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Non-adherence to antihypertensive medication: The role of mental and physical comorbidity☆

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ABSTRACT

Background: Multiple parameters influence adherence to drug treatment, including socio-economic, healthcare, condition, therapy, and patient-related factors. However, studies of the impact of patient-related factors, particularly regarding comorbid conditions, have produced conflicting results.
Objectives: To analyse the association between mental and physical comorbidity and non-adherence to antihypertensive medication in patients attending primary care, after including a comprehensive range of chronic comorbidities and potential confounders.
Methods: Cross-sectional study of 113,397 adults with a diagnosis of hypertension in 2010 assigned to the public health service of a region in northeastern Spain. Pharmacy billing records were linked to data from electronic health records at individual level. Non-adherence was defined as an antihypertensive medication possession ratio (MPR) <80%. Multivariable logistic regression models were used to estimate the odds ratio for non-adherence. Potential predictors included mental and physical comorbidity, age, sex, blood pressure level, nationality, rurality, polypharmacy, and number of visits to the GP and to different specialties.
Results: One fifth of the study population showed poor adherence levels. Female sex, younger age, foreign nationality, living in a rural area, low blood pressure levels, polypharmacy, and mental comorbidity were positively and significantly associated with non-adherence. Conversely, non-adherence was negatively and significantly associated with the presence of cardiovascular risk factors and higher annual rates of GP visits.
Conclusion: The majority of patient-related determinants identified here (e.g., the presence of mental comorbidity, polypharmacy, foreign nationality) underscores the need for a patient- rather than a disease-centred care approach, as well as adequate physician-patient communication.

1. Introduction

Adherence to medication has been defined as the extent to which patients follow the instructions that accompany prescribed treatments [1]. Clinical trials seeking to assess the efficacy of medications are typically conducted using volunteer patients who are closely followed to assure high adherence. However, in real life patients have complex healthcare needs arising from multiple and interrelated health and social problems, all of which can directly and indirectly interfere with health priorities, self-care habits, and ultimately daily drug-taking [2].

Hypertension is one of the most commonly treated cardiovascular risk factors and has been identified as a high-risk condition for adherence to therapy [3]. Despite several studies supporting the protective effect of antihypertensives on cardiovascular morbi-mortality [4,5], many patients fail to adhere to the prescribed treatment, mainly due to the asymptomatic and lifelong nature of hypertension [3]. Furthermore, poor adherence to antihypertensive medication has been shown to result in poorer rates of blood pressure control [6], as well as increases in healthcare utilization and overall health expenditure [7].

Although hypertension rarely occurs in isolation, the influence of comorbidity (particularly physical comorbidity) on adherence to antihypertensive medication is unclear. A Swedish primary care study

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found that cardiovascular comorbidity was not associated with adherence, except in diabetic patients, who showed higher adherence rates [8]. Similar studies carried out in Germany [9] and the US [10] also failed to uncover any association. While cardiovascular complications such as coronary heart disease, congestive heart failure, and arrhythmias have been linked to higher levels of adherence [11–13], Wong and coworkers recently demonstrated a positive association between multimorbidity and poor adherence to cardiovascular medications [14]. This variability across studies is most likely attributable to differences in study populations and adherence measurement techniques, the inclusion of other predictors of adherence, and, most importantly, the number and nature of comorbidities studied. In fact, none of the aforementioned studies included more than 10 comorbidities, and most only analysed cardiovascular risk factors and diseases, thus underestimating the burden and scope of multimorbidity [15]. Moreover, other important predictors of adherence to chronic medication such as polypharmacy, health service utilization, nationality, and rurality have rarely been analysed simultaneously to account for potential confounding effects.

The aim of this study was to analyse the association between mental and physical comorbidity and non-adherence to antihypertensive medication in patients in a primary care setting in a region in northeastern Spain. Routine pharmacy billing records were linked with clinical and demographic data from electronic health records to ensure the inclusion of a comprehensive range of chronic comorbidities and potential confounders.

