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The Five Dimensions of Medication Adherence in patients with multimorbidity and polypharmacy: Results from the MULTIPAP cohort study

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Abstract

Background: Medication adherence is particularly challenging in older adults with multimorbidity (MM) and polypharmacy (PP), who face greater therapeutic complexity and an increased risk of adverse health outcomes when treatment is not followed as prescribed. The World Health Organization (WHO) classifies determinants of medication adherence into five dimensions (socio-economic, condition-related, therapy-related, patient-related, and healthcare system-related factors), providing a comprehensive framework to identify modifiable factors. This study aimed to analyze factors associated with medication adherence across the five WHO dimensions in patients aged 65–74 years with MM and PP.

Methods: This cross-sectional study used baseline data from the MULTIPAP cohort including 1,057 patients aged 65–74 years with MM (≥3 chronic conditions) and PP (≥5 medications prescribed for at least three months). Medication adherence (dependent variable) was assessed using the 4-item Morisky-Green questionnaire. Independent variables were classified according to the five WHO dimensions of adherence, and included social support, number of chronic conditions and medications, health-related quality of life (EQ-5D-5L), and disability (WHODAS 2.0). Descriptive, bivariate, and mixed-effects logistic regression models were performed.

Results: Mean age of patients was 69.79 years (SD 3.47), 57.1% were women, and 727 (68.8%) patients were adherent. Adherent patients had lower urban vulnerability (71% vs 29%), higher social support (mean score 43.71 vs 42.5), fewer prescribed medications (7.8 vs 8.2), better health-related quality of life (mean score 66.66 vs 63.82), and lower disability (mean score 14.35 vs 19.84) compared with non-adherent patients. In the multivariate analysis, higher disability was independently associated with nonadherence (odds ratio 1.02; 95% confidence interval 1.01–1.04).

Conclusions: Self-reported medication adherence was relatively high among older adults with MM and PP.Although significant differences between adherents and nonadherents were observed across nearly all dimensions of factors related to adherence, only disability (dimension of patient-related factors) remained independently associated with nonadherence in the multivariate analysis. A patient-centred approach that incorporates a comprehensive assessment of the five dimensions is necessary to improve treatment adherence in this population.

Trial registration: ClinicalTrials.gov NCT04147130. Registered on 22 October 2019

Background

Medication adherence is defined as the process by which patients take medication according to the instructions provided by a healthcare professional. It comprises three main components: initiation, implementation and discontinuation (1, 2). Nonadherence to medication may occur at any of these (3). Adherence to long-term therapy averages approximately 50% in high-income countries, with even lower rates in low- and middle-income countries (4).

According to the World Health Organization (WHO), a combination of factors determines patients' ability to follow treatment recommendations correctly. These factors interact and potentiate each other's influence in a framework determined by five dimensions: socio-economic, therapy-related, patient-related, health care team and system-related and condition-related factors (4, 5).

Regarding the dimension of socio-economic factors, medication non-adherence has been associated with ethnicity, lack of health insurance, low social class (6, 7), low educational level (7), social stigma (8), and limited social support (8, 9). Social support is defined as the actual or perceived availability of support from an individual's social network (10). It facilitates disease management by providing practical and emotional assistance, including advice, affection, social engagement, and treatment-related support (9).

The dimension of therapy-related factors considers the complexity of the medical regimen, previous treatment failures, treatment duration, frequent changes in treatment, the immediacy of beneficial effects, and side-effects, as well as the availability of medical support to manage them (4). It has been reported that side effects and the complexity of the treatment, like frequent dosing, high number of prescribed medications or longer duration of treatment, make monitoring difficult, increasing the risk of nonadherence (8).

The dimension of patient-related factors represents the resources, knowledge, attitudes, beliefs, perceptions, expectations of the patient, age and sex (4). Regarding the impact of this factor on adherence, evidence suggests that older age (11) and better self-perception of quality of life (9, 12) are related to following the treatment recommendations, but there is no consensus on its effect.

Conversely, there are some factors that are not usually studied and that have a major influence on treatment adherence, like those included in the dimension of healthcare team and system-related factors. This dimension encompasses not only organizational factors but also characteristics of healthcare professionals. A positive doctor–patient relationship has been consistently associated with better adherence through improved communication and mutual trust (7, 8, 11). Likewise, physician characteristics, including age, professional experience, and teaching responsibilities (such as being a residency tutor), may also influence adherence (7), although these factors have been scarcely investigated.

The dimension of condition-related factors refers to the specific demands imposed by a patient's illness and includes the number and type of diseases, the severity of symptoms, the rate of disease progression, and the availability of effective treatments, among others (3, 11).

