 Med [IQR 25–75] 1 [0–3] Number of medicines prescribed at hospital discharge 8.95 (3.24)		
Min–Max0–5Med [IQR 25–75]1 [0–3]Number of medicines prescribed at hospital discharge4Mean (SD)8.95 (3.24)		
Med [IQR 25-75] 1 [0-3] Number of medicines prescribed at hospital discharge Mean (SD) Mean (SD) 8.95 (3.24)		
Number of medicines prescribed at hospital discharge Mean (SD) 8.95 (3.24)		
discharge Mean (SD) 8.95 (3.24)		
Mean (SD) 8.95 (3.24)		
Med [IQR 25–75] 8 [7.50–16.00]		

_
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
16 17
12
18 19
19 20
20 21
21 22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
45 46
47 19
48 40
49 50
50
51
52
53
54
55
56
57
58
59
60

Variables	30-day hospital readmission	<i>p</i> -value
Complete sample	7.8%	
Sex		*
Women vs men	7.3% vs 8.2%	
Year-end age, in years		NS
65–69	7.5%	
70–79	7.6%	
80–89	8.4%	
≥ 90	6.4%	
Mobility cluster:		NS
Preserved mobility vs impaired mobility	7.6% vs 8.5%	
Activities in daily living (ADL):		NS

Complete sample	/.8%0	
Sex		:
Women vs men	7.3% vs 8.2%	
Year-end age, in years	1.576 45 0.276	NS
65–69	7.5%	111
70–79	7.6%	
80-89	8.4%	
≥ 90	6.4%	
Mobility cluster:	0.770	NS
Preserved mobility vs impaired mobility	7.6% vs 8.5%	144
Activities in daily living (ADL):	7.070 V3 0.570	N
Full ADL ability vs impaired ADL	7.8% vs 7.2%	144
Cognitive status:	7.870 VS 7.270	NS
Preserved cognitive status vs cognitive impairment	7.8% vs 7.9%	11.
ICD-10 diagnosis: circulatory problems	7.8% VS 7.9%	*:
	9 20/ (50/	~ ·
ICD-10 diagnosis: infection	8.2% vs 6.5%	٦. ٣
5	7.7%	NS
No vs Yes	7.7% vs 9.9%	
ICD-10 diagnosis: respiratory problems		N
No vs Yes	7.8% vs 8.0%	
ICD-10 diagnosis: trauma		*:
No vs Yes	8.0% vs 5.8%	
ICD-10 diagnosis: tumour		**:
No vs Yes	6.9% vs 15.1%	
Number of ICD-10 conditions		**:
1	1.5%	
2	4.9%	
3	3.6%	
4	4.8%	
5	8.8%	
Number of surgical procedures (CHOP)		:
0	7.7%	
1	7.8%	
2	7.0%	
3	7.3%	
4	7.1%	
5	9.7%	
Year of discharge: 2015–2018		NS
2015	8.3%	
2016	8.0%	
2017	8.0%	
2018	6.8%	

