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Patient-Reported Outcomes

Identifying Adherence Patterns Across Multiple Medications and Their Association With Health Outcomes in Older Community-Dwelling Adults With Multimorbidity

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ABSTRACT

Objectives: To classify older people with multimorbidity according to their adherence patterns and to examine the association between medication adherence and health outcomes.

Methods: This is a secondary analysis of a cohort study. Community-dwelling adults aged ≥70 years were recruited from 15 general practices in Ireland in 2010 (wave 1) and followed up 2 years later (wave 2). Participants had ≥2 RxRisk-V multimorbidity conditions at wave 1 and had ≥2 dispensations of RxRisk-V medications (wave 1-wave 2). Average adherence across RxRisk-V conditions was estimated based on continuous multiple-interval measure of medication availability (CMA7 function in AdhereR). Group-based trajectory models were used to group participants' adherence patterns for RxRisk-V medications. Multilevel regression was used to examine the association between adherence and (1) EuroQol 5-dimension (EQ-5D) utility (linear) and (2) vulnerability, using the Vulnerable Elders Survey (≥3 defined as vulnerable; logistic) at wave 2, controlling for potential confounders.

Results: Average adherence (CMA7) was 77% across 501 participants. Group-based trajectory models identified 5 adherence groups: (1) initial low adherers, gradual increase; (2) high adherers, sharp decline; (3) steady adherers, gradual decline; (4) consistent high adherers; and (5) consistent nonadherers. Higher average adherence was associated with a significant increase in EQ-5D utility (adjusted β = 0.11, robust standard error 0.04). Group 5 was associated with significantly increased vulnerability compared to group 4 (adjusted odds ratio = 1.88; 95% confidence interval 1.01-3.50).

Conclusion: Increased average adherence was associated with higher EQ-5D utility. Adherence grouping did not significantly impact utility. Suboptimal adherence to multiple medications in older adults with multimorbidity was associated with vulnerability.

Keywords: aged, medication adherence, multimorbidity, quality of life.

VALUE HEALTH. 2020; 23(8):1063–1071

Introduction

Medication adherence has been defined as a process by which patients take their medication as prescribed, consisting of 3 main components: initiation, implementation, and discontinuation.[1] Medication nonadherence can occur at any stage in this integrated process; the prescription may not be filled at the pharmacy (noninitiation), the dosing regimen may not be completed as intended (suboptimal implementation), or the treatment may be discontinued early (nonpersistence). Older populations may present a higher risk of nonadherence compared to younger cohorts owing to the increased likelihood of multimorbidity[2] and drug burden (polypharmacy).[3] Multimorbidity increases the risk of functional disability and healthcare utilization, potentially affecting an individual's ability to self-manage their medication regimen. Increasing drug burden may increase the complexity of the dosing regimen, which may be problematic in patients with cognitive problems.

Multimorbidity is commonly defined as the coexistence of ≥2 chronic conditions.[4] In Ireland, the prevalence of multimorbidity has been estimated at 80% in those aged ≥65 years.[5] As people age, the cumulative burden of morbidities has an increased impact on healthcare requirements.[6] Previous studies in multimorbidity have highlighted the need to amend the single-disease framework frequently employed in clinical research,[7,8] especially in older populations. Similarly, research on medication adherence is mostly focused on studies relating to a single medication class, without due consideration for other medications.[9]

Estimating medication adherence in patients with multimorbidity is complicated, which may account, in part, for the

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limited evidence. There is heterogeneity in how measures such as proportion of days covered (PDC) and medication possession ratio (MPR) are operationalized,[10] especially regarding multiple medications, resulting in potentially significant effects on health outcomes.[9,11] To date, the focus of multiple medication adherence studies has been on accounting for polypharmacy within specific conditions, as opposed to across multiple conditions.[10]

Increasing multimorbidity is significantly associated with a decrease in quality of life and poorer functional ability and contributes to high healthcare costs.[12] Nevertheless, the association between medication adherence and health outcomes such as health-related quality of life (HRQoL) in older patients is inconclusive.[13,14] A recent systematic review noted the lack of well-designed studies, with most having a cross-sectional design.[9] Some of the included studies showed a positive association between adherence and HRQoL, while others found no significant relationship.[9] Further research is needed to estimate the association between nonadherence and HRQoL in older populations with multimorbidity.

Objectives

The aims of this study are to (1) classify older people with multimorbidity according to their adherence patterns across multiple medications, and (2) estimate the association between medication adherence and health outcomes in community-dwelling people with multimorbidity.

