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ORIGINAL RESEARCH ARTICLE

Cross-Sectional Study on Factors Associated with Hyperpolypharmacy and Medication Adherence in Older Adults with Multimorbidity and Polypharmacy

Shanthi Beglinger[1] · Lisa Bretagne[1,2] · François Volery[2] · Cinzia Del Giovane[1] · Katharina T. Jungo[1] · Denis O'Mahony[3] · Sophie Marien[4] · Anne Spinewine[5] · Wilma Knol[6] · Ingeborg Wilting[7] · Nicolas Rodondi[1,2] · Christine Baumgartner[2]

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Abstract

Background Knowledge of multiple medication use and medication adherence is important to assess treatment effectiveness and prevent worsening of disease, re-hospitalization, and increased healthcare costs. Limited data exist on individuals with hyperpolypharmacy (ten or more concurrent medications) and their adherence.

Objective The objective of the study was to identify potential factors associated with hyperpolypharmacy, and medication adherence in participants with hyperpolypharmacy, as well as explore the relationship between hyperpolypharmacy and medication adherence.

Methods This is a cross-sectional analysis of baseline data from OPERAM, a multicenter study across four large European hospitals. Adults aged ≥ 70 years with multimorbidity and polypharmacy (five or more regular medications) were included. Demographic, clinical, and healthcare utilization data were assessed. Outcomes were hyperpolypharmacy and low/medium medication adherence (i.e., a score < 8 out of a maximum of 8) based on the Morisky Medication Adherence Scale-8 (MMAS-8©). Multivariable logistic regression was used to identify factors associated with hyperpolypharmacy or low/medium adherence.

Results Of 2005 patients with multimorbidity and polypharmacy, 1029 (51%) exhibited hyperpolypharmacy. In multivariable analyses, the following factors were significantly associated with hyperpolypharmacy: increasing number of comorbidities (p for linear trend < 0.001), nursing home residency (odds ratio [OR] 2.20, 95% confidence interval [CI] 1.42–3.41), and visits to specialists/emergency department (OR 1.60, 95% CI 1.16–2.19) or any hospitalizations (OR 1.89, 95% CI 1.42–2.52) compared with visits to primary care physicians only. In the subgroup of 978 hyperpolypharmacy-only adults with available adherence data, 517 (53%) had low/medium medication adherence. In multivariable analyses, the odds of low/medium medication adherence increased with increasing number of comorbidities (p for linear trend 0.005) but decreased with older age (OR 0.69, 95% CI 0.52–0.92 for ≥ 80 versus < 80 years) and receipt of community nurse care (OR 0.59, 95% CI 0.44–0.81).

Conclusions More than half of older adults with hyperpolypharmacy had suboptimal medication adherence. Our findings suggest that primary care physicians may contribute to reducing hyperpolypharmacy, while introduction of community nurse visits could improve medication adherence.

1 Introduction

Polypharmacy refers to the concurrent use of multiple medications; major polypharmacy, also known as hyperpolypharmacy, is often defined as the use of ten or more daily chronic medications [1, 2]. The prevalence of hyperpolypharmacy in previous studies ranged from 10% to almost 60% among older adults, depending on the setting [3–5], with the highest prevalence reported in nursing home residents and hospitalized patients [4, 6, 7]. Factors known to be associated with hyperpolypharmacy are age as well as number and type of comorbidities, but there are conflicting reports on the association with other factors such as sex, education level, body mass index (BMI), and alcohol consumption [3, 4, 8, 9]. These studies used different definitions for hyperpolypharmacy; e.g., topical drugs or over-the counter medications were not uniformly recorded. Data on

Shanthi Beglinger and Lisa Bretagne: Shared first authorship.

Extended author information available on the last page of the article

Key Points

This study found that patients visiting the emergency department, being hospitalized, or being a nursing home resident were significantly associated with hyperpolypharmacy.

In patients with hyperpolypharmacy, over half did not have high medication adherence, which was significantly associated with increasing number of comorbidities, but medication adherence was better in patients who received regular community nurse visits.

Regular medication review through primary care physicians may limit hyperpolypharmacy, while community nurse visits may improve medication adherence in the vulnerable population of older patients with hyperpolypharmacy.

the relationship between healthcare utilization and the risk of hyperpolypharmacy remain limited. Gaining insights into which types of healthcare service (e.g., hospitalizations or general practitioner [GP] visits) contribute to or help prevent hyperpolypharmacy could guide the development of targeted interventions for pharmacotherapy optimization.

While appropriate medication can treat disease and relieve symptoms, an increasing number of medications can increase the risk of potentially inappropriate prescribing through over- or undertreatment [10], potentially resulting in adverse drug reactions and poor clinical outcomes, such as falls, rehospitalization, or mortality [11]. Furthermore, the use of multiple medications could cause medication adherence problems in older patients [12]. The consequences of medication nonadherance are avoidable hospitalizations, excessive need for emergency care, and increased outpatient visits, which cost an estimated 125 billion euro (€) per year in Europe alone and contribute to nearly 200,000 premature deaths per year [13].

Polypharmacy has a well-known negative effect on medication adherence [12], and the risk of poor adherence may be particularly high in patients with hyperpolypharmacy, simply because of the greater number of medications that can be missed [14, 15]. A systematic review including seven studies on medication adherence in adults aged ≥ 65 years living at home with polypharmacy concluded that the available literature on this topic was scarce, and further studies were needed in this population [16]. These older patients with multimorbidity represent a growing population but are often excluded from clinical trials [17]. Moreover, studies on the association of hyperpolypharmacy with medication nonadherance are sparse, and, in particular, studies examining the factors associated with nonadherance in this vulnerable elderly population with multimorbidity and hyperpolypharmacy are lacking. Furthermore, it is unknown whether the number and type of previous physician contacts are associated with more hyperpolypharmacy, and subsequently worse medication adherence.

