



# BMJ Open Evaluation of adherence to pharmacological treatments by undocumented migrants with chronic diseases: a 10-year retrospective cohort study

Gianfrancesco Fiorini <sup>1,2</sup>, Giacomo Pellegrini <sup>3</sup>, Matteo Franchi,<sup>3</sup> Antonello Emilio Rigamonti,<sup>2</sup> Nicoletta Marazzi,<sup>4</sup> Alessandro Sartorio,<sup>4</sup> Giovanni Corrao <sup>3</sup>, Silvano Gabriele Cella<sup>2</sup>

**To cite:** Fiorini G, Pellegrini G, Franchi M, *et al.* Evaluation of adherence to pharmacological treatments by undocumented migrants with chronic diseases: a 10-year retrospective cohort study. *BMJ Open* 2024;**14**:e078431. doi:10.1136/bmjopen-2023-078431

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<https://doi.org/10.1136/bmjopen-2023-078431>).

Received 01 August 2023  
Accepted 19 April 2024



© Author(s) (or their employer(s)) 2024. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

<sup>1</sup>Istituti Clinici Zucchi Spa, Monza, Italy

<sup>2</sup>Università degli Studi di Milano, Milano, Italy

<sup>3</sup>Università degli Studi di Milano-Bicocca, Milano, Italy

<sup>4</sup>Istituto Auxologico Italiano Istituto di Ricovero e Cura a Carattere Scientifico, Milano, Italy

## Correspondence to

Dr Gianfrancesco Fiorini;  
gfr.fiorini@gmail.com

## ABSTRACT

**Objectives** To investigate the time course of medication adherence and some of the factors involved in this process in undocumented migrants with chronic diseases.

**Design** Retrospective cohort study.

**Setting** A big non-governmental organisation in Milano, Italy, giving medical assistance to undocumented migrants.

**Participants** 1918 patients, 998 females and 920 males, with at least one chronic condition (diabetes, cardiovascular diseases (CVDs), mental health disorders) seen over a period of 10 years (2011–2020). Their mean age was 49.2±13 years.

**Results** Adherence to medications decreased over 1 year in all patients. This was more evident during the first 2 months of treatment. Patients on only one medication were less adherent than those on more than one medication; at 6 months the percentage of patients with high adherence was 33% vs 57% ( $p<0.0001$ ) for diabetes, 15% vs 46% ( $p<0.0001$ ) for mental disorders and 35% vs 59% ( $p<0.0001$ ) for CVDs. Patients with mental disorders had the lowest adherence: 25% at 6 months and 3% at 1 year. Mental disorders, when present as comorbidities, greatly reduced the probability of being highly adherent: risk ratio (RR) 0.72 (95% CI 0.57 to 0.91;  $p=0.006$ ) at 3 months, RR 0.77, (95% CI 0.59 to 1.01;  $p=0.06$ ) at 6 months, RR 0.35 (95% CI 0.13 to 0.94;  $p=0.04$ ) at 1 year. This was especially evident for patients with CVDs, whose percentage of high adherents decreased to 30% ( $p=0.0008$ ) at 6 months and to 3% ( $p=0.01$ ) at 1 year. We also noted that highly adherent patients usually were those most frequently seen by a doctor.

**Conclusions** Interventions to increase medication adherence of undocumented migrants with chronic diseases are necessary, particularly in the first 2 months after beginning treatment. These should be aimed at people-centred care and include more outpatient consultations. Educational interventions should especially be taken into consideration for patients on monotherapy.

## INTRODUCTION

Medication adherence (MA) has been defined by the WHO as ‘the extent to which a person’s behaviour—taking medication, following a diet and/or executing lifestyle

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study describes for the first time the pattern of adherence to medications of undocumented migrants with chronic diseases.
- ⇒ To our knowledge, it is the first study in which adherence is measured at monthly intervals.
- ⇒ One major limitation is the fact that we do not know if patients get medications also from other providers.
- ⇒ It is impossible to be sure that patients actually take their medications. This is another important limitation in adherence studies.
- ⇒ We have no follow-up data.

changes, corresponds with agreed recommendations from a healthcare provider’.<sup>1</sup> MA is a behaviour resulting from the interplay of different factors which ‘include attributes of the patient, the patient’s environment (which comprises social supports, characteristics of the healthcare system, functioning of the healthcare team, and the availability and accessibility of healthcare resources) and characteristics of the disease in question and its treatment’.<sup>1</sup>

MA is a multifaceted issue and non-adherence only seldom stems from the unwillingness of a patient to take the prescribed medications. More often it is non-intentional and due to different causes.