Although most studies focus on the evaluation of medication adherence to a single type of medication (3, 11), few authors have analyzed adherence in patients with multimorbidity (MM) or multiple long-term conditions (13). Reported adherence rates in patients with MM in high- and middle-income countries range from 15% to 43% (14). Improving adherence is a fundamental part of caring for patients with MM (3, 15) to avoid the negative consequences of inadequate clinical treatment like deterioration of

functional status, health outcomes, quality of life, increasing of healthcare utilization and premature mortality (15). This can be more challenging in patients with MM as they are usually prescribed a higher number of medications and present higher rates of polypharmacy (PP), defined as the prescription of five or more chronic drugs, which may hinder adherence to the overall therapeutic plan.

The aim of this study is to analyze medication adherence in patients aged between 65 and 74 years with MM and PP, and to explore the factors associated with low adherence according to the five dimensions of adherence proposed by the WHO.

Methods

Study design and population

This cross-sectional study used baseline data from patients enrolled in the MULTIPAP Plus randomized clinical trial (RCT), which served as the inception of the MULTIPAP cohort (16).

The MULTIPAP PLUS RCT (16) is a pragmatic parallel two-arm, superiority, community based

cluster-randomized controlled clinical trial with a follow-up of 18 months, conducted in 131 health centers from the Spanish regions of Andalucia, Aragon and Madrid, with the participation of 186 general practitioners (GPs). Each GP recruited between 6 and 8 patients, with a total of 1,057 patients included. They represent both the baseline sample of the MULTIPAP cohort and that of the MULTIPAP Plus RCT (in this case, they were later randomly assigned to receive the interventions designed in the clinical trial). The study population analysed in this paper included patients between 65 and 74 years with MM (defined as the simultaneous presence of ≥ 3 chronic diseases) and PP (≥ 5 drugs prescribed for at least three months prior to inclusion in the study), who visited their GP at least once in the year prior to the study and agreed to participate and sign the informed consent form. We excluded institutionalized patients, those with life expectancy of less than 12 months and with physical or mental illness that in the opinion of their GP did not allow them to follow the study requirements. The MULTIPAP PLUS Study was approved by the Clinical Research Ethics Committee of Aragon (CEICA) on April 10, 2019, with approval number PI18/064, and by Clinical Research Ethics Committee of Malaga on March 28, 2019.

Variables

The GPs collected all the study variables through the baseline interview conducted during a consultation. Adherence to treatment, which was the dependent variable of the study, was estimated through the 4-item Morisky-Green questionnaire, which asks four closed questions to the patient: “do you ever forget to take the medicines to treat your illness?”; “do you take the medicines at the indicated times?”; “when you feel well, do you stop taking the medicine?”; “and if you ever feel bad, do you stop taking the medicine?”. A patient was considered adherent if they answered all four questions on the questionnaire No/Yes/No/No, according to the direction of each item, resulting in a score of 4 points; any other combination was classified as non-adherent (17).

Factors associated with adherence were classified into the five dimensions of adherence (4,8). Age and sex were included in patient-related instead of socioeconomic-related factors, following the modification of Kardas et al. (8) of the original WHO report (4).

D1) Dimension 1 of adherence: socio-economic factors. These factors included retirement status (retirement/no retirement), social class (determined according to occupation using the Spanish National Classification of Occupations as applied in the 2011–2012 Spanish National Health Survey, and subsequently grouped into seven categories) (18), education level (primary education incomplete, primary education, secondary or higher education), socioeconomic level (low: ≤1050€/month, middle: 1051–2250€/month and high: ≥2251€/month), and indicators of subjective urban vulnerability (IUVs) that were based on those collected by the Spanish National Health Survey (19) to explore participants' neighborhood (noise level, bad odors, poor-quality drinking water, unclean streets, air pollution, lack of green areas, feral animals and crime) (20). Structural and functional social support were also included in this dimension. The first was characterized by the number of household members and information about marital status; the second was assessed by the 11-item version of the Duke UNC Functional Social Support (DUFSS) questionnaire (21). The DUFSS questionnaire offers a total score of functional support and has two additional scores related to each of the domains revealed by its factor analysis: affective and confidential support (22). Each one uses a Likert-type response scale from 1 ("Much less than I would like") to 5 ("As much as I would like") (23). Confidential support is measured through seven items (4, 5, 6, 7, 8, 10 and 11), with a total score of 35, and affective support is measured through four items (1, 2, 3, and 9), with a total score of 20. The total score for social support was categorized in tertiles, being tertile 1 the lowest (21).

D2) Dimension 2: condition-related factors. We included in this dimension the number of chronic diseases based on the International Classification of Diseases in Primary Care as per O'Halloran list (24).

D3) Dimension 3: therapy-related factors. This dimension included medications for at least three months before study inclusion. They were coded according to the Anatomical Therapeutic Chemical Classification (ATC) System (25).

