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Research Article

Medication Regimen Complexity and Number of Medications as Factors Associated With Unplanned Hospitalizations in Older People: A Population-based Cohort Study

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Abstract

Background: Adverse drug events are a leading cause of hospitalization among older people. Up to half of all medication-related hospitalizations are potentially preventable. The objective of this study was to investigate and compare the association between medication regimen complexity and number of medications with unplanned hospitalizations over a 3-year period.
Methods: Data were analyzed for 3,348 participants aged 60 years or older in Sweden. Regimen complexity was assessed using the 65-item Medication Regimen Complexity Index (MRCI) and number of medications was assessed as a continuous variable. Cox proportional hazard models were used to compute unadjusted and adjusted hazard ratios with 95% confidence intervals (CIs) for associations between regimen complexity and number of medications with unplanned hospitalizations over a 3-year period. Receiver operating characteristics curves with corresponding areas under the curve were calculated for regimen complexity and number of medications in relation to unplanned hospitalizations. The population attributable fraction of unplanned hospitalizations was calculated for MRCI and number of medications.
Results: In total, 1,125 participants (33.6%) had one or more unplanned hospitalizations. Regimen complexity (hazard ratio 1.22; 95% CI 1.14–1.34) and number of medications (hazard ratio 1.07; 95% CI 1.04–1.09) were both associated with unplanned hospitalizations and had similar sensitivity and specificity (area under the curve 0.641 for regimen complexity and area under the curve 0.644 for number of medications). The population attributable fraction was 14.08% (95% CI 9.62–18.33) for MRCI and 17.61% (95% CI 12.59–22.35) for number of medications.
Conclusions: There was no evidence that using a complex tool to assess regimen complexity was better at predicting unplanned hospitalization than number of medications.

Keywords: Medication regimen complexity—Polypharmacy—Hospitalization—Aged—Inappropriate prescribing

Adverse drug events (ADEs) account for 7% of all emergency department visits leading to hospitalizations in the United States (1). Nearly half of hospitalizations due to ADEs are among adults aged 80 years and older with two thirds of these hospitalizations due to unintentional overdose (1,2). Up to half of all medication-related hospital admissions are potentially preventable (3,4).

A range of medication and non-medication related factors have been associated with unplanned hospitalization in older people. These factors include use of multiple and high risk medications, comorbidity, prior hospitalization, advanced age, and being unmarried (2,5–7). The number of medications a person is taking has been strongly associated with ADEs and unplanned hospitalization

(6,8). There is also a strong association between number of prescribed medications and potential drug–drug interactions, with those taking a higher number of medications experiencing more serious interactions (9). During hospitalization older people often experience functional decline and in-hospital adverse events (10). Unplanned hospitalizations may be distressing, with many older people unable to return to their own home following hospital discharge (11).

The median number of medications prescribed to people aged 65 years or older in the United States doubled between 1988 and 2010 (12). The use of multiple medications can result in complex medication regimens. Patients may use tablets, creams, and patches, each with their own dosing instructions. Having a high medication regimen complexity has been associated with hospital discharge to nonhome settings and poor quality of life (13,14). The validated 65-item Medication Regimen Complexity Index (MRCI) takes into account dosage form, dosing frequency, and additional directions for medication use (15). There is mixed evidence for an association between MRCI and unplanned hospital readmissions, although previous studies have been conducted in small and restricted samples of older people (16,17). No population-based studies have investigated whether regimen complexity and number of medications have similar prognostic performance for predicting clinical outcomes. This is important because it is less time consuming for clinicians to count medications than compute regimen complexity in routine clinical practice. We hypothesized that medication regimen complexity would be a better overall predictor of unplanned hospitalizations than number of medications.

The objective of this study was to investigate and compare the association between medication regimen complexity and number of medications with unplanned hospitalizations over a 3-year period.

Methods

Design, Setting, and Participants

This cohort study comprised participants in the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) (18). SNAC-K is an ongoing population-based study on aging and health in older people living in the district of Kungsholmen in central Stockholm. The study contains 11 age cohorts of people aged 60 years and older living at home or in a nonhome setting. Participants were randomly selected according to their date of birth. The youngest and oldest age cohorts were intentionally oversampled. All participants underwent extensive baseline interviews and clinical examinations between 2001 and 2004. Potential participants were excluded from the study if they did not speak Swedish, if the interview could not be conducted because of hearing impairment, or if they no longer lived in the catchment area.