2. Methods

This cross-sectional study included all adult patients (18 years and over) assigned to the Aragon Health Service (a regional health service which is part of the Spanish National Health System) with a diagnosis of hypertension in 2010. The study was approved by the Clinical Research Ethics Committee of Aragon (CEICA). With a population of around 1.3 million inhabitants, the region of Aragon is located in north-eastern Spain, and its regional health service is part of the Spanish National Health System. All patients and health problems are initially attended by primary care GPs, who act as gatekeepers to specialised care. As for the provision of medicines, pharmaceuticals prescribed to people aged under 65 entail a co-payment of 40% (or lower for chronic medication) of the retail price, and medications are otherwise free of charge at the point of delivery.

Demographic information (age, sex, nationality, and rurality) was extracted from patients' health insurance cards, and diagnosis and blood pressure data from primary care electronic health records. Diagnoses, originally coded according to the International Classification of Primary Care, Version 1 (ICPC-1), were grouped in accordance with the internationally validated Expanded Diagnostic Clusters (EDC) of the ACG® system, based on the clinical and diagnostic similarity of diseases. A total of 114 chronic EDCs were considered for this study; those considered chronic as previously described by Salisbury et al. [16].

Data on the prescribed and dispensed medications were obtained from the pharmacy billing records, in which active ingredients are coded according to the Anatomical Therapeutic Chemical Classification (ATC) system. For this study, the 4 first-class antihypertensive groups of drugs were considered [5]; thiazide diuretics (*TD*; C03A); beta blockers (*BB*; C07A, C07B, C07C, C07D, C07F); calcium channel blockers (*CCB*; C08C, C08D); and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (*ACEI*/*ARB*; C09A, C09B, C09C, C09D, C09X).

2.1. Data analysis

2.1.1. Outcome variable

Adherence to antihypertensive medication was measured using the medication possession ratio (MPR) [17], i.e., the ratio of the number of days that the medication would last if taken as prescribed (assuming the defined daily dose (DDD) established by the WHO and excluding the last refill) to the number of days between the first and last prescription during the observation period. If a new prescription for the same drug, or a drug belonging to the same medication class, was dispensed before a previous prescription was due to expire, the new prescription was assumed to start the day after the previous prescription ended, and the days' supply was added to the end of the previous refill. The days of hospital stay between the first and last prescription were excluded from the denominator. MPR values of over 100% were truncated to the maximum possible ratio of adherence.

MPR was first calculated for each antihypertensive medication class (*TD*, *BB*, *CCB*, *ACEI*/*ARB*). A summary MPR was also calculated for each patient, weighting the MPR for each antihypertensive medication class by the time period over which the drug had been prescribed. Medication non-adherence was defined as an MPR < 80%, in accordance with the threshold used in previous studies [17].

2.1.2. Explanatory variables

Chronic comorbidity was the main explanatory variable, classified as mental or physical disorders as shown in Annex 1. The following covariates were also studied: sex, age (18–44; 45–64; ≥65 years); average blood pressure in 2010 (<140/90; ≥140/90 mm Hg); patients' nationality (Spanish/non-Spanish); urban/rural setting; polypharmacy (≥5 different drug groups); number of visits to the GP (0–7; ≥8); and number of different specialties visited during the study year (0–1; ≥2). Mean blood pressure was calculated based on at least two measurements taken in primary care and classified as below or above 140/90 mm Hg, according to the highest systolic or diastolic blood pressure value. The definition of polypharmacy was based on the 2nd level of the ATC classification excluding categories V (Various) and Y (Effects and Accessories).

2.1.3. Statistical analyses

The distribution of the MPR (<25%, 25–49%, 50–79%, ≥80%) according to demographic characteristics, type of comorbidity, and healthcare system factors was analysed using Pearson's chi-squared test. The association between type of comorbidity and non-adherence (MPR <80%) was analysed by means of multivariable logistic regression models, adjusting for the aforementioned covariates. In subsequent analyses (results not shown), physical comorbidities were individually included in the models in order to identify those that were significantly related to the outcome. On the assumption that data from patients who attended the same GP would be in some way correlated [18], robust standard errors were calculated by considering the clustering effect of the GP. Odds ratios and 95% confidence intervals were calculated and statistical significance was set at $p < 0.05$.

The distribution of the MPR was graphically represented depending on the presence or absence of mental and physical comorbidity. Proportions were adjusted for all explanatory variables.

Statistical analyses were performed using STATA/IC 12.

3. Results

Of the 201,880 patients assigned to the public health service with a diagnosis of hypertension in 2010, 113,397 were included in the study (Fig. 1). Patients excluded from the study were younger, healthier, and had a slightly higher probability of being non-Spanish nationals.