Incomplete or non-existent MA is not without consequences. Indeed, it is associated with increased morbidity, mortality and all-cause hospitalisation.<sup>1 2</sup> This is known to occur with all the most widespread chronic diseases. As an example, being non-adherent to treatment of modifiable stroke-related conditions like type 2 diabetes, atrial fibrillation, hyperlipidaemia and hypertension

significantly increases the risk of stroke and/or associated death.<sup>3</sup>

Moreover, incomplete adherence to antihypertensive pharmacological treatment is associated with an increased risk of cardiovascular events and chronic kidney disease; indeed, a large part of resistant hypertension is the so-called pseudoresistant hypertension, due to poor or lacking MA.<sup>4,5</sup>

Low and non-adherence also have an economic impact, both in terms of increased healthcare expenditure and more frequent sick leaves.<sup>5-7</sup>

Non-adherence has large proportions. Overall, 50% of patients are known to be non-adherent to treatment.<sup>8</sup> This percentage further increases when it comes to patients with chronic conditions.<sup>9</sup> Moreover, MA is not an on/off phenomenon, but it can change during the course of treatment.<sup>4,10</sup> Many different time patterns have been described. In Italy, for example, it is usually higher at the beginning of treatment and tends to fade with time with medications for chronic obstructive pulmonary disease and those used to lower uric acid, while antihypertensives, anticoagulants, medications for osteoporosis and for prostate hypertrophy are less frequently discontinued.<sup>11</sup> MA is not the same in all countries. As an example, adherence to pharmacological treatment for hypertension is high in Canada, Germany and the USA and in general in high-income countries (HICs); it is low in low-income and middle-income countries (LMICs), thus yielding a worldwide estimate of adherence around 50%.<sup>5</sup> Age and gender have been differently associated with the degree of MA while it seems more agreed that MA is higher in people who work and do not live alone.<sup>12,13</sup> In addition to these and to the already cited income level,<sup>5,13</sup> other factors have been shown to be related to the degree of MA. Among them one of the most important appears to be health literacy,<sup>14</sup> which affects patients' knowledge of their diseases through their capacity of reading, listening, analysing, decision-making and applying the information they obtain to their health conditions.<sup>15</sup> The WHO considers health literacy fundamental for the prevention and control of non-communicable diseases.<sup>16</sup> It has also warned for long time that non-adherence grows as the burden of chronic diseases grows worldwide and the poor are disproportionately affected by both.<sup>1</sup> Therefore, non-adherence can be especially expected in LMIC and, in HIC, among those minorities who live in poor socio-economic conditions. Among the latter, undocumented migrants, who are now part of the population in all western countries, are certainly worth to be considered. An undocumented migrant is defined by the WHO as 'a person who moves or has moved across an international border and is not authorised to enter or to stay in a state pursuant to the law of that state and to international agreements to which that state is a party'.<sup>17</sup>

In the last decades, migrations have been continually growing. The WHO estimates that from 1990 to 2020, the global population increased from 5.3 billion to 7.8 billion. In the same period, the overall number of international

migrants increased from 153 million (2.9% of the world population) to 281 million (3.6% of the world population). As of 2020, the greatest number of international migrants was hosted in North America and Europe; in Europe, the top hosting countries are Germany and the UK.<sup>17</sup> The growing number of migrants entails a growing number of undocumented migrants, though their number is impossible to define exactly for obvious reasons. In Italy, at the beginning of 2020, they were estimated to be more than 600 000.<sup>18</sup> Usually, they have only limited access to social and health services of the host countries, including Italy, and their medical records are not available in the datasets used for legal residents (both natives and migrants). Information available on their health conditions is, therefore, quite scanty, though some may be obtained from the databases of non-governmental organisations (NGOs) giving them some type of assistance on a voluntary basis. Using this method, it has been shown that these persons have a significant burden of chronic diseases and use a large quantity of medications to treat them if they can access treatments for free.<sup>19,20</sup>

However, no data are available on their attitudes towards their pharmacological treatment and especially on their adherence to it. This issue seems especially relevant in consideration of the many factors potentially reducing MA in such an underprivileged population.

To measure MA in this population, we conducted a cohort retrospective study on undocumented migrants with chronic diseases receiving medical assistance from one of the biggest NGOs in Italy. We restricted our attention to three of the most common and resource-consuming chronic conditions: type 2 diabetes, cardiovascular diseases and mental disorders.

We especially focused on possible time-dependent changes in MA during the first year of treatment with the aim to detect if there are critical periods in which specific interventions could obtain better adherence. To know this can give all the persons assisting such patients a better insight into the behaviour of their patients and a basis to implement correcting strategies if necessary. Moreover, this could represent a preliminary set of information for all the stakeholders interested in further studies and interventions.

## METHODS

### Study design

A retrospective cohort study on drug adherence for the treatment of chronic diseases in undocumented migrants was conducted.