Medication Assessment

Participants were asked to bring all their medications to the baseline clinical examination. Each participant's list of medications was recorded by a physician. If participants lived in a nonhome setting (eg, nursing home, group dwelling, or residential home) their medical records were used to record their list of medications. Use of both prescription and non-prescription medications was recorded (19). The Anatomical Therapeutic Chemical (ATC) Classification system recommended by the World Health Organization was used to categorize medications.

Medication regimen complexity was computed using the MRCI (15). The validated tool scores dosage form, dosing frequencies, and additional directions (eg, multiple units at a time, intake times, and split tablets) with higher MRCI scores reflecting more complex medication regimens. Both prescription and non-prescription medications and both scheduled and as-needed were taken into account (20,21). Specific instructions for medication dosing were not recorded at the time of data collection (eg, take on an empty stomach). For this reason it was assumed that all participants took their medications in accordance with standard dosing instructions in the Australian Pharmaceutical Handbook and Formulary (22), British National Formulary and the electronic Medicines Compendium (23,24).

Main Outcome Measure

The main outcome measure was time to first unplanned hospitalization over a 3-year follow-up period (1,095 days). This follow-up period provided sufficient time for participants to be hospitalized. Limiting the follow-up period to 3 years minimized the impact of possible medication changes that occurred after the baseline medication assessment. We analyzed time to first hospitalization rather than number of hospitalizations because medication changes are often made during hospitalization and we did not have access to these data (25). Follow-up periods were calculated individually for each participant from the date of the baseline medical assessment. Data on unplanned hospitalizations were extracted from the inpatient register maintained by the Stockholm County Council. We considered that all acute admissions were unplanned hospitalizations. This register has established validity. There was a 98% concordance for unplanned hospitalizations over 12 months between the inpatient register in Stockholm and the Swedish National Inpatient Register. The Swedish Inpatient Register is maintained by the National Board of Health and Welfare and includes over 99% of all somatic and psychiatric hospital discharges in Sweden (26).

Covariates

Age was analyzed as a continuous variable and sex as a categorical variable. The Mini-Mental State Examination (MMSE) score was used to adjust for cognitive status and was analyzed as a continuous variable (27). Activities of daily living (ADLs) were measured using the Katz ADL scale (28). This scale assesses dependence in six ADLs (bathing, dressing, toileting, continence, transferring, and feeding) and was analyzed as a continuous variable. An adapted version of the Charlson's Comorbidity Index was used to adjust for comorbidity (29,30). It was computed using the list of diseases that were recorded at the baseline examination and was analyzed as a continuous variable. Education was categorized as elementary school, high school, or university. Living place was categorized as living at home (eg, apartment rental, apartment ownership, detached house) or living in a nonhome setting (eg, nursing home, group dwelling, or residential home) (31). Both education and living place were analyzed as categorical variables.

Data on unplanned hospital admissions 1 year prior to each participant's baseline assessment (365 days) were obtained from the Swedish National Inpatient Register. The number of previous hospital admissions for each patient was treated as a continuous variable. Dates of death were obtained from the Swedish National Cause of Death Register. The analyses were adjusted for receipt of help to sort medications as a dichotomous variable categorized as "participant handles medication entirely alone" and "participant has help sorting medication." Help sorting medications was defined as having medications sorted in a pill organizer, multi-dose drug dispensing, or if a participant self-reported they received help to sort their medications. Self-reported pain was assessed at the physician interview and was analyzed as dichotomous variable ("have you experienced any aches or pain during the last four weeks?"). To account for the participants' dexterity the analyses were adjusted for the ability to open jars with lids ("can you open jars with lids?") as categorical variable with the categories "yes without trouble," "yes with aid," and "no."

Statistical Analyses

Baseline characteristics were presented as frequencies and proportions (%), medians and interquartile ranges (IQRs), or means and standard deviations (*SD*). Chi-square tests were used to investigate potential differences between categorical variables and *t* tests or Mann–Whitney *U* test were used for continuous variables. Kruskal–Wallis test was used to analyze differences between three groups of ordinal variables.

Cox proportional hazards regression analyses were performed to compute unadjusted and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for the association between MRCI and unplanned hospitalization over a 3-year follow-up. In these analyses, MRCI was analyzed as continuous variable in tenths (MRCI continuous divided by 10) (17). Because people in the highest and lowest age cohorts were oversampled, data were weighted by age group and sex. Variables associated with unplanned hospitalization in bivariate analyses ($p < .05$) or those associated with unplanned hospitalization in previous research were included in the multivariate models (5,6). Variables were checked for multicollinearity. To account for deaths during the follow-up period, the analyses were censored at the time of a patient's death or the end of the follow-up period, whichever occurred first.