D4) Dimension 4: patient-related factors. We studied age, sex, disability measured using the WHODAS (World Health Organization Disability Assessment Schedule) 2.0 scale (26), and health-related quality of life (HRQoL) measured by the EuroQol 5-Dimension 5-Level (EQ-5D-5L) (27). WHODAS 2.0 is scored on a scale of 0 to 100 based on the degree of disability, with 0 indicating no disability and 100 indicating total disability (26). The EQ-5D-5L determines the perceived general state of health measured by a visual analog scale (VAS) and utilities.

D5) Dimension 5: healthcare team and system-related factors. This dimension included the characteristics of the participant GPs : age, sex, years of seniority, and residency tutor (yes/no).

Statistical analysis

We performed a descriptive analysis of the sociodemographic and clinical characteristics of the study population, using means and standard deviations (SD), or medians and interquartile ranges (IQR), for continuous variables, and frequencies and percentages for categorical variables. The prevalence of adherence was estimated, and the characteristics of the population were stratified between adherents and nonadherents. We also estimated the distribution of the DUFSS questionnaire items according to adherence. Differences in characteristics between adherent and nonadherent patients were assessed using Student's t test or $\chi 2$ test, as appropriate. Due to the similarity in EQ-5D-5L and WHODAS 2.0 test (28), the degree of correlation between the two variables was measured using Spearman's Rho test.

The association between nonadherence (dependent variable) and the dimensions of adherence considered as independent variables (retirement status, social class, education level, socioeconomic level, urban vulnerability indicators, functional support, number of diseases and drugs, age, sex, EQ-5D-5L-VAS, utilities, WHODAS and GP's seniority) was analyzed using a multilevel mixed-effects logistic regression model with GP set as a random effect. In addition, several models were developed and compared using the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC). The model with the lowest AIC/BIC value was selected.

All statistical analyses were performed in STATA software (Version 14.0, StataCorp LLC, College Station, TX, USA), with the statistical significance set at $p < 0.05$.

Results

The study population included a total of 1,057 subjects with MM and PP. More than half of the sample (604; 57.1%) were women, and the mean age was 69.79 years (SD 3.47), with a mean number of 7.9 drugs (SD 2.79) and a median of 6 diseases (IQR 5-7). The majority of the subjects were retired (983; 93%) and had a middle socioeconomic status (784; 74.2%); more than 60% had primary or incomplete education, lived with two or more people, were married or had partners, and had little urban vulnerability. Of these, 727 (68.8%) were adherent to treatment (Table 1).

Adherent and nonadherent patients showed several significant differences in some of the studied dimensions. In relation to dimension 1 of socio-economic factors, a greater proportion of adherents persons (71% vs. 29%, $p = 0.014$) had less urban vulnerability, and higher social support (43.7 vs. 42.5. $p=0.04$) according to the DUFSS questionnaire. No significant differences were observed between adherent and non-adherent participants with respect to the number of comorbidities in dimension of condition-related factors. In relation to dimension 3 of therapy-related factors, adherent patients were prescribed less drugs on average (7.8±2.71 vs. 8.2±2.94 drugs, $p=0.042$). Dimension 4 of patient-related factors revealed a better quality of life (EQ-5D-5L-VAS score of 66.7 vs. 63.8, $p=0.030$) and utilities (0.8 vs. 0.7, $p<0.001$), and lower disability (WHODAS score of 14.4 vs. 19.8, $p<0.001$) in adherent patients. Regarding healthcare system-related factors (dimension 5), the majority of family physicians in the study were women, 63% had been practicing for more than 20 years, and more than half served as residency tutor.

Table 1. Dimensions of medication adherence in the MULTIPAP Cohort

Dimensions of adherence			Total n (%*)	Adherent n (%)	Nonadherent n (%)	*p-value†*
			1,057 (100)	727 (68.78)	330 (31.22)	
D1	**Socioeconomic factors**	**Retirement status**				0.203
		Retired	983 (93.00)	681(69.28)	302 (30.72)	
		Employed	74 (7.00)	46 (62.16)	28 (37.84)	
		Social class				0.204
		Mid-level supervisors and directors	463 (43.80)	331 (71.49)	132 (28.51)	
		Skilled primary sector	358 (33.87)	242 (67.60)	116 (32.40)	
		Unskilled	236 (22.33)	154 (65.25)	82 (34.75)	
		Education level				0.627
		Primary education incomplete	397 (37.56)	266 (67.00)	131 (33.00)	
		Primary education	398 (37.65)	278 (69.85)	120 (30.15)	
		Secondary or higher education	262 (24.79)	183 (69.85)	79 (30.15)	
		Socioeconomic level#				0.435
		≤550€/month	206 (19.49)	134 (65.05)	72 (34.95)	
		551–1050€/month	784 (74.17)	546 (69.64)	238 (30.36)	
		≥1051€/month	67 (6.34)	47 (70.15)	20 (29.85)	