### Setting

Data were retrieved from routinely collected health databases of Opera San Francesco (OSF) clinics in Milan, Italy. Active since 1959, OSF is committed to ensuring free hospitality and assistance to the poorest, who are almost entirely composed of undocumented migrants.

OSF also guarantees medical assistance with specialist physicians who carry out visits, prescribe and dispense drugs. All information regarding medical visits and medications dispensed is collected in an electronic database. Each subject is identified by a unique individual identification code, and it is, therefore, possible to reconstruct his medical history over the years.

Data refer to the period from 2011 to December 2020.

### Cohort selection and follow-up

Three cohorts of patients with diabetes, mental health and cardiovascular disease were included in the study. Individuals were defined as suffering from a specific condition if they were dispensed with antidiabetic, psycholeptics or cardiovascular drugs, respectively. Drugs were coded through the Anatomical Therapeutic Chemical Classification System and the following codes were used: A10 for identify patients with diabetes, N05 and N06 with mental health disease and C and B01 for cardiovascular disease.

Online supplemental figure 1 provides a graphical representation of the study design and online supplemental figure 2 that of the cohort selection. For each study cohort, subjects were included in the study when they received their first dispensation of drugs between 2012 and 2019. The date of the first drug prescription was defined as the index date. Patients were excluded if they (1) were aged <18 years at index date; (2) did not received at least one drug prescription within 6 months from the index date and (3) did not have a contact with the OSF clinic (visit or prescription) in the period between 1 year and 2 years after the index date. This condition was required to exclude patients lost to follow-up (because of transfer away or dead) during the first year of observation since no information on migrations or death is available in OSF databases.

### Measurement of adherence to therapy

Adherence to therapy was measured at 6 and 12 months after the index date. For each drug prescription, the number of days covered by the prescription was calculated by dividing the total amount of the drug prescribed (available in our database) by the defined daily dose as reported by the WHO (available at [https://www.whocc.no/atc\\_ddd\\_index](https://www.whocc.no/atc_ddd_index)).

Adherence to therapy was calculated as the ratio between the total number of days covered by the class of drugs divided by the number of days of follow-up (ie, 180 or 365 days), a quantity referred to as 'proportion of days covered' (PDC).<sup>21</sup>

The PDC was categorised as low (PDC<25%), intermediate (PDC 25%–75%) and high (PDC>75%) adherence.

The PDC was also calculated monthly for 1 year after the index date for all subjects included.

### Covariates

For each cohort member, the following characteristics were evaluated at baseline: age, gender, year of therapy start, country of origin, comorbidities (previous

consultations or prescriptions in the year prior to the index date for cardiovascular disease, diabetes, cancer, mental health, genitourinary system and endocrine system diseases).

### Statistical analysis

Baseline characteristics and PDC categories were expressed as absolute and percentage frequencies. PDC values were also expressed as mean (with SD).

Differences in the frequencies of adherence levels between categories were assessed by the  $\chi^2$  test, its version for trend or the Fisher's exact test, as appropriate.

Multivariate log-binomial regression models were used to assess the association between baseline characteristics and high adherence (PDC>75%). Models were adjusted by gender, age category, geographical origin area, year of therapy start and comorbidities. Results were expressed as risk ratios (RRs) and 95% CIs. The Statistical Analysis System software (V.9.4; SAS Institute) was used for the statistical analysis. For all hypotheses tested, two-tailed p values <0.05 were considered significant.

### Patient and public involvement

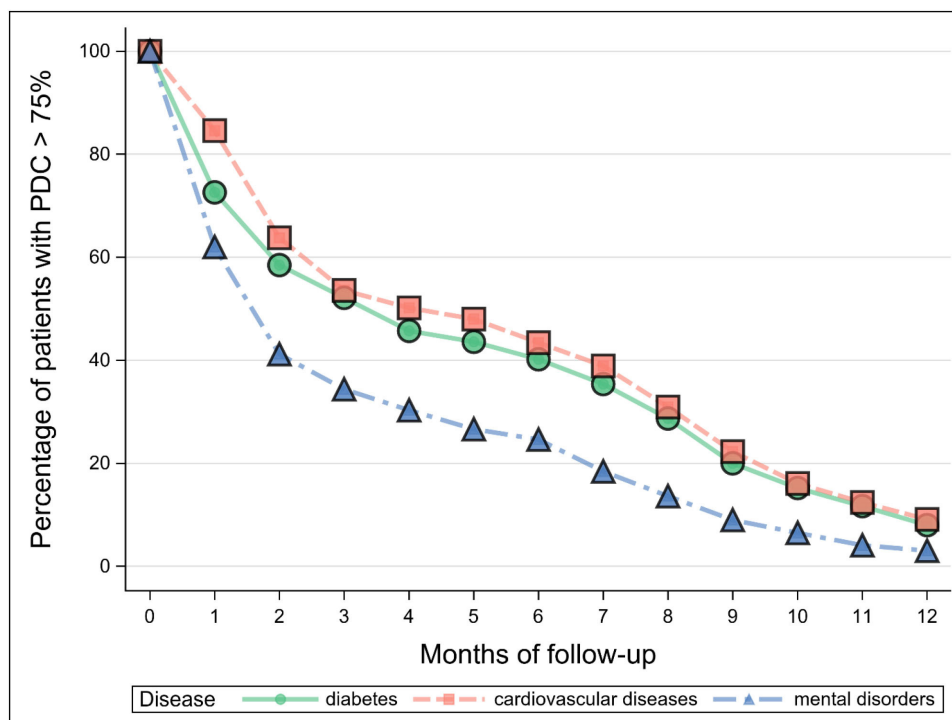
None.