Of those included in the final sample, the mean age was 70.5 years (SD 11.6), over half were women (55.7%), 1.4% were non-Spanish nationals, and 44.5% lived in rural areas. The average number of chronic conditions was 3.2 (SD 2.1) and the mean number of therapeutic groups was 8.9 (SD 4.3). Patients visited their GP an average of 12.6 (SD 10.2) times during the study year and were seen by a mean of 1.9 (SD 2.0) different specialties.

Four fifths of the study population (79.8%) showed a good adherence to medication (MPR > 80%) (Table 1). However, this percentage was

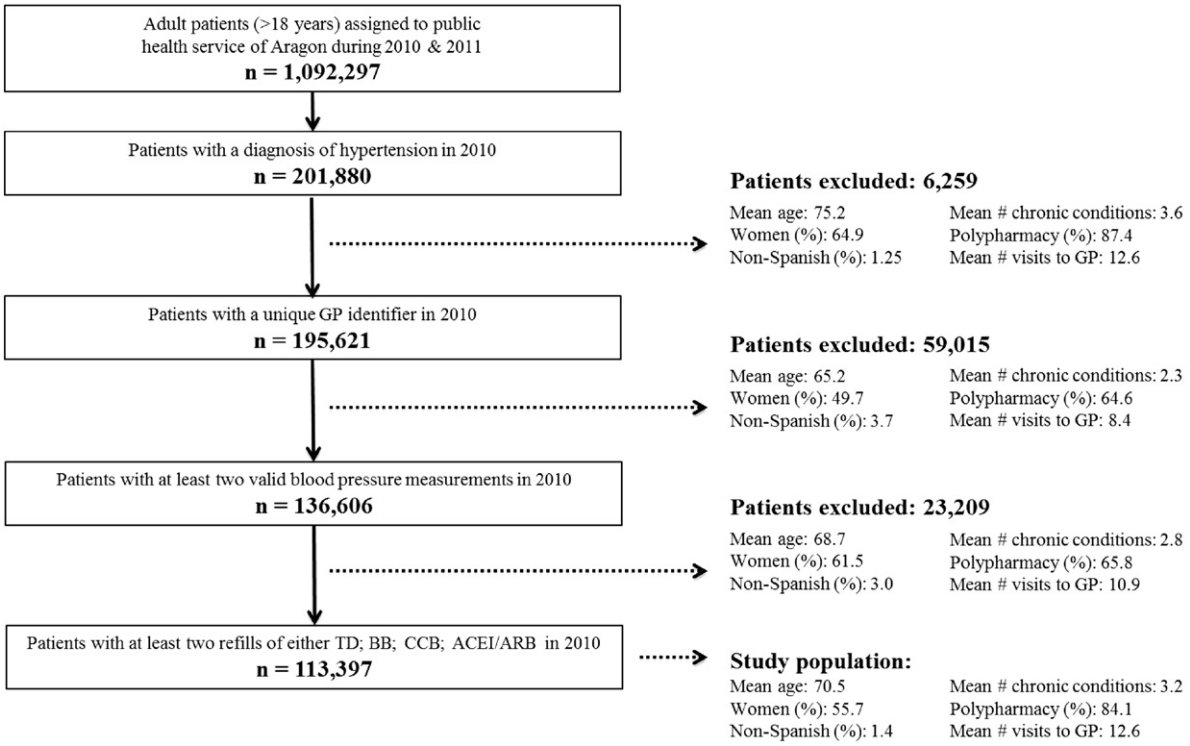

Fig. 1. Flow-chart for study population.

Table 1
Distribution of antihypertensive medication possession ratio (MPR) according to demographic characteristics, type of comorbidity, and healthcare system factors.