		Urban vulnerability indicators				**0.014**
		<4 indicators	752 (71.14)	534 (71.01)	218 (28.99)	
		≥4 indicators	305 (28.86)	193 (63.28)	112 (36.72)	
		Structural social support				
		Household members				
		Lives alone	206 (19.49)	145 (70.39)	61 (29.61)	0.579
		Lives with 1 person	55 (6.46)	37 (67.27)	18 (32.73)	
		Lives with ≥2 people	796 (75.31)	545 (68.77)	251 (31.53)	
		Marital status				0.548
		Single	46 (4.35)	34 (73.91)	12 (26.09)	
		Married or partner	772 (73.04)	532 (68.91)	240 (31.09)	
		Separated	80 (7.57)	50 (62.50)	30 (37.50)	
		Widow	159 (15.04)	111 (69.81)	48 (30.19)	
		Functional social support				
		DUFSS				
		Total score (mean, SD)	43.33 (8.96)	43.71 (8.79)	42.50 (9.28)	**0.040**
		1st tertile (low)	369 (34.91)	239 (64.77)	130 (35.23)	0.095
		2nd tertile (medium)	385 (36.42)	269 (69.87)	116 (30.13)	
		3rd tertile (high)	303 (28.67)	219 (72.28)	84 (27.72)	
D2	**Condition-related factors**	**Number of diseases**	6 (5-7)	6 (5-7)	6 (5-7)	0.194

		(median, IQR)				
D3	**Therapy-related factors**	**Number of drugs (mean, SD)**	7.9 (2.79)	7.8 (2.71)	8.2 (2.94)	**0.042**
		Number of drugs				0.267
		5-6 drugs, n (%)	403 (38.13)	289 (39.75)	114 (34.55)	
		7-9 drugs, n (%)	408 (38.60)	277 (38.10)	131 (39.70)	
		≥10 drugs, n (%)	240 (22.71)	156 (21.46)	84 (25.45)	
D4	**Patient-related factors**	**Age in years, (mean, SD)**	69.79 (3.47)	69.86 (3.77)	69.62 (2.68)	0.304
		Sex				0.939
		Male	453 (42.86)	311 (68.65)	142 (31.35)	
		Female	604 (57.14)	416 (68.87)	188 (31.13)	
		WHODAS				
		Total score (mean, SD)	16.06 (15.95)	14.35 (14.66)	19.84 (17.92)	**0.000**
		HRQoL (mean, SD)				
		EQ-5D-5L-VAS	65.77 (19.77)	66.66 (19.68)	63.82 (19.84)	**0.030**
		Utilities	0.74 (0.22)	0.76 (0.21)	0.70 (0.23)	**0.000**
D5	**System-related factors**	**Family physician characteristics**	186			
		Sex				
		Male	43 (23.12)			
		Female	143 (76.88)			
		Age in years, (mean, SD)	46.68 (8.01)			

	Seniority in years, (mean, SD)	
	1-14	31 (16.67)
	15-19	38 (20.43)
	>20	117 (62.90)
	Residency tutor (n, %)	
	No	81 (43.55)
	Yes	105 (56.45)

D: dimension of adherence; SD: standard deviation; IQR: interquartile range.

*Percentages in the “Total” column were calculated by column using the total number of participants in each category, whereas percentages in the “Adherent” and “Non-adherent” columns were calculated by row.

†The statistically significant results observed are highlighted

#Socioeconomic level is categorized in three categories: low: ≤1050€/month, middle: 1051–2250€/month and high: ≥2251€/month).

The number of patients stratified according to the number of prescribed medications differs from the total study sample (n = 1,057), as ATC codes for prescribed medications were missing for six patients, although they had six pharmaceutical forms prescribed.

Affective and confidential support dimensions were further examined by comparing the mean scores between adherent and non-adherent participants. Adherent participants had significantly higher mean scores on the following items (Table 2): “I have people who care what happens to me” (mean difference 0.18; 95% CI 0.06,0.31), “I receive useful advice about important things in my life” (0.14; 95% CI 0.01,0.28), “I receive invitations to participate in activities and go out with other people” (0.18; 95% CI 0.01,0.36), and “I receive praise and recognition when I do my job well” (0.18; 95% CI 0.02,0.35).