## RESULTS

The main sociodemographic features of the three cohorts of patients are shown in online supplemental table 1. As can be seen, no major differences existed among the three groups for age and sex distribution. In each cohort, about the same number of patients started treatment every year during the period of observation. As for the geographical origin, Latin Americans were largely represented in all the three groups, and Europeans in the group of patients with diabetes and in that of patients with mental disorders. In the non-cardiovascular cohorts, the main comorbidities were cardiovascular diseases. In the cardiovascular cohort, mental disorders were the most frequent comorbidity. In all the three groups, the number of patients on one medication was higher than that of patients on polypharmacy.

MA, measured as PDC, was higher at 6 months after the beginning of treatment and lower at 1 year. It was lower at both time points in patients with mental disorders than in those with either diabetes or cardiovascular diseases. The presence of comorbidities caused a further reduction. This was especially true for cancer and mental disorders. MA was always higher in patients on more than one medication. These observations are summarised in online supplemental table 2.

The number of patients with high adherence (PDC>75%) diminished during time and was always lower in persons with mental disorders. Interestingly, when we analysed this trend in detail we did not find a constant reduction in the percentage of highly adherent patients. This can be observed in figure 1, which shows the monthly percentages of these patients. As can be



**Figure 1** Monthly trend of the percentage of subjects with high adherence calculated from the beginning of follow-up. PDC, proportion of days covered.

seen, in all the three cohorts, the decrease was very steep in the first 2 months, then it was smoother until the end of the observation period of 1 year. The percentage was always lower in the group with mental disorders, but at month 12, the percentages of the three groups tended to converge at very low levels. The progressive reduction in the percentage of patients with high adherence occurred for all medications (online supplemental table 3).

We then looked for possible causes of this time-dependent reduction in the proportion of subjects with high adherence. We started analysing the characteristics of the patients and the proportion of those with high adherence at 6 and 12 months (table 1). The most significant difference was seen between patients on one medication and those on multiple medications. In the cardiovascular group, adherence at 6 months increased with increasing age, but this effect was no longer evident at 12 months; ethnicity appeared to be important, with Europeans being the most adherent at both 6 and 12 months; mental disorders, when present as comorbidities, greatly reduced the number of patients with high adherence; no difference was seen between females and males. In the group with mental disorders, cancer as a comorbidity had an effect; however, the numbers were so small that this observation cannot be taken as reliable.

A further analysis was carried out in the cardiovascular group. We used a log-binomial regression model to evaluate the association between patients' characteristics and high adherence. We also included another time point of observation at 3 months, that is, at the moment of transition from steep to smooth decrease. We saw no effect of gender, while increasing age favoured adherence at 3

and 6 months, but was no longer significant at 12. Using as reference Europeans, who had been noticed as the generally most adherent, we confirmed this observation at 12 months, but at 6 months the RR resulted higher for Asians. The presence of mental comorbidities significantly reduced adherence to cardiovascular medications at 3, 6 and 12 months. Patients on multiple drug regimens were significantly more adherent than those on only one medication (table 2).

Analysing in greater detail the effect of monotherapy versus polytherapy on MA, we saw that its decrease over time was always more evident for monotherapy. The decrease in the first 2 months was particularly rapid for diabetics and patients with mental disorders on monotherapy, with more than half of them already being non-high adherent at this time (figure 2).

Finally, we analysed the number of consultations per patient during the year of observation.

Interestingly, in all the three groups, the number of times patients were seen by a doctor (either internist or specialist) was much lower for those with low adherence compared with those with intermediate and high adherence (figure 3).