30-day

readmission

with NO

drugs in this

class

7.1%

7.7%

7.7%

7.4%

8.0% 7.6%

8.0%

7.8%

7.4%

7.8%

7.8%

7.0%

7.4%

7.7%

7.8%

7.3%

7.7%

7.8%

7.4%

7.5%

7.4%

7.8%

7.6%

7.7%

7.2%

7.8%

7.8%

7.1%

7.7%

8.7%

8.3%

7.8%

7.8%

7.7%

7.8%

6.8%

7.8% 7.9% 30-day

readmission

with drugs in

this class

8.0%

9.4%

8.3%

9.5%

7.2%

12.6%

6.5%

6.6%

9.9%

8.4%

12.2%

8.5%

13.4%

27.7%

14.3%

10.8%

12.9%

10.0%

9.5%

9.9%

8.8%

6.3%

8.9%

14.1%

9.8%

15.2%

9.8%

8.6%

8.6%

7.1%

7.1%

18.8%

7.8%

9.0%

6.9%

9.3%

7.7%

5.1%

р-

value

NS

NS

NS

NS

*

*** ***

NS

NS ***

NS

*** ***

NS ***

** NS

NS ***

NS

NS ***

NS ***

**

*

NS

NS

NS

NS

NS

678 Table 3. 30-day hospital readmissions for different classes of drugs based	ł
Drug class	
First level, anatomical main group	
Blood and blood-forming organ drugs (B)	
Dermatologicals (D)	
Genitourinary system and sex hormones (G)	
Systemic hormonal preparations, excluding sex hormones and insulins (H)	
Anti-infectives for systemic use (J)	
Antineoplastic and immunomodulating agents (L)	
Drugs for the musculo-skeletal system (M)	
Antiparasitic products, insecticides, and repellents (P)	
Respiratory system drugs (R)	
Sensory organ drugs (S)	
Second level, therapeutic subgroup	
Stomatological preparations (A01)	
Drugs for acid-related disorders (A02)	
Drugs for functional gastrointestinal disorders (A03)	
Antiemetics and antinauseants (A04)	
Bile and liver therapy drugs (A05)	
Drugs for constipation (A06)	
Antidiarrhoeals, intestinal anti-inflammatory/anti-infective agents (A07)	
Digestives, including enzymes (A09)	
Drugs used in diabetes (A10)	
Vitamins (A11)	
Mineral supplements (A12)	
Other alimentary tract and metabolism products (A16)	
Cardiac therapy (C01)	
Antihypertensives (C02)	
Diuretics (C03)	
Peripheral vasodilators (C04)	
Vasoprotective drugs (C05)	
Beta-blocking agents (C07)	
Calcium channel blockers (C08)	1
Agents acting on the renin-angiotensin system (C09)	
Lipid-modifying agents (C10)	
Anaesthetics (N01)	
Analgaesics (N02)	
Antiepileptics (N03)	
Drugs for Parkinson's disease (N04)	
Psycholeptics (N05)	
Psychoanaleptics (N06)	
Other nervous system drugs (N07)	_
679 Note. * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$; NS = non-significant	-
680	

678	Table 3. 30-day hospital	eadmissions for different classes	of drugs based on the ATC	(N = 13,802).

57

- 58 59
- 60

681	Table 4. Baseline, multilevel, logistic regression model using 30-day readmission ($0 = no; 1 = yes$) as the
-----	--

dependent variable associated with independent sociodemographic, LOS, and clinical variables

683	(N = 13,802 observations for 8,878 different inpatients readmitted to hospital).
-----	---

Variables	Odds Ratio ³	<i>P</i> > z	95% CI ⁴	
Sex	1.079	0.285	0.938-1.242	
Year-end age, in years	0.999	0.878	0.990-1.00	
Hospital length of stay (LOS), in days	1.014	0.000	1.006-1.02	
Mobility cluster ¹	1.218	0.015	1.039-1.42	
Dependency in the activities of daily living ¹	0.794	0.248	0.537-1.17	
Mental health status ¹	0.992	0.966	0.687-1.43	
CIM 1 diagnosis: circulatory problems ²	0.938	0.491	0.783-1.12	
CIM 1 diagnosis: infection ²	1.381	0.078	0.964–1.97	
CIM 1 diagnosis: respiratory problems ²	1.100	0.414	0.875-1.382	
CIM 1 diagnosis: trauma ²	0.847	0.265	0.633-1.134	
CIM 1 diagnosis: tumour ²	2.538	0.000	2.089-3.082	
Number of CIM	1.419	0.000	1.282-1.572	
Number of CHOP	0.978	0.304	0.938-1.02	
Number of drugs	1.043	0.000	1.028-1.05	
Year: 2015 to 2018	0.933	0.022	0.880-0.99	
Intercept		0.027		

Note. 1: 0 = good state, 1 = impairment; 2: 0 = no, 1 = yes; 3: adjusted Odds ratio; 4:

Table 5. Multilevel logistic regression model results for the drugs prescribed to older patients at discharge home that had significant predictive values (odds ratios) for 30-day hospital readmission (controlled for variables in the baseline model: Table 4) (N = 13,802 observations for 8,878 different inpatients

readmitted to hospital).