Cox proportional hazards regression was also used to investigate the association between number of medications and unplanned hospitalization. In these analyses, number of medications was analyzed as a continuous variable. We analyzed number of medications as a continuous variable rather than polypharmacy as a categorical variable. This was because using the common polypharmacy cutoff of ≥5 medications implies a "threshold effect," and assumes there is no difference between 1 and 4 medications or between 5 and more medications. Sensitivity analyses were performed stratifying the participants by residential status (living at home and living in a nonhome setting). This was because people living in nonhome settings are often supported to take their medications, and therefore the risk associated with complex medication regimens may be different in people living in home and nonhome settings. The same variables were used to adjust the MRCI and number of medications models. It was not possible to include both MRCI and number of medications in the same Cox models because these two parameters were highly correlated. This was confirmed using Pearson's correlation coefficients.

Receiver operating characteristics (ROC) curves with corresponding areas under the curve were calculated for MRCI and number of medications in relation to unplanned hospitalizations over the 3-year period. The Youden Index was used to determine optimal cutoff points of MRCI and number of medications for unplanned hospitalization. The Youden Index is a performance measure utilized in conjunction with receiver operating characteristic curves. It is a function of sensitivity and specificity (sensitivity + specificity − 1) (32). It was applied without adjustment or weighting to the whole study sample (n = 3,348). The population attributable fraction was calculated to determine the proportional reduction in unplanned hospitalization if MRCI and number of medications were reduced to less than the optimal cutoff points identified using Youden's Index. The population attributable fraction analyses were adjusted for the same variables as the Cox proportional hazard analyses. Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 21 (IBM Corporation, Armonk, NY) and STATA version 13 (Stata Corporation).

Ethical Considerations

All potential participants were provided with written information about the study. Written informed consent to participate was obtained for each participant. If the participant was unable to make an informed decision, proxy consent was requested from a close relative. The present study was approved by the Regional Ethical Review Board in Stockholm.

Results

Overall, 5,111 people were invited to participate in the SNAC-K study at baseline. Of these, 1,227 people refused to participate, 262 could not be contacted, 200 died before the baseline examination, 32 no longer lived in the study area, 23 did not speak Swedish, and 4 had hearing impairment. Ten participants did not complete the baseline examination and five participants had missing medication data. The final study sample included 3,348 participants.

The median age of all participants was 72 years (IQR 66–84) (Table 1). Participants were predominately female (n = 2,170, 64.8%). Overall, 2,885 participants (86.2%) used one or more medications on either a scheduled or as-needed basis. For all participants, the median MRCI was 9 (IQR 4–16), and the mean MRCI was 11.0 (*SD* 9.6). The median number of medications was 3 (IQR 1–6), the mean number of medications was 4.0 (*SD* 3.4), and 1,285 people (38.4%) had ≥5 medications. The median MMSE was 29 (IQR 28–30), median Katz ADL index was 6 (IQR 6–6). Participants who had one or more unplanned hospitalizations during follow-up were more likely to be dependent in one or more ADLs than participants without unplanned hospitalizations (13.3% vs 7.8%; $p < .01$). The median Charlson's Comorbidity Index was 0 (IQR 0–1). Similarly, participants who had one or more unplanned hospitalizations were more likely to have a Charlson's Comorbidity Index score ≥2 than participants without unplanned hospitalizations (30.2% vs 18.4%; $p < .01$). For all participants, the highest level of education was elementary school (n = 584, 17.4%) high school (n = 1,644, 49.1%), and university (n = 1,088, 32.5%). In total, 3,053 participants (91.2%) lived at home and 295 (8.8%) lived in a nonhome setting (Table 1). MRCI and number of medications were strongly correlated (Pearson's correlation coefficient 0.96, $p < .001$).