## DISCUSSION

We evaluated the time course of MA in a group of patients with chronic diseases living as undocumented migrants in Italy. Undocumented migrants, though their number is continually increasing, are probably the most neglected and underprivileged part of the population in many western countries. We have already demonstrated



**Table 1** Frequencies (N, (%)) of subjects with high adherence (PDC>75%) by baseline characteristics and conditions

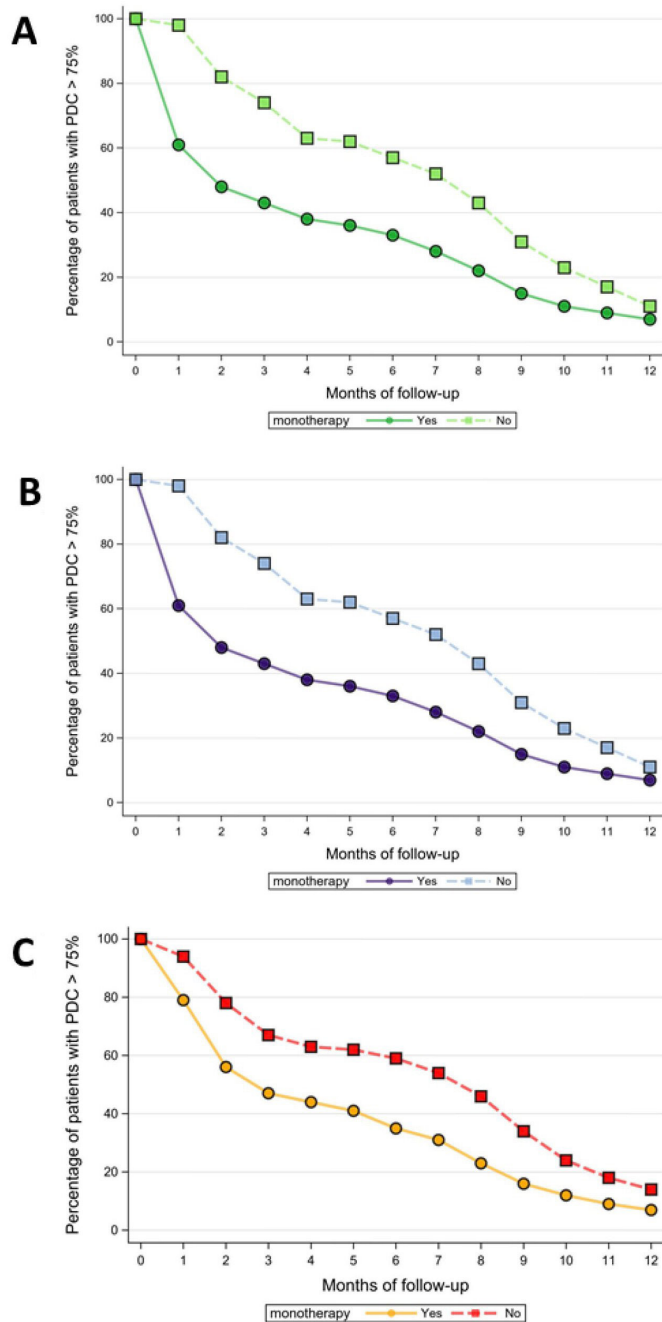
Variable	Category	Diabetes (N=376)			Mental disorders (N=631)			Cardiovascular disease (N=1189)		
		6 months	1 year	P value	6 months	1 year	P value	6 months	1 year	P value
Overall, N (%)		151 (40)	26 (7)		155 (25)	19 (3)		516 (43)	106 (9)	
Age class	18–45	42 (42)	7 (7)	0.833	82 (25)	8 (2)	0.119	105 (35)	18 (6)	0.202
	45–55	49 (39)	7 (6)		42 (26)	9 (6)		153 (41)	38 (10)	
	55–65	41 (42)	7 (7)		23 (20)	1 (1)		167 (48)	31 (9)	
	>65	19 (36)	5 (9)		8 (24)	1 (3)		91 (52)	19 (11)	
Sex	F	62 (37)	11 (7)	0.801	81 (23)	12 (3)	0.520	274 (43)	51 (8)	0.260
	M	89 (43)	15 (7)		74 (27)	7 (3)		242 (44)	55 (10)	
Geographical origin	Africa	35 (41)	7 (8)	0.661	30 (20)	3 (2)	0.712	82 (39)	13 (6)	0.006
	Latin America	53 (38)	8 (6)		55 (25)	6 (3)		172 (43)	31 (8)	
	Asia	30 (48)	3 (5)		17 (39)	1 (2)		65 (54)	5 (4)	
	Europe	33 (38)	8 (9)		53 (24)	9 (4)		197 (43)	57 (12)	
Number of drugs for therapy	1	85 (33)	<0.0001	17 (7)	65 (15)	<0.0001	9 (2)	272 (35)	<0.0001	51 (7)
	>1	66 (57)		13 (11)	90 (46)		10 (5)	244 (59)		57 (14)
Comorbidity	Cardiovascular disease	26 (33)	0.167	4 (5)	30 (20)	0.165	3 (2)	–	–	–
	Mental disorders	3 (25)	0.375	0 (0)	–	–	–	40 (30)	0.0008	4 (3)
	Cancer	1 (14)	0.250	0 (0)	1 (5)	0.032	0 (0)	7 (32)	0.269	1 (5)
	Endocrine system	15 (33)	0.320	1 (2)	19 (21)	0.377	2 (2)	35 (34)	0.053	7 (7)
	Urinary system	6 (33)	0.545	0 (0)	12 (23)	0.795	1 (2)	18 (36)	0.281	4 (8)