Variables	Odds ratio ¹	p > z	95% CI ²			
First level, anatomical main group						
Blood and blood-forming organs drugs (B)	1.089	0.041	1.003-1.181			
Systemic hormonal preparations, excluding sex hormones and insulins (H)	1.207	0.007	1.052-1.385			
Respiratory system drugs (R)	1.146	0.003	1.046-1.254			
Second level, therapeutic subgroup						
Drugs for functional gastrointestinal disorders (A03)	1.424	0.001	1.166-1.739			
Antiemetics and antinauseants (A04)	3.216	0.000	1.842-5.617			
Drugs for constipation (A06)	1.195	0.018	1.031-1.386			
Drugs used in diabetes (A10)	1.125	0.021	1.018-1.243			
Vitamins (A11)	1.201	0.008	1.049-1.374			
Antihypertensives (C02)	1.771	0.000	1.287-2.438			

0.024

0.040

0.015

0.009

1.018-1.296

1.007-1.327

0.732-0.967

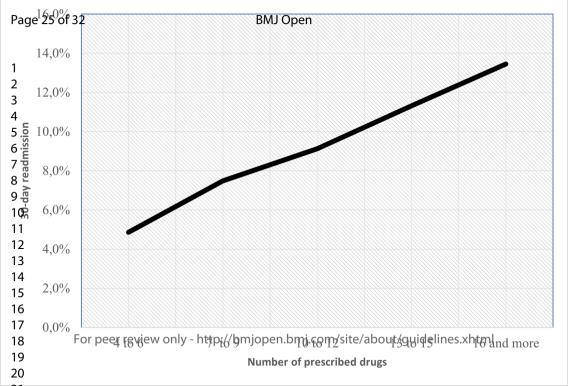
1.031-1.238

	Diuretics (C03)	1.149
	Beta-blocking agents (C07)	1.156
	Lipid-modifying agents (C10)	0.841
	Psycholeptics (N05)	1.130
693	Note. $1 =$ adjusted odds ratio; $2 =$ CI or Confidence Interval	
694		
695		

- Table 6. Drugs and drugs interactions from ATC classes A and B with a significant risk of 30-day
- hospital readmission (controlled for variables in the baseline model: Table 4) (N = 13,802 observations
- for 8,878 different inpatients readmitted to hospital).

First level, anatomical main grou Blood and blood-forming organ drugs (B) Systemic hormonal preparations, excluding sex hormones and insulins (H) Respiratory system drugs (R) Second level, therapeutic subgrous Antiemetics and antinauseants (A04)	1.089 1.210 1.149	0.040 0.007 0.003	1.004–1.182 1.054–1.390
Systemic hormonal preparations, excluding sex hormones and insulins (H) Respiratory system drugs (R) Second level, therapeutic subgro Antiemetics and antinauseants (A04)	1.210 1.149	0.007	
insulins (H) Respiratory system drugs (R) Second level, therapeutic subgro Antiemetics and antinauseants (A04)	1.149		1.054–1.390
Second level, therapeutic subgro Antiemetics and antinauseants (A04)		0.003	1
Antiemetics and antinauseants (A04)	un	0.005	1.049-1.258
	up		
	3.222	0.000	1.844-5.630
Drugs for functional gastrointestinal disorders (A03)	1.428	0.000	1.169–1744
Beta-blocking agents (C07) and drugs for acid-related disorders (A02)	1.367	0.022	1.046–1.788
Drugs for constipation (A06)	1.199	0.017	1.033-1.392
Agents acting on the renin-angiotensin system (C09)	0.892	0.049	0.796-0.999
Lipid-modifying agents (C10)	0.838	0.013	0.729-0.964

Note. 1: adjusted odds ratio; 2: CI = Confidence Interval



3
4
5
6
7
8
9
10
11
12
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
59

1 2 3

Supplementary table. Descriptive statistics of drugs prescribed per hospital stays (N = 13,802 readmissions) at discharge based on the ATC Classification System.