	Population, n (column %)	Non-adherence, n (row %)			Adherence, n (%)	p-Value
		MPR <25%	MPR 25–49%	MPR 50–79%	MPR ≥ 80%	
	113,397	1607 (1.4)	6237 (5.5)	15,108 (13.3)	90,445 (79.8)	–
Sex						
Male	50,242 (44.3)	625 (1.2)[a]	2583 (5.1)[a]	6365 (12.7)[a]	40,669 (81.0)[a]	<0.001
Female	63,155 (55.7)	982 (1.4)[a]	3654 (5.5)[a]	8743 (13.3)[a]	49,776 (79.8)[a]	
Age group (years)						
18–44	2569 (2.3)	60 (2.3)[a]	199 (7.8)[a]	412 (16.0)[a]	1898 (73.9)[a]	<0.001
45–64	29,826 (26.3)	385 (1.3)[a]	1695 (5.7)	3898 (13.1)	23,848 (80.0)	
>64	81,002 (71.4)	1162 (1.4)	4343 (5.4)[a]	10,798 (13.3)	64,699 (79.9)	
Nationality						
Spanish	111,788 (98.6)	1568 (1.4)[a]	6109 (5.5)[a]	14,797 (13.2)[a]	89,314 (79.9)[a]	<0.001
Non-Spanish	1609 (1.4)	39 (2.4)[a]	128 (8.0)[a]	311 (19.3)[a]	1131 (70.3)[a]	
Rurality						
Urban	62,886 (55.5)	904 (1.4)	3243 (5.2)[a]	8226 (13.1)[a]	50,513 (80.3)[a]	<0.001
Rural	50,478 (44.5)	703 (1.4)	2990 (5.9)[a]	6877 (13.6)[a]	39,908 (79.1)[a]	
Blood pressure level (mm Hg)						
<140/90	63,040 (55.6)	1030 (1.6)[a]	4041 (6.4)[a]	9091 (14.4)[a]	48,878 (77.5)[a]	<0.001
≥140/90	50,357 (44.4)	577 (1.2)[a]	2196 (4.4)[a]	6017 (12.0)[a]	41,567 (82.5)[a]	
Mental comorbidity						
No	93,048 (82.1)	1264 (1.4)[a]	5046 (5.4)[a]	12,255 (13.2)[a]	74,483 (80.1)[a]	<0.001
Yes	20,349 (17.9)	343 (1.7)[a]	1191 (5.9)[a]	2853 (14.0)[a]	15,962 (78.4)[a]	
Physical comorbidity						
No	9484 (8.4)	146 (1.5)	638 (6.7)[a]	1300 (13.7)	7400 (78.0)[a]	<0.001
Yes	10,3913 (91.6)	1461 (1.4)	5599 (5.4)[a]	13,808 (13.3)	83,045 (79.9)[a]	
Polypharmacy						
No	18,039 (15.9)	238 (1.3)	1018 (5.6)	2186 (12.1)[a]	14,597 (80.9)[a]	<0.001
Yes	95,358 (84.1)	1369 (1.4)	5219 (5.5)	12,922 (13.6)[a]	75,848 (79.5)[a]	
Visits to GP						
0–7	41,117 (36.3)	630 (1.5)[a]	2387 (5.8)[a]	5435 (13.2)	32,665 (79.4)	<0.001
≥8	72,280 (63.7)	977 (1.4)[a]	3850 (5.3)[a]	9673 (13.4)	57,780 (79.9)	
Different specialties visited						
0–1	76,777 (67.7)	1067 (1.4)	4253 (5.5)	10,118 (13.2)	61,339 (79.9)	0.103
≥2	36,620 (32.3)	540 (1.5)	1984 (5.4)	4990 (13.6)	29,106 (79.5)	

[a] Categories with adjusted residuals <−2 or >2.

significantly lower among those under 45 years (73.9%), non-Spanish nationals (70.3%), and those with lower average blood pressure levels (77.5%). Less than 7% of patients had an MPR < 50%.

According to the multivariable logistic regression analysis (Table 2, Model I), female sex, younger age, foreign nationality, living in a rural area, low blood pressure levels, mental comorbidity, polypharmacy, and a higher number of visits to different specialties were all positively and significantly associated with non-adherence to antihypertensive medication. Conversely, a significant negative association was observed between non-adherence, the presence of physical comorbidity, and higher annual rates of GP visits. Further analyses of individual physical comorbidities revealed that the protective effect of the "physical comorbidity" variable was almost entirely attributable to cardiovascular risk factors (i.e., diabetes, dyslipidaemia, and obesity) (results not shown). Accordingly, we ran a second analysis in which cardiovascular risk factors were studied separately (Table 2, Model II). When cardiovascular risk factors were excluded, physical comorbidity became a risk factor for non-adherence (albeit with a very small effect size), and the association with the number of visits to different specialties was no longer significant. The latter finding is also substantiated in Fig. 2.