PDC, proportion of days covered.

**Table 2** Multivariate risk ratios (RRs), with 95% CIs, estimated from a log-binomial regression model for evaluating the association between patients' characteristics and high adherence (PDC>75%) for cardiovascular therapies

	High adherence—3 months		High adherence—6 months		High adherence—1 year	
	637 with high adherence vs remaining 552	P value	516 with high adherence vs remaining 673	P value	106 with high adherence vs remaining 1083	P value
	RR (95% CI)		RR (95% CI)		RR (95% CI)	
Age class	Ref		Ref		Ref	
18–45						
45–54	1.08 (0.93 to 1.25)	0.3332	1.17 (0.97 to 1.41)	0.0822	1.47 (0.86 to 2.52)	0.1618
55–65	1.11 (0.96 to 1.29)	0.1568	<b>1.29 (1.08 to 1.55)</b>	<b>0.0061</b>	1.19 (0.68 to 2.09)	0.5408
≥65	<b>1.18 (1.01 to 1.38)</b>	<b>0.0428</b>	<b>1.34 (1.10 to 1.64)</b>	<b>0.0035</b>	1.39 (0.75 to 2.57)	0.3023
Sex	Ref		Ref		Ref	
F						
M	0.94 (0.84 to 1.05)	0.2629	1.00 (0.88 to 1.14)	0.9705	1.35 (0.93 to 1.96)	0.1138
Geographical origin	Ref		Ref		Ref	
Europe						
Africa	0.99 (0.83 to 1.17)	0.8784	1.02 (0.84 to 1.24)	0.8306	<b>0.50 (0.28 to 0.90)</b>	<b>0.0217</b>
Latin America	1.03 (0.91 to 1.16)	0.6472	1.09 (0.94 to 1.26)	0.2553	0.67 (0.44 to 1.02)	0.0594
Asia	<b>1.18 (1.01 to 1.38)</b>	<b>0.0383</b>	<b>1.30 (1.09 to 1.54)</b>	<b>0.0031</b>	<b>0.31 (0.13 to 0.75)</b>	<b>0.0099</b>
Number of drugs for therapy	Ref		Ref		Ref	
1						
>1	<b>1.36 (1.22 to 1.51)</b>	<0.0001	<b>1.56 (1.37 to 1.77)</b>	<0.0001	<b>1.91 (1.33 to 2.75)</b>	<b>0.0005</b>
Comorbidities						
Mental disorders	<b>0.72 (0.57 to 0.91)</b>	<b>0.0056</b>	0.77 (0.59 to 1.01)	0.0615	<b>0.35 (0.13 to 0.94)</b>	<b>0.0374</b>
Cancer	0.73 (0.42 to 1.25)	0.2491	0.79 (0.43 to 1.43)	0.4328	0.62 (0.09 to 4.19)	0.6230
Endocrine system	0.88 (0.71 to 1.10)	0.6596	1.00 (0.69 to 1.45)	0.9996	1.04 (0.40 to 2.66)	0.9405
Urinary system	0.91 (0.73 to 1.13)	0.3840	0.88 (0.67 to 1.16)	0.3630	0.98 (0.47 to 2.05)	0.9552

Bold values are statistically significant.  
PDC, proportion of days covered.



**Figure 2** Monthly trend of the percentage of subjects with high adherence calculated from the beginning of follow-up, stratified for number of drugs for diabetes (A), mental disorders (B) and cardiovascular diseases (C). PDC, proportion of days covered.

that they are affected by a considerable amount of non-communicable diseases and that this burden increases with time.<sup>19 20</sup> It is, therefore, interesting to know how they comply with treatment, in the case they can receive it.