Methods

Study Design and Setting

This is a secondary analysis of a cohort study of community-dwelling older adults (N = 904) aged ≥70 years from 15 general practices in the Republic of Ireland. Participants were recruited over a 5-month period in 2010[15] and followed up 2 years later.[16] Participants were community-based and in receipt of a General Medical Services (GMS) card, a state-subsidized scheme under which eligible participants receive free healthcare and partially subsidized prescription medications. Until January 2009, all Irish citizens aged ≥70 years were eligible for GMS coverage. The introduction of income-based eligibility criteria in January 2009 resulted in a small incremental decline in GMS eligibility in adults aged ≥70 years, with 90% of the national population having coverage in 2013.[17] Medications dispensed under the GMS scheme are available in a pharmacy claims database by the Health Service Executive-Primary Care Reimbursement Services. Further details on patient recruitment and eligibility can be found in Supplemental Materials at https://doi.org/10.1016/j.jval.2020.03.016 and elsewhere.[15,16]

Study Population: Patients With Multimorbidity

The RxRisk-V tool was used to identify multimorbidity using World Health Organization Anatomical Therapeutic Codes (ATCs).[18] The RxRisk-V classifies medication refills into 45 chronic conditions in older populations, based on the clinical indication of the medications specified in the algorithm.[18–20] Details of medications and ATC codes used in application of the RxRisk-V tool can be found in Supplemental Materials (see Appendix Table A in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.016). We did not include chronic conditions with no associated medication ATC codes, that is, malnutrition and ostomy. The RxRisk-V tool has demonstrated validity for predicting incident multimorbidity in elderly cohorts.[21] Participants were classified as having a RxRisk-V condition if they had ≥1 dispensation of any RxRisk-V associated medication in the 6 months prior to wave 1 (baseline). Participants were identified as having multimorbidity if they had ≥2 RxRisk-V conditions at baseline.

Implementation Adherence Measurement

Summary adherence measure

Implementation adherence was calculated for RxRisk-V medication(s) that were dispensed at least once in the 6 months before wave 1. Adherence was calculated for these chronic medications over a 24-month period between wave 1 and wave 2, provided there were ≥2 dispensations of the medication within this period.

Continuous multiple-interval measure of medication availability (CMA) was used to calculate adherence, using the AdhereR program (R statistical package).[22] Within AdhereR, users can implement a range of adherence algorithms based on those described by Vollmer et al.[23] Implementation adherence was estimated using the CMA7 measure.[23] The CMA7 is calculated as the number of days of theoretical medication use divided by the duration of the observation period, allowing for carryover of supply from before and within the observation period.[22]

A CMA7 value was obtained for each eligible RxRisk-V medication over the exposure duration. An average adherence value per condition for each patient was calculated by averaging the CMA7 values of relevant medications for each RxRisk-V condition. A composite multimorbidity adherence measure was created for each participant by averaging the CMA7 values across each of their RxRisk-V conditions. This continuous adherence value was used as the primary summary adherence exposure. Secondly, participants were classified as nonadherent if their average composite CMA7 was <80%, the threshold frequently, albeit arbitrarily, employed in adherence research.[11,24] The adherence threshold was altered in sensitivity analyses (60%, 70%, and 90%).

Adherence trajectory groups

A supply diary was created to indicate whether the participant had the RxRisk-V medication available to them for each day over the exposure period (24 months). Similar to CMA measurement, this was calculated for each eligible RxRisk-V medication and averaged across RxRisk-V condition(s) to get an overall adherence value for each month over the exposure period. Using the adherence value for each month, a binary indicator was created indicating if the PDC was ≥80% for each 30-day period.[25] If the duration between wave 1 and 2 was <24 months, participants were classified as missing for the corresponding time indicators, as opposed to nonadherent.

Health Outcomes

Two health outcomes were measured: (1) general health status according to the EuroQol 5-dimension (EQ-5D) utility score, and (2) physical well-being and physical functioning according to the Vulnerable Elders Survey (VES).

EQ-5D Utility

The EQ-5D is a generic health status measure that generates health states based on participant responses across 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[26] The 3-level rating system (ED-5D-3L) used is classified as follows: (1) no problems, (2) moderate problems, or (3) extreme problems.[27] Utility values derived from a UK population, using the time trade-off technique, were employed.[28] The EQ-5D-3L has been validated for measuring health status in elderly populations in the United Kingdom.[29]

Vulnerability

The VES is a 13-item questionnaire that seeks to identify older adults aged ≥65 years who may be at high or moderate risk of functional decline or death.[30] A higher VES score has been shown to predict death and functional decline over short follow-up periods in the United States.[31] Scores of VES ≥3 indicate the presence of vulnerability.

Covariate Selection

The following covariates were included in the multivariable analysis of the association between medication adherence and the 2 health outcomes, as evidenced from the literature[9,15,16]: age (continuous), sex, education level (basic, upper/postsecondary), social class (skilled, unskilled), deprivation score (based on participant's address), Charlson Comorbidity Index weight[32] (0, 1+), polypharmacy (0-4, 5-9, 10-14, 15+ chronic medications), social support (low, medium, high), and social network scale (number of social contacts). All covariates were measured at baseline, apart from polypharmacy. Further details on covariate measurement and description are available in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.016.