Identifying factors that are associated with hyperpolypharmacy and medication nonadherance in older adults with multimorbidity is important to identify patients at risk and to develop targeted interventions to reduce associated morbidity, mortality, and healthcare costs. Thus, the aims of this study were to identify factors associated with hyperpolypharmacy, to investigate the relationship between hyperpolypharmacy and medication adherence, and to identify factors associated with medication adherence among older hospitalized patients with hyperpolypharmacy.

2 Methods

2.1 Study Design and Setting

This is a cross-sectional study using baseline data from the international multicenter, cluster randomized OPERAM trial (OPtimising thERapy to prevent avoidable hospital Admissions in Multimorbid older adults, ClinicalTrials.gov NCT02986425) [18]. In OPERAM, hospitalized older adults with multimorbidity and polypharmacy were randomized to either a control group receiving usual care or an intervention group receiving usual care plus pharmacotherapy optimization based on STOPP/START version 2 criteria [19]. The aim of the trial was to assess the effects of the intervention on drug-related hospital admissions. The trial was conducted in four European university-based hospitals (Bern, Switzerland; Utrecht, Netherlands; Brussels, Belgium; and Cork, Republic of Ireland). Details on the study design of OPERAM have been previously published [20]. Between 1 December 2016 and 31 October 2018, 2008 hospitalized patients were enrolled into the OPERAM trial.

The local ethics committees at the participating sites approved the OPERAM study. All participants or their legal representatives provided written informed consent to enrollment. This present study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [21].

2.2 Participants

For OPERAM enrollment, older adults aged ≥ 70 years admitted to a participating medical or surgical ward were recruited if they had three or more chronic conditions (comorbidities defined by International Classification of Diseases 10th revision [ICD-10] codes with an estimated duration of ≥ 6 months or based on a clinical decision [22]), and five or more regular medications (defined as medications used for > 30 days before eligibility assessment was performed). Exclusion criteria were: (i) planned transfer to palliative care within 24 h after hospital admission, (ii) having already received a medication review within 2 months prior to enrollment, and (iii) inability to provide written informed consent or obtain consent via a proxy.

2.3 Hyperpolypharmacy

Hyperpolypharmacy was defined as the intake of ten or more different concomitant regular medications on the basis of Anatomical Therapeutic Chemical (ATC) classification codes for > 30 days prior to eligibility assessment. Pre-hospital admission medication use was assessed with a Structured History taking of Medication (SHiM) questionnaire administered by a pharmacist [23], followed by verification with the patient's primary care physician and medical records reconciliation. For the current study, participants were divided into two groups: (i) patients with hyperpolypharmacy (i.e., ten or more regular medications) versus patients without hyperpolypharmacy (less than ten regular medications) at baseline.

2.4 Medication Adherence

To assess medication adherence, we used the 8-item Morisky Medication Adherence Scale-8 (MMAS-8©) [24], which was a questionnaire completed by OPERAM study participants together with study team pharmacists at the baseline visit. The MMAS-8© score has been validated across several patient populations and for various chronic conditions [25]. It consists of eight questions, with seven questions having a dichotomous answer (yes/no) to identify barriers to medication adherence, i.e., when and why medications were missed; and the final question that asks about how often individuals forget to take their medication is scored on a 5-point Likert scale. Each item is assigned a maximum of 1 point, and thus, the MMAS-8© score ranges from 0 to 8 points. Morisky et al. have established cut-off scores to place individuals into one of three adherence categories: low adherence is considered as a score below 6 points (i.e., 0–5.75 points), medium adherence is a score between 6 and < 8 points (i.e., 6–7.75 points), and high adherence is defined as the maximum score of 8 points on the basis of validated cut-offs [26, 27]. For the current study, patients were categorized into two groups: low/medium adherence (MMAS score < 8 points) versus high adherence (MMAS = 8 points).

2.5 Covariates

Trained study nurses collected data on self-reported demographics and clinical characteristics, including BMI, Barthel Index of Activities of Daily Living (ADL) [28], number and type of comorbidities as defined by ICD-10 codes [22], as well as type of healthcare utilization (physician visits, nursing home residency, or receipt of community nurse care, i.e., nursing visits at the patient's own home). The type of physician contact in the previous 12 months was defined as (1) no contact, (2) primary care physician or general practitioner (GP) visits only, (3) any hospital specialist or emergency department (ED) visits (with or without GP visits) but no hospitalizations, or (4) at least one hospitalization (i.e., hospital stay of > 24 h), irrespective of any outpatient visits. In all participating countries, nursing home residents still received care from a GP. The Charlson Comorbidity Index as a measure to predict 10-year survival was calculated (range 0–33 points) [29], with lower scores indicating a lower 10-year mortality. Quality of life was assessed using the visual analogue scale of the European quality of life-5 dimensions (EQ-5D) questionnaire (range 0–100 points), with higher scores relating to higher quality of life [30]. EQ-5D™ is a trademark of the EuroQol Group. The full list of variables is presented in Table 1.

2.6 Statistical Analysis

The baseline characteristics of participants were presented as descriptive statistics and compared between patients with and without hyperpolypharmacy using the rank-sum test, or Student's *t*-test for continuous and chi-squared test for categorical variables, as appropriate.

For this analysis, firstly we determined risk factors associated with hyperpolypharmacy. We first included all baseline variables from the OPERAM trial with conceptual importance in a univariable logistic regression. All baseline variables univariately associated with hyperpolypharmacy with a p-value < 0.20 were selected for inclusion in the subsequent multivariable model to explore independent risk factors for hyperpolypharmacy. In a sensitivity analysis, we investigated whether the number of physician contacts (as opposed to type of physician contact such as GP or specialist) was associated with hyperpolypharmacy.