Over a 3-year follow-up period, 1,125 participants (33.6%) had one or more unplanned hospitalizations. Of those, 736 (65.4%) were women, 1,041 (92.5%) were taking one or more medications, their median MRCI was 12 (IQR 6–20), and the median number of medications taken was five (IQR 2–7). The Cox proportional hazards regressions were adjusted for age, sex, Katz ADLs, education, living place, MMSE, modified Charlson's Comorbidity Index, dexterity, self-reported pain, unplanned hospitalizations in the year prior to assessment, and if help sorting medication was received (Table 2). In these models, medication regimen complexity (HR 1.22; 95% CI 1.14–1.34) and number of medications (HR 1.07; 95% CI 1.04–1.09) were associated with unplanned hospitalization (Table 2). For participants living at home, both medication regimen complexity

Table 1. Characteristics of the Participants With and Without Unplanned Hospitalization Over a 3-Year Period

Characteristic	All Participants (n = 3,348)	Unpl. Hospitalization (n = 1,125)	No Unpl. Hospitalization (n = 2,223)	p-Value
Age (IQR)	72 (66–84)	81 (72–90)	72 (61–79)	<.01
Sex female, n (%)	2,170 (64.8)	736 (65.4)	1,434 (64.5)	.60
MRCI (IQR)	9 (4–16)	12 (6–20)	7.5 (3–14)	<.01
Number of medications (IQR)	3 (1–6)	5 (2–7)	3 (1–5)	<.01
Education*, n (%)				<.01
Elementary	584 (17.4)	268 (23.8)	316 (14.2)	
High school	1,644 (49.1)	579 (51.5)	1,065 (47.9)	
University	1,088 (32.5)	267 (23.7)	821 (36.9)	
Living place at home, n (%)	3,053 (91.2)	1,008 (89.6)	2,045 (92.0)	.04
Modified CCI ≥2, n (%)	748 (22.3)	340 (30.2)	408 (18.4)	<.01
Dependent ≥ 1 ADLs†, n (%)	324 (9.7)	150 (13.3)	174 (7.8)	<.01
MMSE‡ (IQR)	29 (28–30)	28 (26–29)	29 (28–30)	<.01
Unplanned hospitalization (one or more) in the previous year, n (%)	442 (13.2)	268 (23.8)	174 (7.8)	<.01
Self-reported pain§, n (%)	1,165 (34.8)	442 (39.3)	723 (32.5)	<.01
Dexterity (can you open jars with lids?)‖, n (%)				<.01
Yes without trouble	2,009 (60.0)	576 (51.2)	1,433 (64.5)	
Yes with aid	997 (29.8)	386 (34.3)	611 (27.5)	
No	204 (6.1)	109 (9.7)	95 (4.3)	
Receives help to sort medications¶, n (%)	427 (12.8)	232 (20.6)	195 (8.8)	<.01

Notes: ADLs = activities of daily living; cont. = continuous; IQR = interquartile range; MMSE = Mini-Mental State Examination; MRCI = Medication Regimen Complexity Index; unpl. = unplanned.

Values are reported as number (%) or as median (IQR).

*education missing for 1.0%.

†ADLs missing for 0.3%.

‡MMSE missing for 0.2%.

§Self-reported pain missing for 3.4%.

‖Self-reported ability to open jars with lids missing for 4.1%.

¶Help to sort medication missing for 2.0%.

(HR 1.21, 95% CI 1.12–1.32) and number of medications (HR 1.06, 95% CI 1.04–1.09) were associated with unplanned hospitalization in adjusted analyses. For participants living in a nonhome setting, both medication regimen complexity (HR 1.12, 95% CI 0.80–1.58) and number of medications (HR 1.06, 95% CI 0.96–1.18) were not associated with unplanned hospitalization in adjusted analyses.

Regimen complexity and number of medications had similar sensitivity and specificity for predicting unplanned hospitalizations (area under the curve 0.641 for regimen complexity and area under the curve 0.644 for number of medications) (Table 3). The maximum Youden Index was 14 for MRCI and 5 for number of medications (Table 3). The population attributable fraction was 14.08% (95% CI 9.62–18.33) for MRCI and 17.61% (95% CI 12.59–22.35) for number of medications.

Discussion

This was the first population-based study to investigate the association between medication regimen complexity and number of medications with unplanned hospital admission. The main finding was that in our cohort of older people in Sweden both medication regimen complexity and number of medications were associated with unplanned hospitalization over a 3-year follow-up period.

This finding is consistent with the knowledge that medications are leading causes of preventable hospitalization in older people (2). There are a number of reasons why regimen complexity may be associated with unplanned hospitalization. Diabetic treatment regimens to achieve optimal blood glucose control are typically complex and suboptimal use of diabetic medications may result in hypoglycemia and falls, which are among the leading causes of medication-related hospitalization in older people (2,3,33). Similarly, warfarin dosing regimens are often complex and bleeding among older people taking warfarin is a leading cause of medication-related hospitalization (2).