Statistical Methods

Descriptive statistics including means, medians, and variance were calculated for implementation adherence, EQ-5D utility, and vulnerability. Chi-square tests (categorical variables) and Wilcoxon rank-sum tests (nonparametric continuous variables) were used to determine significant differences in characteristics of participants (covariates) based on adherence classification using the CMA7 measurement and trajectory groupings, respectively, using SAS software version 9.4 (Cary, North Carolina).

In group-based trajectory modeling (GBTM), the probability of participants' membership in a certain adherence group was estimated based on a multinomial logistic regression model with no predictors.[33] Within each adherence grouping, a logistic model was used to calculate the probability of being adherent versus nonadherent as a smooth function of time.[25,34] The time variable was months since wave 1 consent (1-24). Time was modeled as a cubic polynomial in each group. This model was implemented using Proc Traj, which is available as a free downloadable add-on package (https://www.andrew.cmu.edu/user/bjones/download.htm) for use in SAS. The maximum number of groupings was set at 5 based on previous studies using GBTM.[34,35] The final model was selected based on the following[33]: (1) Bayesian information criteria (BIC) value (the lower the BIC, the better the model fit); (2) each group had to contain a minimum proportion of 5% of the entire study sample; and (3) the average posterior probability of group membership for participants assigned to each group ≥70% (entropy).

Multilevel linear regression was used to model the association between (1) average implementation adherence (continuous variable) and EQ-5D utility at follow-up, and (2) adherence trajectory group and EQ-5D utility at follow-up, controlling for the possible confounding variables mentioned. Multilevel modeling was used to account for clustering by general practice. Robust standard errors (RSEs) associated with the β coefficients were calculated. Significance from β = 0 was examined.

Multilevel logistic regression was used to model the association between adherence and vulnerability (VES score ≥3), controlling for confounding models mentioned. Unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) are presented. Multilevel modeling was performed using STATA version 14 (StataCorp, Texas).

Results

In total, of the 904 participants who completed wave 1, 807 (89%) had ≥2 RxRisk-V conditions at baseline based on dispensed medications in the 6 months prior to wave 1. From this cohort, 501 (62%) participants were followed up in wave 2 and had ≥2 RxRisk-V medications dispensed between waves 1 and 2 (Fig. 1). Details on participants who were lost to follow-up can be found elsewhere.[16]

Table 1 describes the baseline characteristics of participants included in this study (n = 501).

RxRisk-V Conditions

The most common RxRisk-V condition was hyperlipidemia (n = 320, 63.9%). The median number of RxRisk-V conditions per participant was 4 (interquartile range [IQR] 3-6). Considering the top 10 RxRisk-V conditions, the most common pair of chronic conditions was hyperlipidemia and cerebrovascular disease (n = 266, 53.1%), with cardiovascular-related conditions dominating the most frequent combinations. Further details on the most common pairs of RxRisk-V conditions can be found in Supplemental Materials (see Appendix Table B in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.016).

Adherence Classification

Summary adherence measure: CMA7 calculation

The average adherence level for the study cohort was 77% (standard deviation [SD] 19%). Setting the adherence threshold at CMA7 < 80%, 48% (n = 240) were considered nonadherent (see Appendix Table C in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.016).

Differences in covariates based on whether participants were classified as nonadherent (CMA7 < 80%) or adherent are described in Supplemental Materials (see Appendix Table D in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.016). There were a significantly higher proportion of women (P = .0001), people on ≥10 medications (P = .006), and participants with a Charlson Comorbidity Index weight of 0 (P = .004) in the nonadherent group.

Adherence group based on GBTM

The 5-group model was deemed to be most suitable, based on model selection criteria (see Appendix Table E in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.016). This trajectory model identified the following adherence groups within the population (Fig. 2).

Group 1: Initial low adherers, gradual increase (7.6% of study cohort). The average adherence value of this group was 72% (SD 8%).

Group 2: High adherers, sharp decline (12.5%). The average adherence value of this group was 71% (SD 11%).