Table 2. Distribution of the DUFSS questionnaire items according to adherence

	Total	Adherent	Nonadherent	Difference of means	*p-value*
Confidential Domain Mean (SD)					
Item 7. I have chances to talk to someone I trust about my personal and family problems	4.08 (1.20)	4.08 (1.18)	4.06 (1.24)	0.02 (-0.14,0.17)	0.812
Item 8. I have chances to talk to someone about money problems	3.97 (1.21)	4.01 (1.17)	3.90 (1.29)	0.13 (-0.03,0.28)	0.112
Item 6. I have chances to talk to someone about problems at work or at home	4.13 (1.15)	4.14 (1.15)	4.12 (1.16)	0.01 (-0.14,0.16)	0.876
Item 5. I receive love and affection	4.34 (1.03)	4.37 (1.02)	4.28 (1.06)	0.08 (-0.05,0.22)	0.221
Item 4. I have people who care what happens to me	4.41 (0.97)	4.46 (0.92)	4.28 (1.07)	0.18 (0.06,0.31)	0.005
Item 11. I receive help when I am sick in bed	4.39 (1.01)	4.40 (0.99)	4.35 (1.06)	0.05 (-0.08,0.19)	0.418
Item 10. I receive useful advice about important things in my life	4.06 (1.08)	4.11 (1.05)	3.96 (1.15)	0.14 (0.01,0.28)	0.047
Affective Domain Mean (SD)					
Item 2. I receive help in matters related to my home	3.30 (1.37)	3.36 (1.35)	3.18 (1.42)	0.17 (-0.01,0.35)	0.054
Item 1. I get visits from friends and family	3.34 (1.36)	3.36 (1.38)	3.30 (1.32)	0.06 (-0.11,0.24)	0.494
Item 9. I receive invitations to participate in activities and go out with other people	3.72 (1.34)	3.78 (1.32)	3.60 (1.37)	0.18 (0.01,0.36)	0.042
Item 3. I receive praise and recognition when I do my job well	3.59 (1.27)	3.65 (1.25)	3.46 (1.33)	0.18 (0.02,0.35)	0.031

The correlation between utilities and the WHODAS test score was -0.72, $p < 0.001$. Three multilevel mixed-effects logistic regression models were conducted—including WHODAS and utilities together and separately—and they were compared by AIC and BIC. It was found that the best model included WHODAS but not utilities with AIC 1284.74 and BIC 1388.85. This model is shown in table 3, where nonadherence was only associated with higher score in WHODAS scale (OR 1.02; 95% CI 1.01-1.04). In Additional file 1, it is shown the model only including EQ-5D-5L without WHODAS, in which adherence was related to higher quality of life (OR 0.22; 95% CI 0.10-0.52).

Table 3. Factors associated with nonadherence among people with multimorbidity and polypharmacy			
		OR (95% CI)	***p-value***
D1	**Retirement status**		
	Retired	ref.	
	Employed	1.42 (0.80-2.55)	0.235
	Social class		
	Unskilled	ref.	
	Mid-level supervisors and directors	0.76 (0.50-1.18)	0.222
	Skilled primary sector	0.93 (0.61-1.44)	0.729
	Education level		
	Primary education incomplete	ref.	
	Primary education	0.88 (0.61-1.28)	0.510
	Secondary or higher education	1.07 (0.69-1.65)	0.760
	Socioeconomic level		
	≤550€/month	ref.	
	551-1050€/month	0.95 (0.64-1.41)	0.801
	≥1051€/month	0.87 (0.42-1.78)	0.701
	Urban vulnerability indicators		
-	≥4 indicators	ref.	
	<4 indicators	0.77 (0.55-1.09)	0.135
	Functional support		
	1st tertile (low)	ref.	
	2nd tertile (medium)	0.97 (0.68-1.40)	0.889
	3rd tertile (high)	0.85 (0.57-1.26)	0.411
D2	**Number of diseases**	1.00 (0.93-1.08)	0.973
D3	**Number of drugs**		
	5-6	ref.	
	7-9	1.07 (0.76-1.52)	0.686

	≥10	1.11 (0.70-1.74)	0.656
D4	**Age in years**	0.97 (0.93-1.02)	0.207
	Sex		
	Woman	ref.	
	Man	1.26 (0.92-1.74)	0.153
	WHODAS	1.02 (1.01-1.04)	<0.001
	EQ-5D-5L-VAS	1.00 (0.99-1.01)	0.512
D5	**GP´s seniority**		
	1-14 years	ref.	
	15-19 years	0.70 (0.37-1.31)	0.262
	≥20 years	0.64 (0.38-1.09)	0.098
	Variance	0.70 (0.38-1.29)	

D: dimension of adherence; OR: odds ratio; CI: confidence interval; ref: reference; GP: general practitioner

Discussion

This study has analyzed the relationship between several factors on medication nonadherence in patients with MM and PP according to the framework of five dimensions proposed by the WHO (4). It was conducted across three Spanish autonomous communities with different sociodemographic and healthcare contexts, thereby enhancing the representativeness and diversity of the study population and strengthening the generalizability of the findings. Patient's disability according to the WHODAS scale was the only factor associated with nonadherence after adjusting for other adherence dimensions, like socioeconomic factors, condition (number of chronic diseases), treatment and patient related factors (quality of life, age and sex). Nonetheless, some of the differences observed in the univariate analysis between adherents and non-adherents are worth considering urban vulnerability indicators and social support (dimension 1), number of drugs (dimension 3), and disability and quality of life (dimension 4).