Secondly, we assessed the association between hyperpolypharmacy and medication adherence using multivariable logistic regression adjusted for potential confounders. Hyperpolypharmacy was included in the model as the independent variable and medication adherence as the dependent variable. To identify confounding variables for this association, we used a directed acyclic graph (DAG) to select the covariables for inclusion in the regression model [31]. These variables included age, sex, Charlson Comorbidity

Table 1 Baseline characteristics of all study participants according to hyperpolypharmacy (HPP) status

Characteristics	HPP (n = 1029)	No HPP (n = 976)	p-value
Age (years)	79 (74–84)	79 (74–84)	0.57
Female sex	492 (47.8)	403 (41.3)	0.003
Number of medications	13 (11–16)	7 (6–8)	< 0.001
Number of comorbidities	12 (9–18)	10 (7–14)	< 0.001
BMI (kg/m^2), mean (SD)	27.5 (6.4)	26.4 (4.9)	< 0.001
Education			< 0.001
Less than high school	342 (33.7)	253 (26.3)	
High school	476 (46.9)	433 (45.0)	
University	198 (19.5)	277 (28.8)	
Current smoker	79 (7.7)	79 (8.1)	0.73
Alcohol consumption[a]			< 0.001
None	654 (64.0)	531 (54.9)	
Moderate	316 (30.9)	347 (35.9)	
Heavy drinker	52 (5.1)	90 (9.3)	
Number of falls in last year			< 0.001
0	588 (57.7)	632 (65.2)	
1	196 (19.2)	178 (18.4)	
≥ 2	236 (23.1)	159 (16.4)	
Health indexes			
CCI, mean (SD)[b]	6.6 (2.3)	5.9 (2.2)	< 0.001
HrQoL EQ-VAS score[c]	70 (50–80)	75 (60–90)	< 0.001
MMAS-8© total score[d]	7 (6–8)	7 (6.25–8)	0.13
ADL (Barthel's index)[e]			< 0.001
Independent	318 (31.6)	430 (45.3)	
Slightly dependent	114 (11.3)	128 (13.5)	
Moderate dependency	396 (39.3)	279 (29.4)	
Severe dependency	146 (14.5)	94 (9.9)	
Total dependency	34 (3.4)	18 (1.9)	
Healthcare utilization[f]			
Type of physician contact prior to baseline visit			< 0.001
No contact	10 (1.0)	22 (2.3)	
GP contact only	158 (15.4)	233 (24.0)	
Any specialist/ED visit, but no hospitalizations	256 (25.0)	298 (30.7)	
Any hospitalizations	600 (58.6)	419 (43.1)	
Nursing home resident	138 (13.5)	54 (5.6)	< 0.001
Receipt of community nurse care	328 (32.1)	195 (20.1)	< 0.001

Numbers are presented as no. (%) or median (interquartile range) unless otherwise indicated. p-values were calculated using the rank-sum test or Student's t-test for continuous variables and chi-squared test for categorical variables, as appropriate

ADL activities of daily living, *BMI* body mass index, *CCI* Charlson Comorbidity Index, *ED* emergency department, *GP* general practitioner/family physician, *HPP* hyperpolypharmacy, *HrQoL EQ-VAS* health-related quality of life EuroQol visual analogue scale, *MMAS-8©* Morisky Medication Adherence Scale-8, *SD* standard deviation

[a]A heavy drinker is defined as consumption of > 14 units of standard alcoholic drinks per week for men and > 7 units per week for women [52]

[b]The CCI predicts 10-year survival in patients with multiple comorbidities. The total score ranges from 0 (highest survival) to 37 points (lowest survival); 7 points correspond to an estimated 0% 10-year survival

[c]HrQoL EQ-VAS is a measure of self-rated health on a vertical visual analogue scale ranging from 0 ("worst health you can imagine") to 100 points ("best health you can imagine")

[d]The MMAS-8© is a 8-item questionnaire used to assess a patient's medication adherence. The scale ranges from 0 (nonadherance) to 8 points (high adherence). Low/medium adherence was defined as < 8 points (Use of Morisky medication adherence measure questionnaire MMAS© is protected by US copyright laws. Permission for use is required. A license agreement was obtained from Professor Donald E. Morisky, ScD, ScM, MSPH, Department of Community Health Sciences, UCLA Fielding School of Public Health, 650 Charles E Young Drive South, Los Angeles, CA 90095-1772, USA. dmorisky@ucla.edu

[e]The Barthel index assesses functional independence in the activities of daily living and ranges from 0 (total dependency) to 100 points (independent) [53]

[f]Healthcare utilization refers to GP visits, specialist/emergency department visits, any time spent in a nursing home, or receipt of community nurse home visits within 6 months; or hospitalizations within the last 12 months prior to the baseline visit

Index score, education level, as well as diagnoses of depression, dementia, and psychosis on the basis of ICD-10 codes [29, 32–34]. In a sensitivity analysis, we replaced the binary independent variable “hyperpolypharmacy” with a multilevel categorical independent variable “number of medications.”

Thirdly, we identified risk factors for low/medium medication adherence in the subgroup of patients with hyperpolypharmacy. We examined the association between all baseline variables and low/medium medication adherence, first using univariable logistic regression. All variables with a p-value < 0.20 in the univariable analyses were then included in a multivariable logistic regression model to identify independent factors for low/medium medication adherence in the same way as was carried out for our first aim (i.e., identification of risk factors for hyperpolypharmacy).

Missing data on our outcome medication adherence were < 5%, and in this case, the potential impact of this missing at random data is likely small. Therefore, in keeping with accepted convention (< 5% missing), multiple imputation was not performed here [35–37].

Two-sided p-values of < 0.05 were considered statistically significant. All analyses and figure graphs were performed using STATA version 17 software (StataCorp, College Station, TX, USA) [38].

3 Results

Of 2005 older patients with multimorbidity and polypharmacy included in this study, 1029 (51.3%) had hyperpolypharmacy (Fig. 1), with a median number of 13 daily medications versus 7 daily medications in those without hyperpolypharmacy. Compared with those on polypharmacy with less than ten medications, patients with hyperpolypharmacy were more likely to be female (47.8 versus 41.3%), to have more chronic diseases (median 12 versus 10), to have a lower education level (less than high school 33.7 versus 26.3%), to have suffered two or more falls in the last year (23.1 versus 16.4%), and to be a nursing home resident (13.5 versus 5.6%) (Table 1). With an increasing number of medications, the proportion of patients in the overall study population who had any hospitalizations within the previous 12 months increased, while the proportion of patients who had only GP visits decreased (p-value = < 0.001; Supplementary Fig. 1).