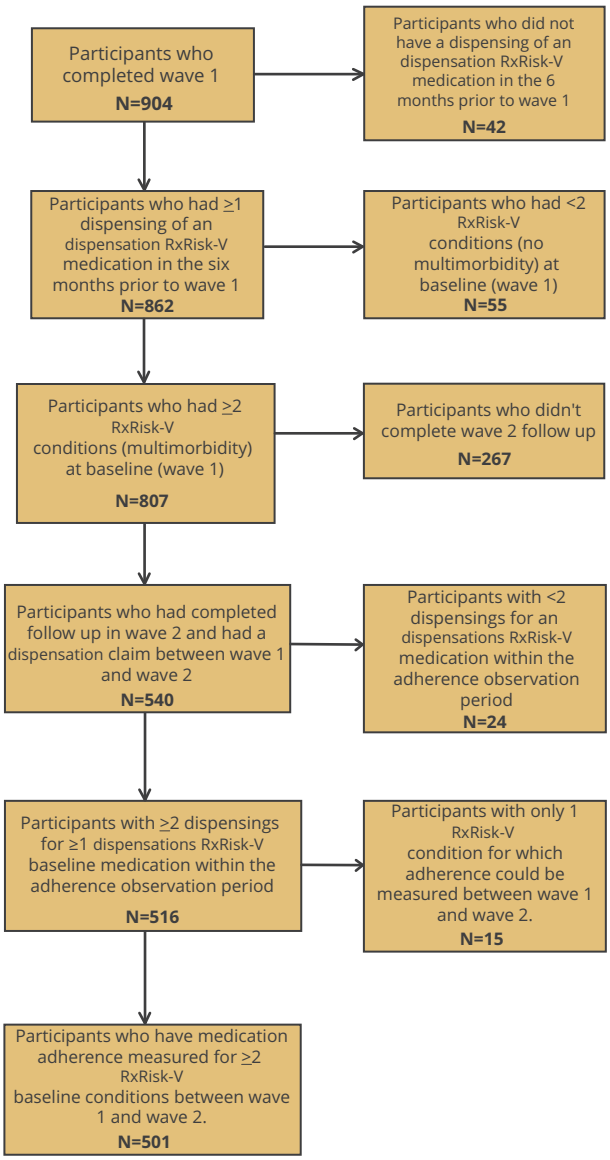
Group 3: Steady adherers, gradual decline (18.3%). The average adherence value of this group was 82% (SD 5%).

Group 4: Consistent high adherers (37.4%). The average adherence value of this group was 93% (SD 5%).

Group 5: Consistent nonadherers (24.2%). The average adherence value of this group was 52% (SD 18%).

The median number of RxRisk-V conditions within groups 1, 2, and 3 was 5 (IQR 4-7 for groups 1 and 2, IQR 3-7 for group 3), while groups 4 and 5 had a median of 4 RxRisk-V conditions per participant (IQR 3-5 for group 4 and IQR 3-6 for group 5). The most common RxRisk-V condition pair in each group, except group 1, was hyperlipidemia and cerebrovascular disease. For group 1, the

Figure 1. Study flow diagram for participant selection.



most common pair was cerebrovascular disease and chronic heart failure.

The average predicted probability of membership in each trajectory grouping with associated SD among participants assigned to each grouping is presented in Figure 2.

Differences in baseline characteristics of participants assigned to each adherence trajectory grouping are presented in Supplemental Materials (see Appendix Table F in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.016). There were a significantly higher proportion of women in groups 1 and 5 compared to the other adherence groups ($P = .0007$). Group 4 had a significantly lower proportion of participants on ≥15 regular medications compared to the other trajectory groups ($P = .0007$). Group 5 had a significantly higher proportion of participants with a Charlson Comorbidity Index score of 0 ($P = .006$).

EQ-5D Utility

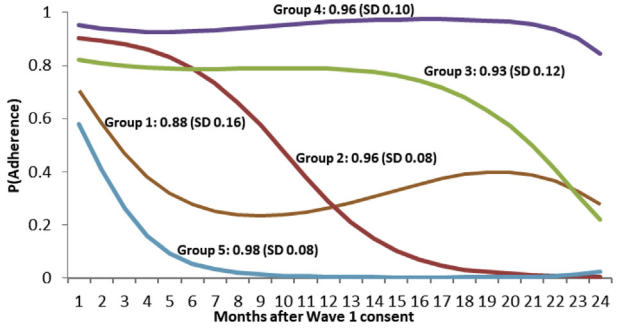
The mean EQ-5D utility in the study population at follow-up was 0.73 (SD 0.23). In the nonadherent population (CMA7 < 80%), the mean EQ-5D utility was 0.70 (SD 0.22) and in the adherent population, the mean EQ-5D was slightly higher at 0.76 (SD 0.22). Results of the multilevel linear regression model are presented in Table 2 and show a significant association between average adherence and EQ-5D utility. A one unit (100%) increase in average adherence (CMA7) was associated with a significant 0.11 increase in EQ-5D utility. Results of multilevel regression models including the dichotomized adherence exposure can be found in Supplemental

Table 1. Baseline characteristics of participants included in this study (n = 501).