4. Discussion

Our analyses revealed non-adherence to antihypertensive medication in one in every five patients, a phenomenon that was positively associated with mental comorbidity, and negatively associated with cardiovascular risk factors, after adjusting for potential confounders such as polypharmacy, health service utilization, nationality, and rurality. The rate of non-adherence observed in our study population falls within the 9–37% range described in a previous systematic review [19].

Two main aspects of our approach strengthen the validity of our findings. First, by focusing on primary care patients, we ensured minimal selection bias for patients with hypertension, allowing us to study adherence in real-life conditions, outside of the context of randomized trials. Second, the method chosen to measure adherence (i.e., the use of routine pharmacy refills) most effectively blinds both patients and providers to the measurement of adherence, leading to more objective results [17]. Other techniques such as self-reporting, electronic monitoring devices, and/or pill-counts have proven less accurate and reliable for the measurement of adherence, making it harder to detect true differences.

The most important limitation of this study pertains to its cross-sectional design; this prevented distinguishing between incident and prevalent cases of hypertension, and treatment duration has been shown to significantly influence non-adherence [20]. We were also unable to differentiate between the three main components of patient adherence, i.e., initiation, implementation, and discontinuation, each of which is likely to be affected by different factors [21]. By using the DDD to calculate the MPR, we assume that all patients are taking the standard dose of antihypertensives. However, this may not apply in all situations, e.g., patients prescribed beta blockers for ischemic heart disease, cardiac arrhythmia, or congestive heart failure. Nonetheless, the exclusion of patients with the aforementioned cardiovascular complications (results not shown) had little effect on the overall results. While blood pressure measurement is likely to be biased towards patients with more severe forms of hypertension, this group of patients may be of special interest in studies targeting patient adherence. The classification of immigrants by nationality results in an overly heterogeneous sample. Therefore, differences across groups should be further studied to better understand and target immigrants' needs. A WHO report suggests that factors associated with non-adherence differ by disease type [3]. This may limit the external validity and transferability of our findings to other health conditions, particularly where multimorbidity is concerned.

Mental comorbidity increased the risk of non-adherence to antihypertensive medication by 8%. The mechanisms by which mental disorders can affect adherence may include poor motivation, pessimism about treatment effectiveness, diminished attention, memory, and cognition, decreased self-care, and even intentional self-harm [22]. Although significant, the effect size detected for mental comorbidity was smaller than that reported by other authors [22–24]. This may be due to differences in the diagnosis, coding, and type of mental disorders included in each study, or the inclusion in our study of several confounding variables that could account for part of the association previously described through mental health.

In agreement with previous findings, adherence to antihypertensive medication was higher in patients with higher cardiovascular risk [13], probably owing to increased awareness of the importance of treatment on the part of both the patient and their GP, as well increased motivation to follow the treatment course. After accounting for the independent effect of cardiovascular risk factors, the presence of physical comorbidities had a small but significant negative effect on adherence to antihypertensive medication. While our findings are consistent with those published recently by Wong and coworkers [14], other authors have reported positive associations between multiple comorbid conditions and antihypertensive medication adherence [25]. Thus, further investigation based on longitudinal data will be necessary to elucidate the nature of the relationship between multimorbidity and poor adherence, as well as the underlying mechanisms.

There is broad consensus on the positive association between increased age and higher levels of compliance [26–28]. Potential

Table 2
Risk of non-adherence (MPR <80%) to antihypertensive medication. Adjusted odds ratios (OR) resulting from multivariable logistic regression models. Confidence intervals (CI) adjusted for clustering effect of GP.