Medication regimen complexity and number of medications had a similar sensitivity and specificity for predicting unplanned hospital admission. This suggests that both these parameters could be used to identify older people at risk of unplanned hospitalization. The MRCI has recently been suggested as a tool to identify people for referral for medication therapy management (34). Unlike number of medications, which can be identified with relative ease in clinical practice, the MRCI is a 65-item tool which may be challenging to compute in a busy clinical practice environment. However, recently the MRCI has been computerized for use with electronic medical records (20,21). Both regimen complexity and number of medications are explicit indicators for predicting medication-related hospitalizations. It has been recognized that explicit indicators are best used in conjunction with implicit or judgment-based assessment of medication appropriateness which may include pharmacist-led medication review. A recent systematic review and meta-analysis reported that comprehensive medication review can reduce hospitalization (35).

The optimal cut-points of MRCI for predicting unplanned hospital admission in our sample were different to those reported for other samples. In a recent study that included people with a mean MRCI of 26.8, those with an MRCI of 22 or above at hospital discharge were at increased risk for unplanned hospital readmission within 30 days (36). Another study that investigated the value of a decision support tool for recipients of home care who had a mean MRCI of 35.4 concluded that an MRCI cutoff of 33 was optimal for predicting

Table 2. Unadjusted and Adjusted HRs for the Associations With Unplanned Hospitalization Over a 3-Year Period (1,095 d), Weighted by Age Group and Sex

Characteristic	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)
MRCI cont.	1.51 (1.42–1.60)	1.22 (1.14–1.34)
Age	1.06 (1.06–1.07)	1.06 (1.05–1.07)
Sex female	1.04 (0.92–1.18)	0.75 (0.65–0.88)
Education†		
High school	0.64 (0.54–0.74)	0.84 (0.71–0.98)
University	0.42 (0.35–0.50)	0.79 (0.65–0.97)
Living place at home	0.55 (0.45–0.66)	1.49 (1.07–2.06)
Modified CCI	1.38 (1.31–1.45)	1.09 (1.03–1.17)
Katz ADLs	0.88 (0.84–0.93)	1.26 (1.06–1.45)
MMSE	0.64 (0.55–0.74)	0.99 (0.97–1.01)
Unplanned hospitalization previous year	1.45 (1.33–1.58)	1.24 (1.14–1.35)
Self-reported pain	1.26 (1.11–1.43)	1.15 (0.99–1.32)
Dexterity (can you open jars with lids?)‡		
Yes without trouble	0.36 (0.29–0.46)	0.87 (0.65–1.15)
Yes with aid	0.54 (0.43–0.68)	0.84 (0.63–1.11)
Receives help sorting medication	3.07 (2.63–2.59)	1.55 (1.21–1.97)
Number of medications	1.13 (1.11–1.15)	1.07 (1.04–1.09)
Age	1.06 (1.06–1.07)	1.06 (1.05–1.07)
Sex female	1.04 (0.92–1.18)	0.75 (0.64–0.87)
Education†		
High school	0.64 (0.54–0.74)	0.84 (0.71–0.98)
University	0.42 (0.35–0.50)	0.79 (0.65–0.96)
Living place at home	0.55 (0.45–0.66)	1.48 (1.07–2.04)
Modified CCI	1.38 (1.31–1.45)	1.09 (1.02–1.16)
Katz ADLs	0.88 (0.84–0.93)	1.26 (1.09–1.45)
MMSE	0.64 (0.55–0.74)	0.99 (0.97–1.01)
Unplanned hospitalization previous year	1.45 (1.33–1.58)	1.24 (1.15–1.35)
Self-reported pain	1.26 (1.11–1.43)	1.14 (0.99–1.31)
Dexterity (can you open jars with lids?)‡		
Yes without trouble	0.36 (0.29–0.46)	0.86 (0.65–1.14)
Yes with aid	0.54 (0.43–0.68)	0.83 (0.63–1.10)
Receives help to sort medication	3.07 (2.63–2.59)	1.54 (1.21–1.96)

Notes: ADL = activities of daily living; CCI = Charlson's Comorbidity Index; cont. = continuous; HR = hazard ratio; MMSE = Mini-Mental State Examination; MRCI = Medication Regimen Complexity Index (tenths, MRCI continuous divided by 10).

*Adjusted for age, sex, education, living place, modified CCI, ADLs, MMSE, unplanned admission in the previous year, self-reported pain, dexterity, receives help to sort medication.

Reference categories: †education = elementary, ‡dexterity = cannot open jars with lids.