Characteristic	N = 501
Age, median years (IQR)*	76 (73-80)
Deprivation score, mean (SD)*	1.47 (2.54)
Female, n (%)	264 (53%)
Male, n (%)	237 (47%)
Education level*	N = 498
Basic level of education, n (%)	304 (61%)
Upper and post-secondary education, n(%)	194 (39%)
Polypharmacy†	Measured over adherence period (2 years)
0-4 medications, n (%)	77 (15%)
5-9 medications, n (%)	220 (44%)
10-14 medications, n (%)	157 (31%)
15+ medications, n (%)	47 (9%)
Marital status*	N = 500
Married, n (%)	243 (49%)
Never married/single, n (%)	78 (15%)
Separated/divorced, n (%)	25 (5%)
Widowed, n (%)	154 (31%)
Living arrangements*	N = 500
Family/relatives	55 (11%)
Spouse/partner, n (%)	232 (46.5%)
Lives alone, n (%)	186 (37%)
Other, n (%)	27 (5.5%)
Private health insurance,* n (%)	225 (45%)
Social class*	
Skilled, n (%)	381 (76%)
Unskilled, n (%)	120 (24%)
Charlson Comorbidity Index weights*	
0, n (%)	244 (49%)
1, n (%)	257 (51%)
Social support*	N = 500
Low, n (%)	34 (7%)
Moderate, n (%)	115 (23%)
High, n (%)	349 (70%)
Social network score,* median (IQR)	8 (7-9)

IQR indicates interquartile range; SD, standard deviation.
*Measured at baseline.
†Polypharmacy was measured over the adherence exposure period (2 years).

Figure 2. Adherence trajectory groups assigned based on overall adherence to multiple RxRisk-V medications. Group 1 (7.6% of population), group 2 (12.5% of population), group 3 (18.3% of population), group 4 (37.4% of population), and group 5 (24.2 % of population).



P(Adherence) indicates the proportion of adherent participants (PDC ≥ 80%) at a particular point. The average predicted probability of membership of each trajectory grouping is presented beside each trajectory group. The associated standard deviation for the posterior probability of grouping assignment is indicated in brackets. PDC indicates proportion of days covered.

Materials (see Appendix Table G in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.016). Setting the adherence threshold at 90% resulted in nonadherence having a significant effect on EQ-5D utility (adjusted β = −0.04, RSE = 0.02, P = .046), whereas nonsignificant results were observed for the other dichotomous exposures.

The average EQ-5D utility score by adherence trajectory grouping was as follows: group 1: 0.68 (SD 0.24); group 2: 0.68 (SD 0.28); group 3: 0.72 (SD 0.25); group 4: 0.78 (SD 0.20); and group 5: 0.71 (SD 0.22).

The unadjusted and adjusted β coefficients, along with RSEs, for the association between adherence trajectory groupings and EQ-5D utility are also presented in Table 2. Membership in different adherence trajectory groupings was not associated with a significant change in EQ-5D utility compared to the consistent high adherers.

Vulnerability

Forty percent (n = 203) of participants were categorized as vulnerable at follow-up. Forty-seven percent of participants in the nonadherent group were classified as vulnerable at follow-up, compared to 33% of adherent participants (χ^2 = 12.95, P <.001). Similarly, different adherence trajectory groupings included significantly different proportions of participants defined as vulnerable at follow-up (χ^2 = 14.64, P = .006). Consistent high adherers contained 32% of vulnerable elders, compared to the consistent nonadherers, where 51% were deemed vulnerable at follow-up.

Results of the multilevel logistic regression are presented in Table 3. A one unit (100%) increase in average adherence was associated with a significantly reduced likelihood of being defined as vulnerable (adjusted OR 0.16; 95% CI 0.05-0.55). Results of analyses involving dichotomized adherence exposures are available in Supplemental Materials (see Appendix Table H in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.016). Decreasing the adherence threshold from 80% resulted in an increase in the strength of the association between nonadherence and vulnerability risk, whereas an increase to 90% caused the relationship to become statistically nonsignificant.

In adjusted analyses, consistent nonadherers remained significantly associated with vulnerability classification compared to consistent high adherers (adjusted OR 1.88, 95% CI 1.01-3.50).

Discussion

Overall, average adherence to regular prescribed medications in community-dwelling older adults with multimorbidity was suboptimal, with almost half of the study population classified as nonadherent according to the 80% threshold. Five distinct adherence groups were identified in this population, based on pharmacy refill claims for RxRisk-V medications over a 2-year period. Medication nonadherence for chronic conditions in adults aged ≥70 years may significantly impact EQ-5D utility scores and vulnerability risk. This is the first study, to our knowledge, to use GBTM to model multimorbidity medication adherence in older community-dwelling adults and its association with health outcomes.