Drug classes based on the ATC Classification System	Min-Max	Mean (Sl
First level, anatomical main group		
Blood and blood forming organs (B)	0-5	1.15 (0.8
Dermatologicals (D)	0–3	0.04 (0.2
Genitourinary system and sex hormones (G)	0-4	0.21 (0.4
Systemic hormonal preparations, excl. sex hormones and insulins (H)	0-4	0.20 (0.4
Anti-infectives for systemic use (J)	0-4	0.24 (0.4
Antineoplastic and immunomodulating agents (L)	0-5	0.05 (0.2
Musculo-skeletal system (M)	0–3	0.15 (0.3
Antiparasitic products, insecticides and repellents (P)	0-2	0.02 (0.1
Respiratory system (R)	0-7	0.28 (0.7
Sensory organs (S)	0–6	0.10 (0.3
Second level, therapeutic subgroup		
Stomatological preparations (A01)	0-1	0.00 (0.0
Drugs for acid-related disorders (A02)	0–3	0.56 (0.5
Drugs for functional gastrointestinal disorders (A03)	0–3	0.07 (0.2
Antiemetics and antinauseants (A04)	0-1	0.01 (0.0
Bile and liver therapy (A05)	0-1	0.00 (0.0
Drugs for constipation (A06)	0–3	0.15 (0.4
Antidiarrhoeals, intestinal anti-inflammatory/anti-infective agents (A07)	0-2	0.03 (0.1
Digestives, incl. Enzymes (A09)	0-2	0.02 (0.1
Drugs used in diabetes (A10)	0–5	0.26 (0.6
Vitamins (A11)	0-4	0.15 (0.4
Mineral supplements (A12)	0–3	0.29 (0.5
Other alimentary tract and metabolism products (A16)	0-1	0.00 (0.0
Cardiac therapy drugs (C01)	0-4	0.14 (0.4
Antihypertensives (C02)	0–2	0.02 (0.1
Diuretics (C03)	0–3	0.27 (0.5
Peripheral vasodilators (C04)	0-1	0.00 (0.0
Vasoprotectives (C05)	0–3	0.02 (0.1
Beta-blocking agents (C07)	0–2	0.46 (0.5
Calcium channel blockers (C08)	0–2	0.16 (0.3
Agents acting on the renin-angiotensin system (C09)	0–3	0.64 (0.6
Lipid modifying agents (C10)	0-3	0.43 (0.5
Anaesthetics (N01)	0-1	0.00 (0.0
Analgaesics (N02)	0-7	1.02 (0.9
Antiepileptics (N03)	0-5	0.11 (0.3
Drugs for Parkinson's disease (N04)	0-5	0.04 (0.2
Psycholeptics (N05)	0-6	0.53 (0.7)
Psychoanaleptics (N06)	0-3	0.20 (0.4
Other nervous system drugs(N07)	0-3	0.03 (0.1
Total number of drugs	5-30	8.95 (3.24

BMJ Open

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items ar reported
Title and abstra	ct				-
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b)Provide in the abstract an informative and balanced		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included.	Title Abstract (lines 2 8)
		summary of what was done and what was found	Pr	RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract.	Line 6 Lines 118-121
			ierie	RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Not applicable, only one hospit register
Introduction			-		
Background rationale	2	Explain the scientific background and rationale for the investigation being reported		0/1/	Lines 39-101
Objectives	3	State specific objectives, including any prespecified hypotheses			Lines 101-107
Methods					
Study Design	4	Present key elements of study design early in the paper			Lines 110-114
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			Lines 117-133

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using

Participants	6	(a) Cohort study - Give the	RECORD 6.1: The methods of study	in press/
1		eligibility criteria, and the	population selection (such as codes or	forthcoming
		sources and methods of selection	algorithms used to identify subjects)	JMIR article:
		of participants. Describe	should be listed in detail. If this is not	https://www.ncl
		methods of follow-up	possible, an explanation should be	nlm.nih.gov/pul
		<i>Case-control study</i> - Give the	provided.	ed/management
		eligibility criteria, and the	1	alidator/909A44
		sources and methods of case	RECORD 6.2: Any validation studies	74F70/citations
		ascertainment and control	of the codes or algorithms used to	tart=0
		selection. Give the rationale for	select the population should be	
		the choice of cases and controls	referenced. If validation was conducted	
		Cross-sectional study - Give the	for this study and not published	
		eligibility criteria, and the	elsewhere, detailed methods and results	
		sources and methods of selection	should be provided.	
		of participants	1	
			RECORD 6.3: If the study involved	
		(b) Cohort study - For matched	linkage of databases, consider use of a	Not applicable,
		studies, give matching criteria	flow diagram or other graphical display	only one hospit
		and number of exposed and	to demonstrate the data linkage	register
		unexposed	process, including the number of	C .
		<i>Case-control study</i> - For	individuals with linked data at each	
		matched studies, give matching	stage.	
		criteria and the number of		
		controls per case		
Variables	7	Clearly define all outcomes,	RECORD 7.1: A complete list of codes	Lines 152-177
		exposures, predictors, potential	and algorithms used to classify	and
		confounders, and effect	exposures, outcomes, confounders, and	in press/
		modifiers. Give diagnostic	effect modifiers should be provided. If	forthcoming
		criteria, if applicable.	these cannot be reported, an	JMIR article:
			explanation should be provided.	https://www.nc
				<u>nlm.nih.gov/pu</u>
				ed/managemen
				alidator/909A4
				74F70/citations
				<u>tart=0</u>
Data sources/	8	For each variable of interest,		Lines 122-128
measurement		give sources of data and details		and