3.1 Factors Associated with Hyperpolypharmacy

Among all included participants, multivariable logistic regression analyses showed that the following factors were independently associated with hyperpolypharmacy: female sex (odds ratio [OR] 1.28, 95% confidence interval [CI] 1.02–1.61), nursing home residency (OR 2.20, 95% CI 1.42–3.41), and receipt of community nurse visits at home (OR 1.51, 95% CI 1.16–1.97). An increasing number of comorbidities was positively associated with hyperpolypharmacy (p for linear trend < 0.001; Fig. 2). Compared with normal BMI (18.5–24.9 kg/m^2), an increasing BMI was also positively associated with hyperpolypharmacy (p for linear trend 0.004; Fig. 2). In contrast, older patients (OR 0.78, 95% CI 0.62–0.98 for age ≥ 80 years versus < 80 years) and those with a higher education level (high school OR 0.81, 95% CI 0.63–1.04; university OR 0.67, 95% CI 0.50–0.90; p for linear trend 0.009) were less likely to have hyperpolypharmacy (Fig. 2, Supplementary Table 1a). The type of physician visit was significantly associated with hyperpolypharmacy, with both visits to specialists/ED (OR 1.60, 95% CI 1.16–2.19), as well as any hospitalizations (OR 1.89, 95% CI 1.42–2.52) being associated with increased odds of hyperpolypharmacy compared with GP-only visits (Fig. 2, Supplementary Table 1a). In a sensitivity analysis exploring the total number of physician contacts (regardless of type of physician contact), an increasing number of physician visits (GP, specialist/ED, or hospitalization) was associated with hyperpolypharmacy (Supplementary Table 1b).

3.2 Association Between Hyperpolypharmacy and Low/Medium Medication Adherence

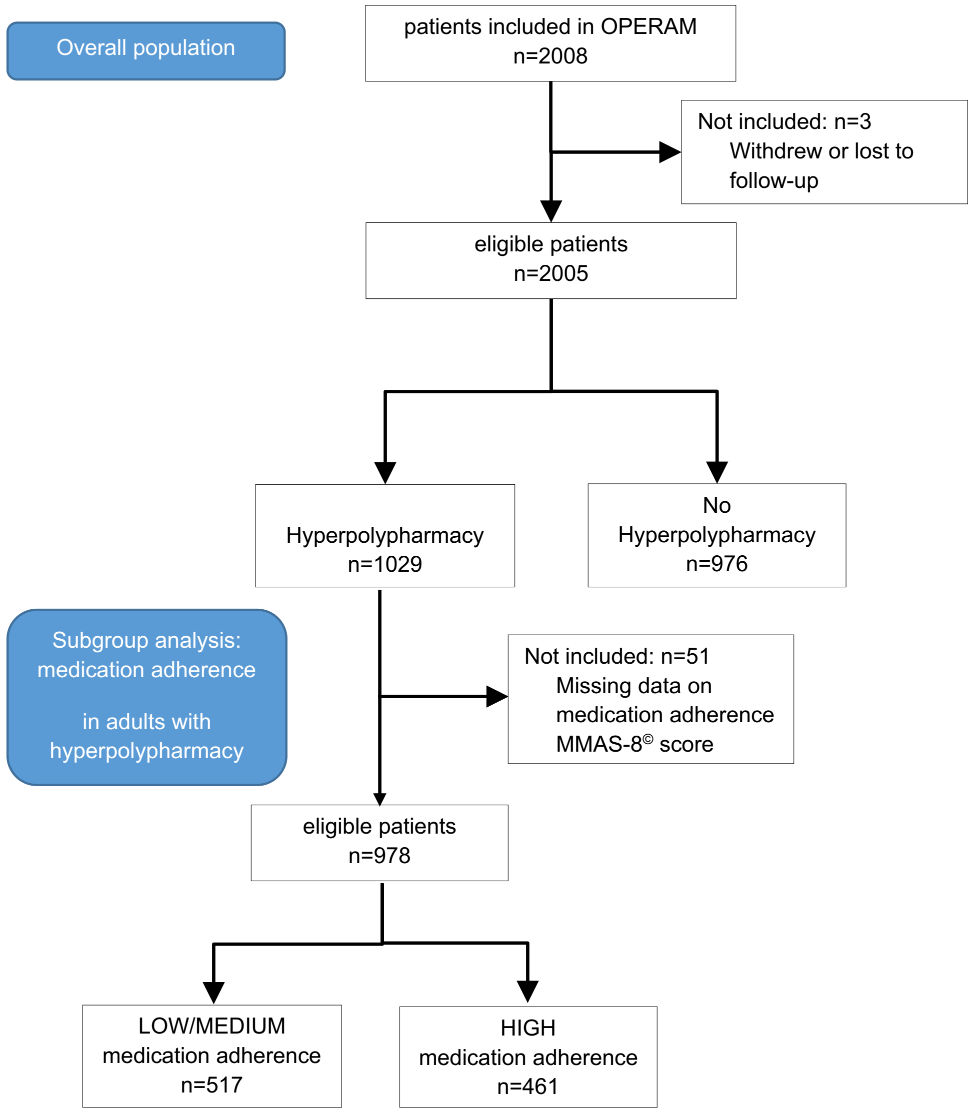
Patients with hyperpolypharmacy tended to have lower odds of low/medium medication adherence (adjusted OR for low/medium medication adherence 0.84, 95% CI 0.69–1.01, p-value 0.066) in multivariable adjusted analyses compared with those with polypharmacy on less than ten medications. However, this observation did not reach statistical significance.