Table 3. Cutoffs of MRCI and Number of Medications for Unplanned Hospital Admission, Derived From Receiver Operating Characteristics Curve Analyses

	Cutoff	Sensitivity	Specificity	Youden Index	AUC ROC Curves
MRCI	14	0.46	0.75	0.20	0.641
Number of medications	5	0.53	0.70	0.23	0.644

Notes: AUC = area under the curve; MRCI = Medication Regimen Complexity Index; ROC = receiver operating characteristics.

medication-related readmission risks (37). These results suggest that cutoffs are specific to the population in which the MRCI is applied. This suggests that there is not necessarily one cut-point that could be used to identify older people at risk of medication-related hospitalizations in all settings. Interestingly, however, the optimal cut-point of five medications for predicting unplanned hospital admission in our sample was consistent with the common definition of polypharmacy as "five or more medications" (38).

The adjusted proportion of unplanned hospitalization that would not occur in a scenario without high MRCI and number of medications was approximately 14.08% and 17.61%, respectively, over 3 years (95% CI). This suggests both regimen complexity and number of medications are both clinically and statistically significant predictors of unplanned hospitalization.

Previous studies have reported that lower education levels are associated with inappropriate medication use (39). In our study, lower education level was associated with unplanned hospital admission in both unadjusted and adjusted analyses. This suggests that the association between lower education and unplanned hospitalization is not fully explained by people with lower education having a higher regimen complexity or a higher number of medications. Other factors associated with unplanned hospitalizations were number of unplanned hospitalizations in the previous year and receipt of help to sort medications. Previous research has also found an association between previous and future unplanned hospitalizations in people aged 65 years or older (6). The association between receipt of help to sort medications and unplanned hospitalizations was unlikely to have been causal. People who needed help to sort medications were likely to have been frail and at greater susceptibility to unplanned hospitalizations for a range of reasons. We found no association between regimen complexity and unplanned hospitalization among participants living in nonhome settings. Even though we adjusted for receipt of help to sort medications, this was likely to be because people living in nonhome settings received support to administer their medications and may have been more closely monitored for ADEs. This needs to be investigated in future research.

Strengths and Limitations

Strengths of the study include the large population-based sample. Since unplanned hospitalization is dependent upon many interrelated factors, the large sample size allowed us to determine the effect related to medications by adjusting for a large number of confounding factors. The study sample was population-based and medication regimen complexity was measured with a widely used and validated index. All variables were collected by trained staff using validated scales (15,27,28). Data on unplanned hospitalization and death were comprehensive as they were obtained from the inpatient register in the Stockholm area, Swedish National Inpatient Register, and the Swedish National Cause of Death Register. Furthermore, the study sample comprised participants living in home and nonhome settings (18).

Neither number of medications nor regimen complexity considers the use of specific high risk medications that may contribute to the risk of unplanned admissions such as warfarin, insulin, oral antiplatelets, oral hypoglycemics, or anticholinergic or sedative medications (2). It was a limitation that we did not have access to data on directions for medication use that clinicians may have provided to specific participants. We overcame this by using standard dosing instructions to compute the MRCI. However, this may have over or underestimated participants' true regimen complexity. The median age of our sample was 72 years and therefore the results might not be generalizable to older populations. Within our study sample, the MRCI had a wide range from 1.5 to 76. We deemed that a one-unit increase in complexity index was unlikely to be clinically relevant and therefore analyzed the MRCI as continuous variable divided by 10 (17). We were unable to directly consider the possible impact of medication non-adherence but by interviewing participants we ascertained which medications were actually taken rather than those which were dispensed or prescribed. It was not possible to determine the proportion of unplanned hospitalizations that were directly or indirectly medication-related. However, ADEs are considered a leading cause of preventable hospitalizations among older people. Our results suggest that there is a modest but statistically significant association between both regimen complexity and number of medications and unplanned hospitalization. Finally, we assessed the number of medications and regimen complexity cross-sectionally at baseline. Further studies are needed to determine whether simplifying medication regimens or "deprescribing" medications reduces unplanned hospitalizations (40).

In conclusion, medication regimen complexity and number of medications were both associated with unplanned hospital admissions after adjustment for clinically important covariates. There was no evidence that using a complex tool to assess regimen complexity was better at predicting unplanned hospitalization than number of medications.

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Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication to this article.

Author contributions: B.C.W. conceptualized the study, analyzed the data, and drafted the manuscript. J.S.B. and K.J. conceptualized the study and critically revised the manuscript for intellectual content. J.F. and M.D.W. contributed to the design of the study and critically revised the manuscript for intellectual content. All authors approved the final manuscript submitted for publication.

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