In this cohort of patients between 65 and 74 years with MM and PP two out of three patients were adherent to treatment according to the self-reported Morisky-Green test. This test assesses the patient's self-reported behaviour and is considered a proxy for the implementation phase in relation to medication adherence according to ABC taxonomy (1, 2, 29). The WHO estimated a similar prevalence of adherence (4), as did other studies, such as a Spanish study similar to ours, which reported 59.2% medication adherence, whereas among the younger population, adherence to long-term medication has been

reported at 55.5% (9). However, other studies had estimated higher adherence prevalence in patients with chronic diseases (7, 11), like a study in the United Arab Emirates with an adherence of 78.57% (7). These differences in adherence rates across various studies may be due to variability in the tools used to measure adherence (30, 31), differences in the prevalence and distribution of factors associated with medication adherence across study populations, as well as differences in patient's family, culture, spiritual and religious beliefs and the geographical settings in which the studies were conducted (32). In particular, our study included participants from three Spanish autonomous communities with potentially distinct cultural and health care contexts, which may have influenced medication adherence.

With regard to the *socio-economic factors in dimension 1* (retirement status, social class, educational level, socio-economic status, living arrangements or marital status), no differences were reported according to treatment adherence. Whereas differences were found regarding factors related to indicators of urban vulnerability and functional social support. Adherent patients had less urban vulnerabilities (9, 31, 33). One possible explanation could be that, when patients are facing housing instability, they tend to prioritise meeting their basic needs over their health needs, leading to greater non-adherence (31). Another possible explanation could be that indicators of urban vulnerability reflect a level of heterogeneity that other variables do not capture (10, 29). Also urban vulnerability can be interpreted as a proxy for social class, educational level, or the neighborhood in which a person lives, and it has been shown to influence the level of self-care (9). In our study, non-adherents had lower total scores for social support, as has been previously reported (9, 31, 33). Other studies revealed association with other factors of socio-economic dimension like occupation (7), food insecurity (29), ethnicity, lower socioeconomic status (6, 7), cultural context, spiritual beliefs, and family support (34). In this dimension 1, we also observed relation with functional social support, especially in some affective and confidential domains, as others studies did (9, 35). In people with chronic conditions, a lack of understanding on the part of those around them has been identified as a barrier to manage their diseases. As Lozano et al. reported, communication needs were not associated with adherence, but social needs, receiving praise and recognition at work were (9). This previous evidence suggests that these social and cultural factors can influence behaviors related to medication use and self-care. Therefore, medication adherence should be understood not only as an individual behavior but also as a phenomenon influenced by a person’s social and cultural context (34).

The *dimension 2 of adherence (condition-related factors)* was estimated based on the number of medical conditions, and although we did not observe a relationship with adherence, other authors have linked non-adherence to a higher number of medical conditions (11, 36, 37), including those with highly symptomatic diseases (38). The fact that we have not observed a correlation between the number of medications and adherence may be due to other factors that could be more relevant than the number itself, such as type, duration and severity of the disease, comorbidities, frequency of healthcare use and patient satisfaction (36). Another possible explanation for the lack of an association between the number of chronic conditions and adherence is the homogeneity of the study sample. All participants had multimorbidity and polypharmacy according to the inclusion criteria, with a median of six chronic conditions (IQR 5–7), which reduced the variability of this variable. This limited dispersion may have

reduced the study's ability to detect differences in adherence based on disease burden. Furthermore, Skou et al. stated that the number of diseases, although widely used as a measure of multimorbidity, may be insufficient to capture the clinical complexity of patients with a high disease burden; aspects such as the severity of the conditions, the burden of symptoms, the interaction between conditions, or the associated therapeutic burden may be more relevant (14).

Dimension 3 of therapy-related factors was characterised by more drugs in the group of nonadherent patients. The presence of treatment regimens that are difficult to follow, or the occurrence of drug interactions, likely increase the risk of poor adherence (39). However, other authors considered that patients with PP were more adherents, because of their perception of worse health status and quality of life (7, 11, 40). In these patients, it would be necessary to review their medication on a regular basis, as they are at risk of medication-related harm, such us side effects and drug–drug interactions (39), taking into account the simplification of treatment as a way of improving adherence to it (38).