In a sensitivity analysis investigating the association of the number of regular medications with medication adherence, we observed a quadratic “U-shaped” pattern, with a trend toward low/medium medication adherence at both extremes of the spectrum (i.e., in those with a low number and those with a very high number of regular medications), but the overall association was not statistically significant (Supplementary Fig. 2).

3.3 Factors Associated with Low/Medium Medication Adherence in the Subgroup of Adults with Hyperpolypharmacy Only

In the subgroup of 978 participants with hyperpolypharmacy and available data on medication adherence (adherence data were missing in 51 patients), 517 (52.9%) had low/medium adherence (Fig. 1), with a median MMAS-8© score of 6.75 points. Compared with those with high medication adherence, patients with low/medium adherence were younger (median age 78 versus 80 years) and had more comorbidities

Fig. 1 Flow diagram of the study population



(median 14 versus 12; Supplementary Table 2 provides further baseline characteristics).

Compared with the high adherence group, the odds of low/medium medication adherence increased with increasing number of comorbidities (p for trend 0.005), but decreased with older age (OR 0.69, 95% CI 0.52–0.92 for age ≥ 80 versus < 80 years), receipt of community nurse care at home (OR 0.59, 95% CI 0.44–0.81), and better self-reported health-related quality of life (OR 0.99, 95% CI 0.98–0.99 per 1-point increase in EuroQol visual analogue scale [EQ-VAS] score) in multivariable adjusted analyses (Fig. 3). Type of physician contact was not significantly associated with medication adherence (Fig. 3, Supplementary Table 3).

4 Discussion

In this cross-sectional analysis, hyperpolypharmacy was independently associated with female sex, more comorbidities, higher BMI, nursing home residency, and increasing healthcare utilization, when compared with polypharmacy participants. However, patients with a higher education level, older age, and only GP contact (as compared with specialist/ED visits or any hospitalizations) had a lower risk of hyperpolypharmacy. Hyperpolypharmacy was not significantly associated with medication adherence in our study. Among adults with hyperpolypharmacy, high medication adherence (i.e., 8 points on MMAS-8©) was more likely in those aged ≥ 80 years, individuals receiving community nurse visits at home, and in those with better self-reported health-related quality of life.