Previous studies that have measured adherence to multiple medications using pharmacy refill claims have largely done so within a specific disease population, making it difficult to contextualize our findings.[9,10] A similar study, using this same baseline cohort, estimated medication adherence across most RxRisk-V conditions using the MPR, finding 31% of the population was nonadherent (MPR < 80%).[19] Nevertheless, this study was not limited to those with multimorbidity and measured adherence over a 6-month period using MPR. Numerous formulas have been used to calculate the denominator period used in MPR in the literature, leading to possible overestimation or underestimation of adherence rates, which may affect association estimates with health outcomes.[11] This present study expands on previous research by restricting inclusion to those with multimorbidity and establishing a range of adherence patterns longitudinally across multiple conditions and their association with health outcomes.

The use of GBTM demonstrated the dynamic nature of longitudinal adherence patterns. A recent use of GBTM in a similar population identified 3 distinct adherence trajectory groups within a cohort of prevalent antihypertensive users.[36] Nevertheless, overall adherence was >90% for 2 of the groups, with the low-adherence group still having a relatively high PDC value.[36] By contrast, greater heterogeneity was observed in this sample regarding adherence, which may be attributed to inclusion of multiple long-term conditions and the longer duration of adherence measurement. Previous GBTM studies of single medication or disease regimens have identified 4 or more trajectory groups within their study populations,[25,37] although larger sample sizes were used.

Also, a copayment of €0.50 per item was introduced to all prescription items dispensed under the GMS scheme in October 2010, capped at €10/month per household. This may account for an increase in nonadherence, particularly to those considered less-essential medications, such as anxiolytics and nonsteroidal anti-inflammatories.[38] The consistent high adherers group had the lowest proportion of participants on medications for anxiety (0.25%) and inflammatory pain (1.74%), compared to the other trajectory groups, where adherence was lower.

It has been previously stated that the minimal clinically important change in EQ-5D utility is 0.074.[39] While there was a statistically significant increase in EQ-5D utility associated with average adherence, a 68% increase in average adherence would be required to achieve this level of clinically important change in

Table 2. Multilevel linear regression unadjusted and adjusted results of the association between adherence and EQ-5D utility score at follow-up.

	Unadjusted β	Robust SE	*P* value	Adjusted β	Robust SE	*P* value
Average adherence						
Average adherence*	0.17	0.04	<.001	0.11	0.04	.01
Adherence trajectory group						
Group 4: consistent high adherers	–			–		
Group 1: initial low adherers, gradual increase	−0.10	0.04	.005	−0.04	0.03	.16
Group 2: high adherers, sharp decline	−0.10	0.03	.004	−0.05	0.03	.09
Group 3: steady adherers, gradual decrease	−0.06	0.04	.09	−0.04	0.03	.26
Group 5: consistent nonadherers	−0.07	0.03	.02	−0.03	0.03	.41
Sex†						
Male	–			–		
Female	−0.06	0.01	<.001	−0.04	0.01	.007
Age (continuous)†	−0.01	0.002	<.001	−0.01	0.002	<.001
Social class†						
Skilled	–			–		
Unskilled	0.03	0.03	.28	0.04	0.02	.06
Education level†						
Basic level	–			–		
Upper and post-secondary	0.05	0.01	<.001	0.04	0.02	.05
Charlson Comorbidity Index weights†						
0	–			–		
1+	−0.03	0.02	.11	0.006	0.01	.66
Polypharmacy†						
0-4 medications	–			–		
5-9 medications	−0.07	0.02	<.001	−0.05	0.02	.01
10-14 medications	−0.18	0.02	<.001	−0.15	0.02	<.001
15+ medications	−0.29	0.04	<.001	−0.24	0.04	<.001
Deprivation score (continuous)†	−0.01	0.004	.13	−0.002	0.003	.53
Social support†						
Low	–			–		
Moderate	0.05	0.06	.46	0.05	0.06	.40
High	0.08	0.05	.11	0.07	0.05	.18
Social network score (continuous)†	0.02	0.005	.001	0.01	0.004	.007

There were missing covariate data for 6 people in the sample (adjusted results n = 495).
β indicates beta coefficient; EQ-5D, EuroQol 5-dimension; SE, standard error.
*For the continuous CMA adherence measure a 1 unit increase is equivalent to 100% increase in adherence.
†Note adjusted results for covariates are from multivariable analysis that includes continuous average adherence.

health status. No significant association was observed between the adherence trajectory groups and EQ-5D utility. Cross-sectional studies of self-reported medication adherence have indicated a positive relationship between good medication adherence and EQ-5D utility.[40,41] By contrast, a longitudinal study of patients with chronic obstructive pulmonary disease using administrative databases did not find a significant relationship between medication adherence and EQ-5D utility.[42] Nevertheless, a meta-analysis of adherence improvement interventions found that such interventions resulted in small but significant improvements in QoL.[43] The authors postulated 2 mechanisms through which this effect might be mediated: directly through reduced symptoms and indirectly through an improvement in self-efficacy.[43] It is likely that any short-term improvement in HRQoL, owing to an increase in adherence obtained in an interventional setting, is attenuated in the real world. Polypharmacy demonstrated a strong dose-response inverse association with EQ-5D utility that was clinically significant. A reduction in EQ-5D utility of 0.05 has been shown to accurately predict 5-year mortality in adults aged ≥65 years,[44] which contextualizes the potential harm associated with older people being on ≥15 regular medications.