Dimension 4 of patient-related factors showed that disability increased the risk of nonadherence, as it has been shown previously (36, 37, 41). This relationship could be explained as functional disability is associated with greater use of healthcare services, higher likelihood of receiving more intensive treatments, such as a combination of medication (41), need for help within the home (36), limitations in self-care, mobility, or dependence on others (41). These difficulties could affect treatment adherence. This reinforces the importance of activities aiming to prevent or delay the onset of functional disability, improving autonomy in managing their own healthcare and treatment (36), especially in primary care settings (42). Quality of life has been widely linked in the literature to greater adherence (9, 11, 40), due to the influence of some psycho-social characteristics related to the ability to manage chronic diseases (11). The relationship between quality of life and adherence is considered bidirectional. One reason for this is that when disease, pain, mobility, and the ability to perform daily activities are well managed, adherence improves; however, adherence can sometimes lead to side effects and, in turn, worsen quality of life (43). In this study we observed more frequency of adherence in patients with higher quality of life, but no statistically significant association was found. WHODAS 2.0 and the EQ-5D-5L show a high correlation between data reported by patients and caregivers, particularly in the domains of mobility, self-care, and activities of daily living (28, 44). This dimension 4 of patient-related factors also included sex, but there is no consensus about this effect (8, 31). The lack of an association between age and medication adherence observed in our study may be attributable to the cohort's relatively narrow age range. In contrast to previous studies that included participants with a wider age distribution, our cohort comprised only individuals aged 65–74 years, potentially limiting the ability to detect age-related differences in adherence. In general, adherence is associated with older age (7, 11, 45), as younger people may perceive less severity of disease. This association continues until the onset of some aging processes, such as cognitive impairments, which usually occurs around the 70 years of age, in which adherence starts to decline (7, 38). However, another study explained that the influence of age in adherence could be inconsistent, as we observed, because this relationship involves multifactorial behavioral, social, and clinical factors, among others (45).

Dimension 5 of healthcare team and system-related factors was assessed on the basis of GP's seniority, and we observed no association with treatment adherence. However, it is important to take this dimension into account, as it is key to proper treatment management. A positive doctor-patient relationship is related to high medication adherence (7, 11, 36, 38, 46). Other professional-related factors that influence adherence include a clear explanation of medication regimen (40, 46), regular follow-ups, the opportunity to address questions (40), and the use of motivational interviewing and educational interventions (11, 36, 38). In the literature, pharmacy is also included in this dimension: visiting the same pharmacy and having a trusting relationship with the pharmacist is an important factor (11, 38, 46), because they can reinforce patient's education by providing information such as proper use of drugs, dosing schedules, potential interactions and side effects, and healthy lifestyles (11). Policymakers also are important to medication adherence as they can address variables that include the availability and accessibility of services, community support to patients, support for patient education, or training provided to the health care team (7). The type of insurance also has an important role (33, 36), high copayments and restrictive healthcare use affects patient treatment (33).

Classifying adherence—a multidimensional phenomenon—into five sets of factors, referred to here as "dimensions," as we have done, allows for a structured view of the elements involved and, above all, highlights that patient-related factors are only one of the determining factors. This is particularly relevant in complex patients, such as those with MM and PP, in whom numerous factors are at play that interact and reinforce one another. This classification has enabled us to observe how the degree of disability plays a particularly important role in the risk of non-adherence to treatment, alongside the number of medicines and other factors that are not usually taken into account when proposing healthcare interventions, such as indicators of urban vulnerability, social support and quality of life. This reinforces the need to incorporate a systematic assessment of these factors into primary care practice. Interventions focused exclusively on treatment and comorbidities may be insufficient for this population group (38). Tailored and targeted interventions designed to improve medication adherence, which combine multiple components, could contribute to the success of adherence interventions in clinical practice (31, 40, 44) while also ensuring patient-centred care.

Strengths and limitations

This study has several limitations. First, its cross-sectional design, based on baseline data from the MULTIPAP cohort, does not allow causal relationships to be established between adherence and associated factors, although causality may be assessed in the future through the ongoing prospective follow-up within the cohort. Second, medication adherence was assessed using the Morisky-Green questionnaire, a self-reported measure with high specificity and validated with a high positive predictive value, although it may be subject to recall and social desirability bias (9). Although this instrument has been widely validated and shows high specificity, more objective methods for assessing adherence could be implemented alongside the Morisky-Green questionnaire to supplement the information obtained (30). Furthermore, some relevant factors influencing adherence, such as patients' beliefs, experiences, and behaviors, were not included and may have influenced the results (40).

The lack of a strong association between the studied factors and adherence may be explained by the simultaneous inclusion of structural determinants (employment, income, and education) and health intermediary factors (psychosocial, behavioral, biological, and healthcare system-related factors). These factors are closely interrelated and often interdependent, and mediation analysis may be required to determine the extent to which the influence of structural determinants is explained by health intermediaries (31).