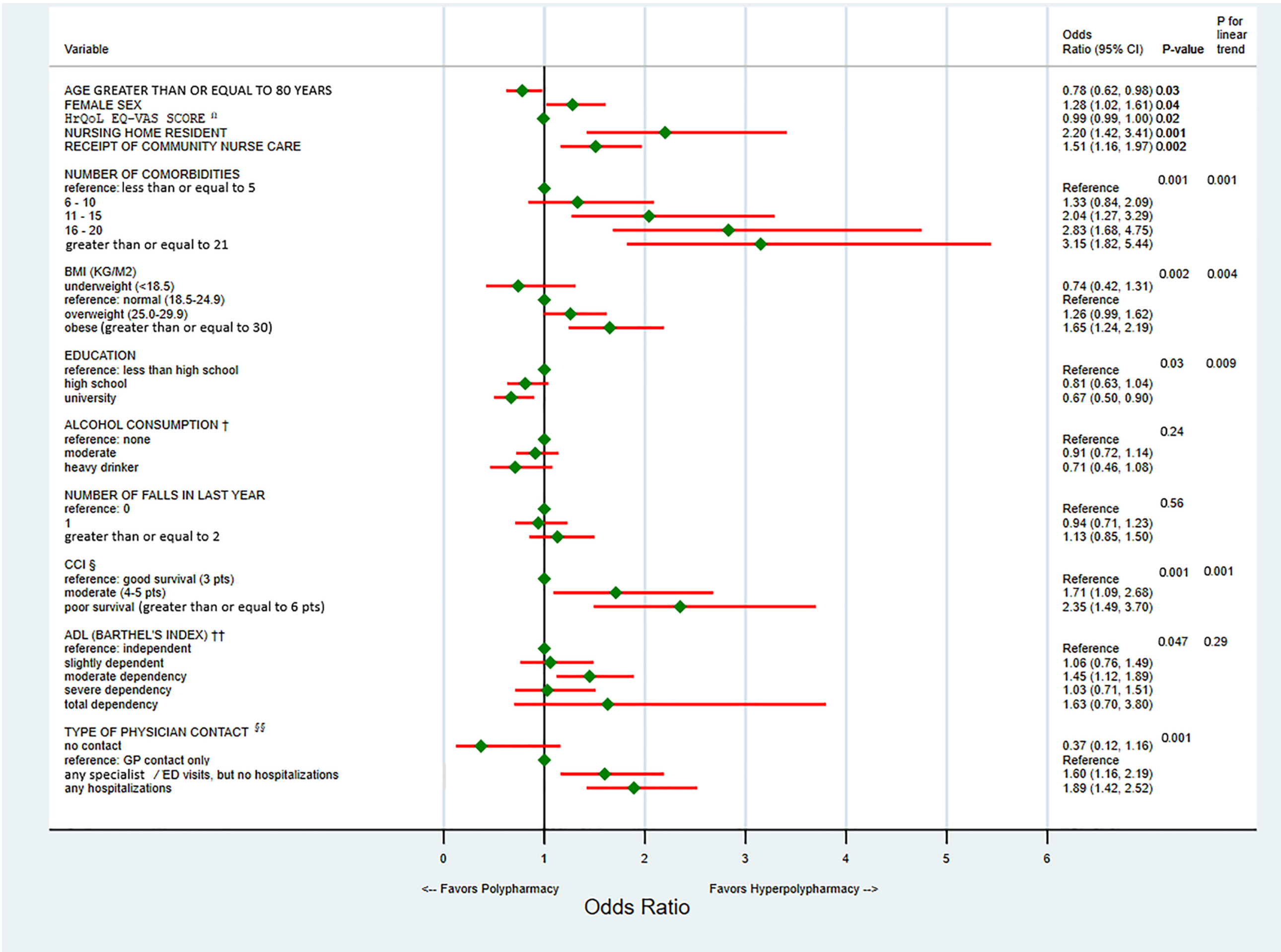


Fig. 2 Factors associated with hyperpolypharmacy in multivariable analyses. Only variables with a *p*-value < 0.2 for overall significance in univariable analyses were included in the multivariable analyses. [Ω]HrQoL EQ-VAS is a measure of self-rated health on a vertical visual analogue scale ranging from 0 ("worst health you can imagine") to 100 points ("best health you can imagine"). [§]The CCI predicts 10-year survival in patients with multiple comorbidities. The total score ranges from 0 (highest survival) to 37 points (lowest survival); 7 points correspond to an estimated 0% 10-year survival. [†]A heavy drinker is defined as consumption of > 14 units of standard alcoholic drinks per week for men and > 7 units per week for women [52]. [††]The Barthel index assesses functional independence in the activities of daily living and ranges from 0 (total dependency) to 100 points (independent) [53]. [§§]Type of physician contact refers to GP visits, specialist/emergency department visits within 6 months; or hospitalizations within the last 12 months prior to the baseline visit. *ADL* activities of daily living, *BMI* body mass index, *CCI* Charlson Comorbidity Index, *CI* confidence interval, *ED* emergency department, *GP* general practitioner/primary care physician, *HrQoL EQ-VAS* health-related quality of life EuroQol visual analogue scale, *pts* points

4.1 Comparison with Prior Evidence

4.1.1 Factors Associated with Hyperpolypharmacy

Our finding of an increasing risk of hyperpolypharmacy with increasing number of healthcare utilization is in keeping with results from a US cross-sectional study in a selected population of primary care patients with heart failure [39], as well as a nationwide South Korean cohort study in older individuals [40]. This is not surprising, since increasing healthcare utilization provides more opportunity for physicians to prescribe medications leading to hyperpolypharmacy. Given that our analyses were adjusted for the number of comorbidities and predicted mortality (as measured by the Charlson Comorbidity Index), differences in severity of illness are unlikely to fully explain the association of healthcare utilization and hyperpolypharmacy. Both the US and Korean studies showed that ambulatory healthcare visits carried higher risk of hyperpolypharmacy than hospitalization