Table 3. Multilevel logistic regression results of the association between adherence and vulnerability at follow-up.

Variable	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Average adherence				
Average adherence*	0.15 (0.06-0.40)	<.001	0.16 (0.05-0.55)	.004
Adherence trajectory groupings				
Group 4: consistent high adherers	1.00		1.00	
Group 1: initial low adherers, gradual increase	1.45 (0.71-2.96)	.71	1.57 (0.64-3.87)	.32
Group 2: high adherers, sharp decline	2.09 (1.15-3.78)	.02	1.64 (0.78-3.44)	.19
Group 3: steady adherers, gradual decline	1.19 (0.69-2.04)	.53	0.76 (0.38-1.51)	.44
Group 5: consistent nonadherers	2.20 (1.34-3.53)	.001	1.88 (1.01-3.50)	.046
Sex†				
Male	1.00		1.00	
Female	2.05 (1.41-2.97)	<.001	1.95 (1.18-3.21)	.01
Age (continuous)†	1.32 (1.25-1.40)	<.001	1.33 (1.25-1.41)	<.001
Social class†				
Skilled	1.00		1.00	
Unskilled	0.97 (0.63-1.51)	.91	0.99 (0.58-1.70)	.97
Education level†				
Basic level	1.00		1.00	
Upper and post-secondary	0.79 (0.53-1.20)	.27	0.96 (0.56-1.64)	.87
Charlson Comorbidity Index weights†				
0	1.00		1.00	
1+	1.48 (1.02-2.14)	.04	1.58 (0.96-2.61)	.07
Polypharmacy†				
0-4 medications	1.00		1.00	
5-9 medications	2.58 (1.33-4.99)	.005	2.52 (1.09-5.83)	.03
10-14 medications	5.61 (2.85-11.06)	<.001	5.51 (2.31-13.17)	<.001
15+ medications	8.50 (3.61-20.00)	<.001	5.61 (1.90-16.54)	.002
Deprivation score (continuous)†	1.08 (0.99-1.17)	.08	1.09 (0.99-1.20)	.10
Social support†				
Low	1.00		1.00	
Moderate	1.53 (0.69-3.43)	.30	0.96 (0.35-2.61)	.93
High	1.23 (0.58-2.59)	.59	0.95 (0.36-2.50)	.91
Social network score (continuous)†	0.94 (0.86-1.03)	.18	0.91 (0.80-1.03)	.12

There were missing covariate data for 6 people in the sample (adjusted results n = 495).
CI indicates confidence interval; OR, odds ratio.
*For the continuous CMA adherence measure a 1 unit increase is equivalent to 100% increase in adherence.
†Note adjusted results for covariates are from multivariable analysis that includes continuous average adherence.

Higher overall adherence was associated with a reduced likelihood of being defined as vulnerable at follow-up, with consistent nonadherers associated with a 88% increased likelihood of vulnerability compared to the consistent adherent group. Although the result for consistent nonadherers was statistically significant, the CI around this estimate was wide and, as such, should be interpreted with caution. Vulnerability, as measured using the VES-13, has been to shown to have high sensitivity for predicting death, disability, and institutionalization in older populations.[45]

Strengths and Limitations

This is the first study to examine adherence to multiple medications in an older, community-dwelling Irish population and associated outcomes using the CMA approach. This analysis has attempted to address a gap in the literature regarding the measurement of medication adherence across multimorbidity using pharmacy refill claims. Use of GBTM provides greater insight into the dynamics of medication-taking behavior, allowing for increased precision in the design of adherence interventions.

Important confounding variables that may affect the relationship between adherence and HRQoL, such as social support, deprivation, and social network, were controlled for in multivariable analyses. These confounders are often absent from studies involving electronic healthcare data, highlighting an added strength from linking administrative data to cohort study data. In addition, adherence was measured over the 2 years prior to measurement of health outcomes, providing insight into longitudinal adherence behaviors in older people with multimorbidity.