Regarding social support, different definitions and measurement instruments exist. The DUFSS questionnaire is used to assess functional support, but it presents important differences in terms of the items included across domains and the reporting of results (10). It has been validated in the Spanish population (47), but variability remains in the interpretation of results, as authors may report them either qualitatively or quantitatively (10). Such variability in the measurement and interpretation of constructs such as social support may limit comparability with other studies.

However, this study also has important strengths. It includes a large multicenter sample of 1,057 patients recruited from primary care centers across different regions of Spain, enhancing the external validity and representativeness of the findings. Moreover, it focuses on a clinically relevant population with MM and PP and adopts a comprehensive approach based on the five dimensions of adherence proposed by the WHO. The availability of detailed clinical and psychosocial variables, not commonly included in routine databases, together with the use of validated instruments such as Morisky-Green, EQ-5D-5L, WHODAS 2.0, and DUFSS, and the application of robust statistical methods, strengthens the methodological quality and reliability of the results.

Conclusions

Self-reported medication adherence was relatively high among 65–74 years patients with MM and PP. Adherent and non-adherent participants differed across several WHO dimensions of medication adherence, including socioeconomic factors (urban vulnerability and social support), treatment-related factors (number of prescribed medications), and patient-related factors (disability and quality of life). However, after adjustment for potential confounders, disability—the patient-related dimension—was the only factor independently associated with non-adherence. These findings support the use of a comprehensive, patient-centred approach to assessing the risk of medication non-adherence, taking into account the multiple dimensions proposed by the WHO, including socioeconomic, healthcare system, condition-related, treatment-related, and patient-related factors.

Abbreviations

AIC→ Akaike Information Criterion

ATC→ Anatomical Therapeutic Chemical Classification

BIC→ Bayesian Information Criterion

CEICA→ Aragon Ethics Committee

DUFFSS→ Duke Functional Social Support Scale

GPs→ General Practitioners

HRQoL→ Health-Related Quality of Life

IC→ Confidence Interval

IQR→ Inerquartile Range

ISCIII→ Instituto de Salud Carlos III

IVUs→ Urban Vulnerability

MM→ Multimorbidity

OR→ Odds Ratio

PDC→ Proportion of Days Covered

PP→ Polypharmacy

RCT→ Randomized Clinical Trial

RICAPPS→ Network for Research on Chronicity, Primary Care, and Health Promotion

RICORS→Health-Outcomes-Oriented Cooperative Research Networks

SD→ Standard Deviation

VAS→ Visual Analog Scale

WHO→ World Health Organization

WHODAS→ World Health Organization Disability Assessment Schedule

Declarations

Ethics approval and consent to participate

This study respected the basic ethical principles of autonomy, justice, beneficence, and no maleficence, and it followed the principles of Good Clinical Practice, the principles stated in the most recent Declaration of Helsinki (Seoul 2013) (48), and the Oviedo Convention (1997). MULTIPAP PLUS Study (16) was approved by the Clinical Research Ethics Committee of Aragon (CEICA) on April 10, 2019, with approval number C.P. - C.I. PI18/ 064. Once patients were selected based on the inclusion and exclusion

criteria, they were invited to participate; if they agreed, they were required to sign an informed consent form, as explained in the methodology section. The informed consent form was also approved by the CEICA.

Consent for publication

Not applicable

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Author Contribution

Conceptualisation, J.L.M., A.M.J., F.L.F.; methodology, A.M.J., F.L.F., C.L.B, and A.G.M.; formal analysis, C.L.B., investigation, J.L.M., A.M.J., F.L.F., C.L.H. and A.G.M.; resources, F.L.F., and A.G.M.; data curation, C.L.B.; writing—original draft preparation, A.M.J., and J.L.M.; writing—review and editing, A.M.J, J.L.M., F.L.F., C.L.H., S.M., F.G.R., M.A.P., LA.G.F., A.G.M., and C.L.B.; visualisation, F.L.F.; supervision, F.L.F. and A.G.M.; funding acquisition, F.L.F. and A.G.M. All authors from the MULTIPAP plus group have read and agreed to the published version of the manuscript.

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Data Availability

Regards data sharing, the Aragon Ethics Committee (CEICA, ceica@aragon.es), approved this research without considering the option of data sharing. The data contain sensitive clinical information about the patient, so there are ethical and legal restrictions to sharing the data set. The data are part of the MULTIPAP study and can be requested from the Principal Investigators of the project (Antonio Gimeno Miguel at agimenomi.iacs@aragon.es; Francisca Leiva Fernandez at francisca.leiva.sspa@juntadeandalucia.es; and Isabel del Cura at isabel.cura@salud.madrid.org). The MULTIPAP Group may establish future collaborations with other groups based on the same data. However, each new project based on these data must be previously submitted to CEICA for approval.

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