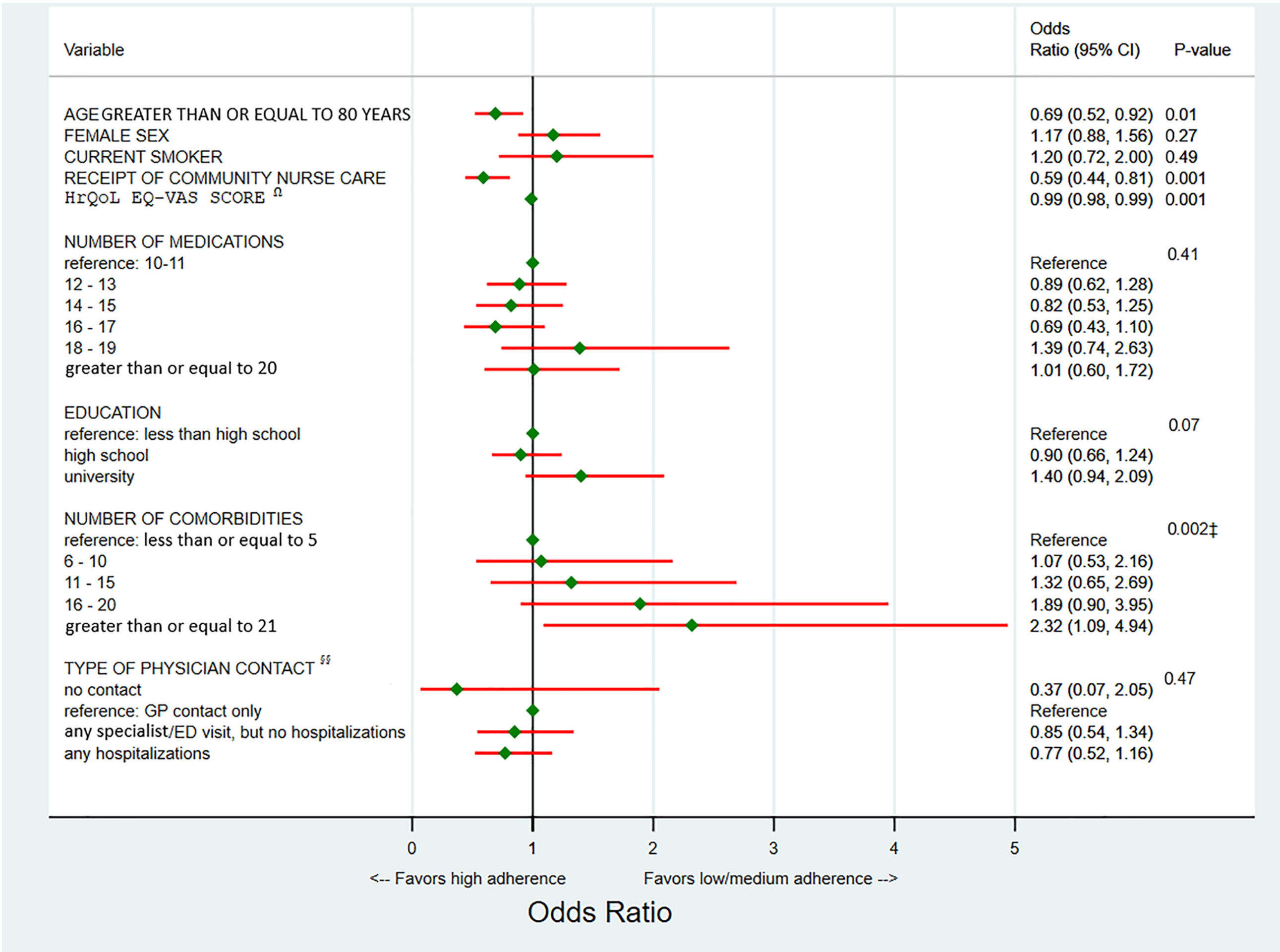


Fig. 3 Factors associated with low/medium medication adherence in patients with hyperpolypharmacy. Only variables with a p-value < 0.2 for overall significance in univariable analyses were included in the multivariable analyses. Low/medium medication adherence was defined as < 8 points on the Morisky Medication Adherence Scale-8 (MMAS-8©) (Use of Morisky medication adherence measure questionnaire MMAS© is protected by US copyright laws. Permission for use is required. A license agreement was obtained from Professor Donald E. Morisky, ScD, ScM, MSPH, Department of Community Health Sciences, UCLA Fielding School of Public Health, 650 Charles E Young Drive South, Los Angeles, CA 90095-1772, USA. dmorisky@ucla.edu. ΩHrQoL EQ-VAS is a measure of self-rated health on a vertical visual analogue scale ranging from 0 ("worst health you can imagine") to 100 points ("best health you can imagine"). §§Type of physician contact refers to GP visits, specialist/emergency department visits within 6 months; or hospitalizations within the last 12 months prior to the baseline visit. ‡This refers to a p-value for linear trend = 0.005. *CI* confidence interval, *ED* emergency department, *GP* general practitioner/primary care physician, *HrQoL EQ-VAS* health-related quality of life EuroQol visual analogue scale

[39, 40]; whereas we observed the opposite in our study. One possible explanation could be different definitions used for "ambulatory/outpatient" visits. For example, we combined specialist and ED visits together into one category, and this was recorded separately to GP visits. In the other studies, although ED visits were determined, it is not clear whether GP visits were included in "ambulatory healthcare services." In addition, in our unadjusted sensitivity analysis, (Supplementary Fig. 1) we noted that fewer hospitalizations and more GP-only contacts were associated with fewer medications. However, this could be explained by patients being less sick or having fewer comorbidities, therefore naturally requiring fewer medications and being less likely to be hospitalized.

Regarding age, we noted that age ≥ 80 years appeared to be associated with lower rates of hyperpolypharmacy. This could be because of deprescribing in the oldest old, in whom the risks of medication side effects increase (e.g., intensive glycemic control among older adults can be harmful [41]), and the benefits of preventive medication decrease (e.g., statin deprescribing in primary prevention for patients with limited life expectancy [42, 43]). Our findings concur with two other European multicenter studies conducted in home care-dependent patients with high levels of complexity [4] and nursing home patients with severe cognitive impairment

[44], which found an inverse association between hyperpolypharmacy and age. Conversely, data from the English Longitudinal Study of Ageing showed that individuals aged ≥ 80 years carried a fivefold greater risk of hyperpolypharmacy [3]. A possible explanation for this is that in this study, data were collected in 2012, which was before deprescribing health initiatives and incentives such as medication review, patient and physician educational materials, cost savings analysis, and improved quality of life were promoted [45]. There may also have been less awareness at the time among physicians regarding potentially inappropriate medication (PIM) prescribing and medication overuse.

4.1.2 Association Between Hyperpolypharmacy and Low/Medium Medication Adherence

In a sensitivity analysis we observed a U-shaped pattern between number of medications and adherence, with a trend toward low/medium medication adherence in participants with either a low or high number of regular medications. Though this finding did not reach statistical significance, this U-shaped pattern has been described before when exploring the impact of number of medications on adherence to antihypertensive medications [46]. It is to be expected that medication adherence decreases as the number of medications increase, e.g., because of regimen complexity, the challenges of remembering too many medications, drug–drug interactions, and side effects promoting nonadherance. Surprisingly, adherence worsened with a low number of regular medications [47]. This phenomenon has been observed before, and can be explained by the health belief model [46, 48], whereby someone taking less medications believes they are not as sick and therefore will not put much effort into maintaining their health and taking medication prescribed by physicians.

4.1.3 Factors Associated with Low/Medium Medication Adherence in Patients with Hyperpolypharmacy

In a systematic review of older patients receiving polypharmacy, the prevalence of nonadherance ranged from 6 to 55% [16]. By comparison, in our population of patients with hyperpolypharmacy, 53% were not taking their medication as prescribed. Thus, in keeping with results from the polypharmacy systematic review [16], in our study more medication (i.e., hyperpolypharmacy) did not appear to lead to more nonadherance.

We observed that receipt of community nursing care, better self-reported quality of life, and age ≥ 80 years favored medication adherence. We suspect these factors are interrelated. The prevalence of cognitive impairment and frailty increases with advancing age, making the requirement of community nurse visits more likely in the oldest old. Community nursing care in the four European countries included in this study is common and involved nurses visiting patients in their own homes to provide personal and social care such as administering medication, measuring blood pressure and glucose, or assisting with personal hygiene (community nurse visits did not involve care of patients living in nursing homes or long-term residential care). It is unsurprising that having a healthcare professional prepare, check, or administer the medications contributes to better medication adherence. While previous data showed that visiting the same physician regularly was associated with better medication adherence [49], we did not find an association between GP/type of physician contacts and medication adherence in our study.

4.2 Clinical Implications

This study identifies factors associated with hyperpolypharmacy, which may help healthcare professionals to detect a vulnerable, at-risk population and intervene with early medication reviews and drug optimization. Medication optimization trials in polypharmacy have demonstrated a reduction in inappropriate prescribing [18], as well as reductions in hospitalizations and healthcare costs [50]. In particular, we have shown that visits to specialists, EDs, or hospitals are associated with greater hyperpolypharmacy prevalence compared with contacts with the GP alone. These results reinforce the central role of the primary care physician as the coordinator of patient healthcare in the older population with multimorbidity and support the introduction of screening criteria for high-risk groups, i.e., all patients discharged from hospital, as well as the implementation of regular medication reviews, or medication adherence risk assessments every 6 months performed in the GP practice or by community pharmacists.