	Model I[a]			Model II[b]		
N = 113,397	OR	95% CI		OR	95% CI	
Sex						
Male	1			1		
Female	1.13	1.09	1.16	1.12	1.09	1.16
Age group (years)						
18–44	1			1		
45–64	0.75	0.68	0.82	0.75	0.68	0.82
>64	0.75	0.68	0.83	0.74	0.67	0.81
Nationality						
Spanish	1			1		
Non-Spanish	1.64	1.46	1.84	1.64	1.46	1.84
Rurality						
Urban	1			1		
Rural	1.11	1.05	1.17	1.11	1.05	1.17
Blood pressure level (mm Hg)						
<140/90	1			1		
≥140/90	0.73	0.71	0.76	0.74	0.71	0.76
Mental comorbidity						
No	1			1		
Yes	1.08	1.04	1.12	1.08	1.04	1.12
Physical comorbidity						
No	1			1		
Yes	0.88	0.83	0.93	1.05	1.00	1.10
Cardiovascular risk factors						
No	–	–	–	1		
Yes	–	–	–	0.81	0.78	0.84
Polypharmacy						
No	1			1		
Yes	1.12	1.07	1.17	1.12	1.07	1.18
Visits to GP						
0–7	1			1		
≥8	0.93	0.89	0.97	0.93	0.89	0.97
Different specialties visited						
0–1	1			1		
≥2	1.04	1.00	1.07	1.03	0.99	1.07
	Wald chi2(11) < 0.001			Wald chi2(12) < 0.001		
	# clusters in GP: 993			# clusters in GP: 993		

[a] In Model I, cardiovascular risk factors (i.e. diabetes, dyslipidemia and obesity) are included as part of the variable "Physical comorbidity".
[b] In Model II, cardiovascular risk factors (i.e. diabetes, dyslipidemia and obesity) are classified as a separate variable "Cardiovascular risk factors".