		of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		in press/ forthcoming JMIR article: https://www.ncl nlm.nih.gov/pul ed/management alidator/909A44 74F70/citations/ tart=0
Bias	9	Describe any efforts to address potential sources of bias Explain how the study size was	rev.	Lines 180-200 and in press/ forthcoming JMIR article: <u>https://www.nc</u> <u>nlm.nih.gov/pui</u> <u>ed/management</u> <u>alidator/909A44</u> <u>74F70/citations</u> <u>tart=0</u>
Study size	10	Explain how the study size was arrived at	4	Lines 141-144
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	n n n n n n n n n n n n n n n n n n n	Lines 139-150 and in press/ forthcoming JMIR article: https://www.nci nlm.nih.gov/pui ed/management alidator/909A44 74F70/citations tart=0

Statistical methods	12	 (a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> - If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> - If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses 			Lines 180-200
Data access and cleaning methods			0	RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Lines 118-122 and in press/ forthcoming JMIR article: https://www.ncbi. nlm.nih.gov/pubm ed/management/v alidator/909A44E 74F70/citations/?s tart=0
Linkage				RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of	in press/ forthcoming JMIR article: <u>https://www.ncbi.</u> <u>nlm.nih.gov/pubm</u>

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

				linkage quality evaluation should be provided.	ed/manageme alidator/909A 74F70/citation tart=0
Results	1				I
Participants	13	 (a) Report the numbers of individuals at each stage of the study (<i>e.g.</i>, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non- participation at each stage. (c) Consider use of a flow diagram 	2	RECORD 13.1: Describe in detail the selection of the persons included in the study (<i>i.e.</i> , study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Lines 142-143
Descriptive data	14	 (a) Give characteristics of study participants (<i>e.g.</i>, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) <i>Cohort study</i> - summarise follow-up time (<i>e.g.</i>, average and total amount) 	revie	201/2	Lines 152-177
Outcome data	15	Cohort study - Report numbers of outcome events or summary measures over time Case-control study - Report numbers in each exposure category, or summary measures of exposure Cross-sectional study - Report numbers of outcome events or summary measures			Lines 142-144

Page	32 of	32
------	-------	----

Main results	16	 (a) Give unadjusted estimates and, if applicable, confounder- adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period 			Lines 207-285
Other analyses	17	Report other analyses done— e.g., analyses of subgroups and interactions, and sensitivity analyses			Lines 207-285
Discussion		unuryses		l	
Key results	18	Summarise key results with reference to study objectives			Lines 289-294
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	2	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Lines 369-378
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			Lines 294-361

Generalisability	21	Discuss the generalisability		Lines 349-355
		(external validity) of the study		
		results		
Other Information	on			
Funding	22	Give the source of funding and		Line 399
-		the role of the funders for the		
		present study and, if applicable,		
		for the original study on which		
		the present article is based		
Accessibility of			RECORD 22.1: Authors should	in press/
protocol, raw			provide information on how to access	forthcoming
data, and			any supplemental information such as	JMIR article:
programming			the study protocol, raw data, or	https://www.ncb
code			programming code.	nlm.nih.gov/pub
				ed/management/
				alidator/909A44
				74F70/citations/
				tart=0

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. PLoS Medicine 2015; in press.

*Checklist is protected under Creative Commons Attribution (CC BY) license.