Nevertheless, there are a number of limitations to be considered. As previously highlighted, the study sample may not be representative of all adults aged ≥70, because participants were recruited from 15 practices in 1 large region in Ireland.[15,16] Sample size was relatively small compared to other studies that have used GBTM to model adherence. There may have been a lack of statistical power to detect statistically significant differences between adherence groupings in relation to the EQ-5D utility score. Results from our analysis of GBTM models should be interpreted as hypothesis-generating rather than hypothesis-confirming. Nevertheless, research is ongoing to extend this type of adherence measurement to a nationally representative sample. Although pharmacy refill claims can be considered an objective measure of medication adherence, it is based on the assumption that all medication dispensed is consumed. Conversely, it is not subject to recall bias as self-report methods and can be useful for ascertaining adherence estimates in a real-world setting.[24] Group-based trajectory modeling can identify the treatment stage at which nonadherence may occur in treatment initiators. As this study contained prevalent users, all participants had previously received the RxRisk-V medications, making it difficult to estimate an individual's stage of treatment or disease. Owing to the sample size, it was not possible to restrict the population to new users only, which would minimize potential healthy adherer bias.[46] As a result, the population may be more adherent than those initiating RxRisk-V medications for the first time, because previous adherence behavior may influence future adherence behavior. The appropriateness of therapy was not considered in this study, but has been discussed elsewhere.[16] As there is no clinical decision-making information available, it may have been that early discontinuation of a medication or when required use was clinically indicated. In such a situation, nonadherence may be appropriate. Future research involving electronic healthcare databases containing medication instructions and clinical notes may consider the appropriateness of adherence.

Implications for Future Research/Policy

This study has indicated that suboptimal adherence to multiple medications may increase older people's susceptibility to adverse health outcomes. Conducting trajectory analyses allowed for identification of groups that may benefit from medication management interventions. Targeting those with consistent non-adherer characteristics (female, low social support, low comorbidity burden) may help to improve health outcomes.

The significant adverse impact that polypharmacy had on both health status and vulnerability in this study population cannot be ignored. It has been suggested there should be increased consideration of inappropriate polypharmacy, where prescribing of multiple medications is not clinically indicated.[47] Such interventions may also incorporate a deprescribing aspect, identifying medications that unnecessarily contribute to the drug burden of vulnerable older adults. A review of medication adherence interventions found that only a minority of included randomized controlled trials, with complex, difficult-to-implement interventions, were effective at improving adherence and clinical outcomes for patients with chronic long-term conditions.[48] A European-wide project whose primary aim was to reduce inappropriate polypharmacy in the elderly, with a secondary focus on medication nonadherence, identified the Scottish healthcare system's approach as the preferred approach.[49] One component of this policy was the addition of polypharmacy medication reviews to the general practitioner's contract in 2013, largely delivered by independent pharmacist prescribers.[49] Further exploration of the potential role of pharmacists, nurses, and other allied health professionals in delivering adherence interventions has been suggested in the literature.[48] Nevertheless, choice of medication management intervention(s) needs to reflect the feasibility of implementation within the relevant health system. Increased collaboration between pharmacists and general practitioners within the Irish primary care setting, facilitated through the allocation of protected funding for clinical services, such as medication reviews and adherence assessments, is required. Clear communication between secondary care, where many prescriptions are initiated, and general practice, where most of repeat prescribing occurs, is critical to optimize prescribing for people with multimorbidity and polypharmacy.[50]

Further research in this area should focus on the clinical-economic burden of multiple medication nonadherence in older patients in healthcare utilization. Such information would be useful for any potential future economic evaluations of medication management interventions.

Conclusion

Some older people with multimorbidity have suboptimal medication adherence patterns that adversely affect health outcomes. Medication management interventions, delivered by a multidisciplinary team of healthcare professionals, should address medication nonadherence in the multimorbid population by targeting those most at risk of adverse health outcomes.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2020.03.016.

Article and Author Information

Accepted for Publication: March 31, 2020

Published Online: July 22, 2020

doi: https://doi.org/10.1016/j.jval.2020.03.016

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Conflict of Interest Disclosures: Drs Bennett and Walsh reported receiving grants from the Health Research Board during the conduct of the study. No other disclosures were reported.

Funding/Support: Data collection for this study was funded by grants HRC/1/2007 (wave 1 and 2) and HPF/2012/20 (wave 2) from the Health Research Board of Ireland. This study was funded by grant HRB RL-2015-1579 from the HRB Research Leaders Award and under grant SPHeRE/2013/1 as part of the SPHeRE Programme.

Role of the Funder/Sponsor: The funding bodies had no role in the study design, data analysis, writing of the manuscript, or the decision to submit the manuscript for publication.

Acknowledgment: The authors would like to thank the Health Service Executive-Primary Care Reimbursement Service for providing access to dispensing data and the researchers involved in data collection for wave one and wave two of the study. We would like to thank Samuel Allemann and Jessica Franklin for assistance with coding queries. We are grateful to all the study participants and the staff within the 15 general practices who generously gave their time to participate in the study.

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