The consequences of nonadherance are far-reaching and amount to billions of euros in preventable healthcare costs, many thousands of avoidable hospitalizations, and premature deaths in Europe [13], representing a missed opportunity for healthcare providers and healthcare systems to intervene. Greater knowledge on medication nonadherance and its risk factors in older people with multimorbidity is important to prevent worsening of disease, re-hospitalization, and increased healthcare costs. Importantly, in this study, we have identified community nurse visits and self-reported quality of life as significant factors associated with better medication adherence. These are modifiable factors and could be used to develop personalized medication adherence interventions. Currently, medication adherence-enhancing interventions are used infrequently, and even more rarely reimbursed [51]; representing further aspects for improvement.

4.3 Strengths and Limitations of This Study

To our knowledge, this is the first study to explore the association between medication adherence in an older population experiencing hyperpolypharmacy. While there is an abundance of data on polypharmacy in this population, the outcomes do not automatically translate over to hyperpolypharmacy given that pharmacological side effects and interactions increase with increasing number of medications. The multinational design of this study included patients from four large European centers and enrolled many older medical inpatients with multimorbidity, increasing generalizability of results. The granular, prospectively collected data improve the quality of our findings.

However, this study has some limitations. First, while the cross-sectional design allowed us to explore associations, we cannot assess causal relationships. Second, healthcare utilization (e.g., number of physician visits, nursing home residency, or receipt of community nurse visits), as well as medication adherence, was self-reported from a patient questionnaire, meaning that we cannot exclude recall bias or social-desirability bias. As a disadvantage, the MMAS-8© and other adherence scales provide information on medication adherence in general, i.e., for all medications prescribed, but do not consider that adherence may be medication specific (e.g., only for statins or diuretics but not for analgesics). Third, unmeasured confounders may have affected our results, as is the case for all observational studies. For example, there was no information on pill burden (e.g., number of pills taken per day versus multiple drugs combined into one daily pill), or presence of a caregiver versus living alone, which could all act as confounders for the association between hyperpolypharmacy and medication adherence. Fourth, the generalizability of our results to a multiracial population outside Europe is limited by the very low number of non-white participants enrolled in the study. Fifth, we were not able to specifically differentiate ambulatory specialist visits from ED visits owing to the way the data were collected. Finally, we did not account for clustering by study site, and we cannot exclude that country differences in the organization and provision of healthcare may have affected our results.

5 Conclusions

This study addressed important aspects of drug utilization in older adults, by identifying various risk factors for hyperpolypharmacy (e.g., nursing home residency, increasing healthcare utilization), as well as risk factors for low/medium medication adherence (e.g., number of comorbidities, poorer self-reported quality of life). Our findings reinforce the important role that regular community nurse visits play toward improving medication adherence. The type and number of physician visits appear to play a role, e.g., patients with any specialist/ED visits or any hospitalizations had significantly higher odds of hyperpolypharmacy compared with GP-only contact. Our findings suggest that GPs may provide opportunities for deprescribing, particularly after a recent hospitalization.

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Declarations

Conflict of interest Denis O'Mahony is an Editorial Board member for *Drugs & Aging*. Denis O'Mahony was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. The other remaining authors have no competing interests to declare that are relevant to the content of this article.

Data availability The data used in this study originated from the OPERAM Trial (ClinicalTrials.gov NCT02986425). The subsequent datasets generated and analyzed in this current substudy are not publicly available but are available to others in the scientific community upon reasonable request to the corresponding author after publication. Data will be made available for scientific purposes for researchers whose proposed use of the data has been approved by a publication committee.

Ethical approval This study makes use of existing OPERAM trial data. No new data were collected for this study. The OPERAM trial was approved by the independent research ethics committees at each participating site (lead ethics committee: Cantonal Ethics Committee Bern, Switzerland, ID 2016-01200; Medical Research Ethics Committee Utrecht, Netherlands, ID 15-522/D; Comité d'Ethique Hospitalo-Facultaire Saint-Luc-UCL: 2016/20JUL/347—Belgian registration no. B403201629175; Cork University Teaching Hospitals Clinical Ethics

Committee, Cork, Republic of Ireland; ID ECM 4 (o) 07/02/17), and Swissmedic as responsible regulatory authority. The OPERAM trial was conducted in accordance with the Declaration of Helsinki.

Consent to participate In the OPERAM trial, all participants or their proxies gave their written informed consent prior to enrollment.

Consent for publication Not applicable.

Code availability Not applicable.

Author contributions Shanthi Beglinger wrote the first version of the manuscript. Shanthi Beglinger, Lisa Bretagne, and Christine Baumgartner performed statistical analyses. Cinzia del Giovane and Katharina Tabea Jungo contributed to the analytical methods. Shanthi Beglinger, Lisa Bretagne, François Volery, and Christine Baumgartner conceived and developed the project idea. Katharina Jungo, Denis O'Mahony, Sophie Marien, Anne Spinewine, Wilma Knol, Ingeborg Wilting, and Nicolas Rodondi contributed to the design of the study and interpretation of results. Christine Baumgartner supervised the project. All authors contributed to the final version of the manuscript.

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Authors and Affiliations

Shanthi Beglinger[1] · Lisa Bretagne[1,2] · François Volery[2] · Cinzia Del Giovane[1] · Katharina T. Jungo[1] · Denis O'Mahony[3] · Sophie Marien[4] · Anne Spinewine[5] · Wilma Knol[6] · Ingeborg Wilting[7] · Nicolas Rodondi[1,2] · Christine Baumgartner[2]

✉ Christine Baumgartner
Christine.Baumgartner@insel.ch

[1] Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland

[2] Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

[3] Department of Medicine (Geriatrics), University College Cork and Cork University Hospital, Cork, Ireland

[4] Department of Geriatrics, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium

[5] Louvain Drug Research Institute, Clinical Pharmacy Research Group, Université Catholique de Louvain, Brussels, Belgium

[6] Department of Geriatric Medicine and Expertise Center Pharmacotherapy in Old Persons, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

[7] Department of Clinical Pharmacy, University Medical Center Utrecht/Wilhelmina Children's Hospital, Utrecht, The Netherlands