The first finding of the present study is that, as it generally happens, MA is far from satisfactory in these patients. It is known that MA depends on many factors,<sup>1 4 10 12</sup> which can also be important in the population of this study. In such a population, some factors could have a

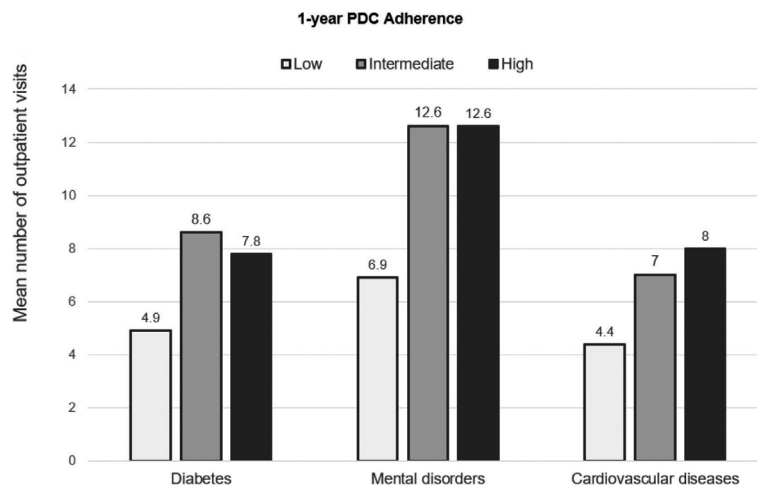
more important role. This could happen, for example, for health literacy, which is undoubtedly scanty in our patients but has been suggested to have a promoting effect on MA,<sup>13 22</sup> though this has not yet been definitely confirmed.<sup>23</sup> A low level of medical literacy could also entail a reduced awareness of one's disease and of the necessary treatment, and eventually lead these patients not to take the medications they are given for free. Other known factors having a role in MA are higher income, being working and not living alone.<sup>5 12 13</sup> All of them can be encountered less frequently by undocumented migrants, who can also have important practical barriers such as fear of detention, unstable settling and transport problems to reach the clinic.

In the population of our study, there were important differences in MA also among different chronic conditions, and patients with mental disorders were the lowest adherent. This is a well-known problem, which could in part depend also on different pharmacological agents and route of administration, with patients on long-lasting injectables being the most adherent.<sup>24</sup> We did not see the same pattern in our patients, but it should be noted that none of them was on long-lasting injectables, which are not available at OSF, and this can represent a limitation in our study. Moreover, we observed that psychiatric comorbidities reduce the adherence to treatments for other conditions as cardiovascular diseases and this is in line with previous observations.<sup>25–27</sup>

No gender differences were noticed, and also age had very little impact on MA. Because of its relevance, this latter observation should be confirmed by further studies since the consequences of reduced or absent MA are higher in patients aged 50 years or more.<sup>2</sup> This is a limitation of our study, since undocumented migrants, who are predominantly young or young adults when they arrive, can become elderly without obtaining a permanent resident visa, as demonstrated by the high contribution given by patients aged 50 or more to all the three groups of our patients.

As for geographical origin, our findings are less clear. In general, MA in undocumented migrants was comparable to that found by other in Italian patients with the same chronic conditions (online supplemental table 4), but we cannot make any direct comparison. Taking Europeans as the reference geographical group, MA was the highest at 6 months for Asians, but it fell significantly below that of Europeans for all ethnicities at 12 months. It is known that many factors affect MA, including belonging to an ethnic minority,<sup>27 28</sup> and having cultural beliefs about medications,<sup>29</sup> with even differences between migrants and refugees.<sup>30</sup> However, we favour the hypothesis that comparable personal, social and economic determinants are important in our patients independently from their ethnicity and that their interplay is responsible for similar patterns of MA. To confirm this hypothesis, however, further research is necessary.

A more interesting issue is the time course of MA in our patients over the entire period of the study. We noted



**Figure 3** Mean outpatient visits during first year of follow-up of patients grouped by chronic drug therapy and class of adherence. PDC, proportion of days covered.

an important decrease in the percentage of patients with high adherence, which was more pronounced for patients with mental disorders. The three curves (for diabetes, mental disorders and cardiovascular diseases) had a comparable shape with the sharpest decrease in the first 2 months. Few data are available in literature on the time course of MA, possibly as a consequence of the different methods and periods used in its measurement.<sup>31</sup> MA has been shown to drop in the first weeks following discharge after a cardiac event,<sup>32</sup> though doctors in charge of patients with cardiovascular diseases do not seem to be aware of this behaviour.<sup>33</sup> It also decreases at the beginning of therapy for chronic obstructive pulmonary disease,<sup>11</sup> and in the first period of topical treatment for psoriasis.<sup>34</sup> For adjuvant oral endocrine therapy in patients with breast cancer, it has been suggested that the risk not to be adherent is greater during the first of the five recommended years.<sup>35</sup>