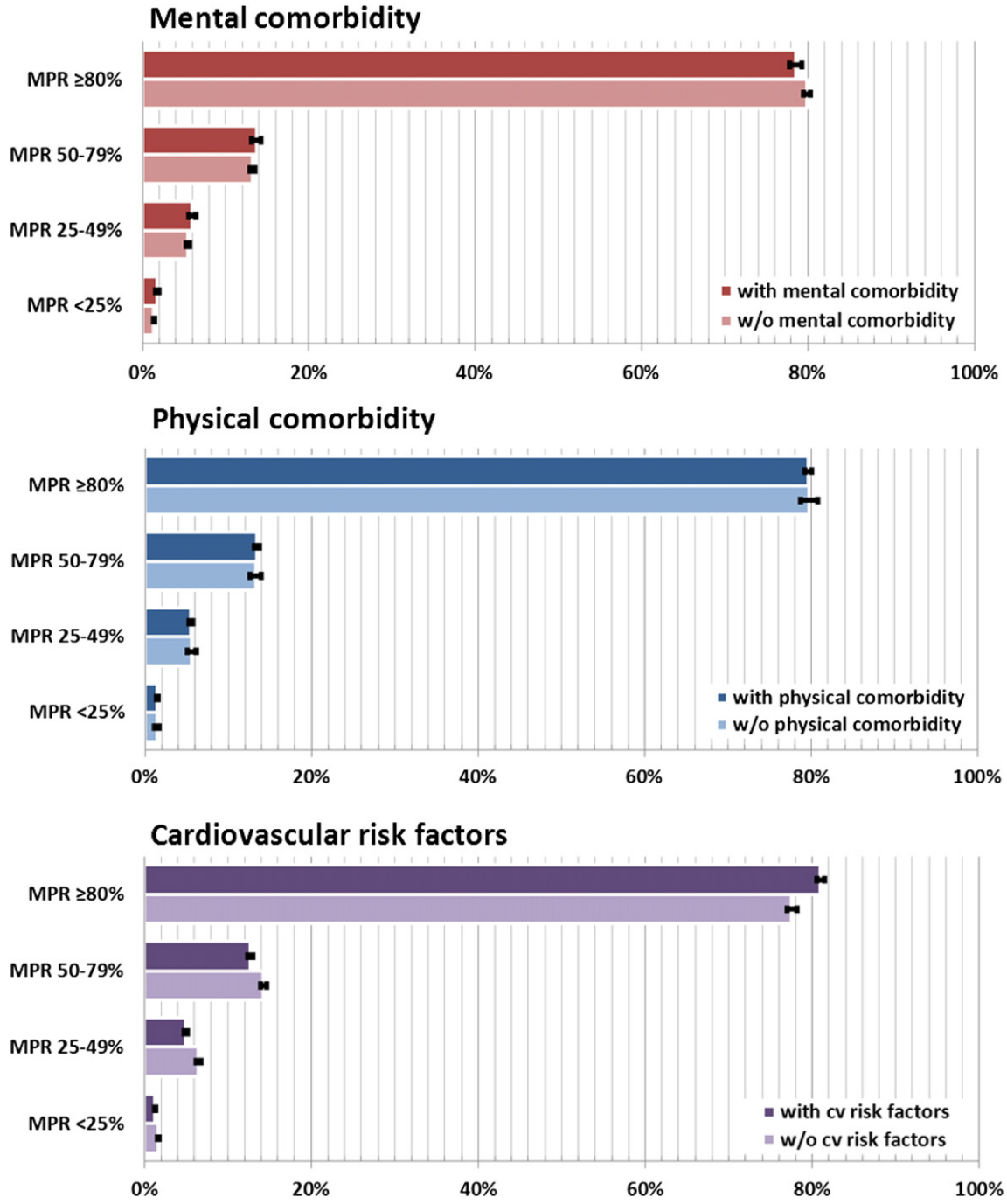

Fig. 2. Distribution of antihypertensive medication possession ratio (MPR) according to mental and physical comorbidity. Proportions adjusted for all covariates and for the clustering effect of GP.

mechanisms linking adherence and age include greater motivation on the part of patients with more severe illnesses, assistance with drug use provided by informal caregivers, survival bias, and the fact that in younger patients blood pressure can be reduced by non-pharmacological means such as weight loss or exercise [29]. While we observed lower adherence in women, the literature contains conflicting data on the influence of sex [20,27].

The prescription of complex regimens including multiple drugs has been widely acknowledged as a barrier to patient adherence [20]. While this view is supported by the present findings, Mazzaglia and co-workers reported an inverse association for antihypertensive medication [13], although that study did not include adjustment for patient morbidity burden.

Immigrants showed greater vulnerability to non-adherence, regardless of geographic region of origin (Asia, Africa, Eastern Europe, Latin America, and Western Europe/North America; results not shown), in line with previous reports [8,18,30]. Potential explanations for this phenomenon include lower socio-economic status, health beliefs, and poor verbal communication between physician and patient. Previous studies have described decreased adherence to antihypertensives due to a lack of understanding of the objective and potential benefits of treatment, especially in cases of treatments that cause side effects [31].

Because the majority of studies of adherence have been conducted in urban settings little is known about the impact of rurality. We found that the risk of non-adherence to antihypertensives was increased by 11% in patients living in rural areas, in agreement with Lee et al. [25],

but contrary to the findings of Friedman and coworkers [32]. Further research is required to consider all potential confounders associated with geographical location.

While higher rates of GP visits have consistently been linked to better adherence in patients with cardiovascular conditions [27], a higher number of prescribing physicians, measured in our study as the number of different specialties involved in the patient's care process, has been negatively associated with medication adherence [33]. Both of our findings emphasize the key role of GPs, via their long-lasting relationships with patients and their responsibility for continuity and coordination of care, in successful pharmacotherapy [34].

4.1. Implications for practice

For drugs with a positive benefit–risk ratio, such as antihypertensives, improved adherence could enhance patient outcomes, mainly by achieving intermediate targets such as lower blood pressure levels, but also through the overall "healthy adherer" effect [35]. Nonetheless, recent studies have suggested that older adults taking antihypertensives are at increased risk of fall injuries such as hip fracture [36]. Moreover, the secondary cardiovascular prevention benefit of antihypertensives in older adults has been questioned [37].

There is no evidence that low adherence can be "cured" [38]. However, in a context in which physicians attempt to deliver patient-centred care by means of shared decision-making and adequate communication, patients should adhere to the medications that they have already decided they are happy to take. Communication between professionals and patients, particularly regarding medication experiences, is especially important in cases of complex patients with multiple chronic conditions [39]. These individuals often suffer from the cumulative burden of treatments, and patient-centred prioritization of available therapies is a key issue when seeking a minimally disruptive medicine approach [40]. Unfortunately, health services have largely shied away from adequately investigating and addressing these issues [41].

5. Conclusions

Our analysis of adults in primary care reveals a rate of non-adherence to antihypertensive medication of 20%. Moreover, most of the patient-related determinants identified (the presence of mental comorbidity, polypharmacy, foreign nationality) underscore the need for patient rather than disease-centred care and adequate physician–patient communication.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2016.01.069.

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Ethical approval

The study was approved by the Clinical Research Ethics Committee of Aragon (CEICA).

Competing interests

None.

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