Certainly, in our population of undocumented migrants with chronic diseases, MA drops in the first 2 months of treatment. This seems an important observation also in consideration of the fact that the degree of adherence during the early phase of a treatment is important to predict its degree in subsequent phases.<sup>36</sup>

When we analysed the time course of MA dividing patients into those on monotherapy and those on two or more medications, the curves had shapes similar to the preceding. No major difference was noticed among the three cohorts, but, interestingly, in all of them, the percentage of highly adherent patients remained always higher if they were on polytherapy. In the literature, findings on the association between degree of MA and number of medications are not always in agreement. On one hand, it has been observed that patients with chronic conditions are more adherent if they need to take less pills per day.<sup>37</sup> On the other, it has also been reported that in some chronic patients, MA is better with more than one medication. This has been observed for example in a large population of diabetics in whom MA was better

with three or more medications than with one only.<sup>38</sup> In patients receiving prophylactic migraine treatment, no difference in MA was seen between patients receiving monotherapy and those on up to four medications.<sup>39</sup> Others have found that MA in chronic diseases can be best described by an inverted U-shaped curve, with adherence being worse either with fewer or with more than nine medications.<sup>40</sup> We still have no explanation for the behaviour of our patients. We can make the hypothesis that being on a greater number of medications implies worse health conditions and this entails an increased awareness of one's diseases and increases MA. At least, what we can say is that they can be put on multiple-drug regimens without hampering MA. The information needed from further studies is how many drugs at maximum can these regimens include.

Finally, we evaluated the possible role of follow-up in determining the level of MA. We used the only available data in OSF datasets, that is, the number of consultations per year, and we found that a low adherence was correlated with a lower number of consultations. The interpretation must be cautious since it is possible that patients performing well even with a low MA felt a lesser need to see a healthcare professional. This issue should be dealt with by ad hoc studies since ours, because of its design, has the limitation of giving no detailed answer. However, consultations and visits are an essential part of people-centred care (PCC), which is now starting to be recognised as a factor necessary to improve MA.<sup>41</sup> Even interventions of non-medical professionals can improve MA in very underserved areas.<sup>42</sup> Moreover, since both modifiable and non-modifiable factors (such as economic factors and lack of family support) are equally important for MA in chronic diseases,<sup>14</sup> acting on modifiable factors appears to be extremely important especially in patients with limited health literacy.

On the basis of our observations, better PCC is needed to obtain better MA for patients belonging to the poorest segments of western countries populations



as undocumented migrants. Since we can assume that they appreciate easily accessible consultations and free dispensations of appropriate treatments,<sup>43</sup> in the absence of involvement by health authorities, it is advisable that voluntary healthcare providers involved in the cure of these patients make every effort to implement better PCC. These can include, for example, family assistance when a family is present,<sup>44</sup> and bundle format interventions including patient education and follow-up phone calls which are known to be effective also for patients with mental disorders.<sup>45</sup>

Telemedicine interventions could also be considered for some groups of patients.<sup>46 47</sup>

Beside this, we should always consider that undocumented migrants experience policy and health system-related barriers to healthcare which are only due to their legal status. These include legal impossibility to get a coverage, need of documents to get assistance, external resource constraints, discrimination and bureaucracy.<sup>48</sup> It is evident that these issues cannot be dealt with only by volunteers of NGOs, but, if we aim to realise universal health coverage for everybody, it is now becoming clear that national policies are necessary to ensure that at least essential health needs are taken care of, independent of migrant status.<sup>49</sup>

## Conclusions

Our study demonstrates for the first time that in undocumented migrants with chronic conditions, MA decreases with a non-linear trend, which is especially sharp in the first 2 months of treatment.

Beside the many known factors that usually reduce adherence, in such a peculiar population other could also be important, such as practical barriers due to many causes, lack of confidence, language difficulties, etc.

Adherence is lower in patients on a single medication, compared with those on two or more. This can be due to low health literacy; therefore, educational interventions appear to be important in our patients since it is possible that those on only one medication have a lower awareness of the importance of their health problem.

However, in consideration of the many factors affecting MA in undocumented migrants, multifaceted interventions should be implemented, including more frequent consultations, telephone follow-up calls and family counselling, when feasible.

All these interventions should be mainly concentrated in the first 2 months after the beginning of a treatment since this is when MA especially drops and the attitude of patients are shaped, with possible important impact on their subsequent behaviour.

**Acknowledgements** The authors gratefully acknowledge the precious support of the staff of Opera San Francesco.

**Contributors** GF and SGC conceived and designed the study, supervised it and wrote the manuscript. GP and MF extracted data from databases and performed the statistical analyses. AER, NM and AS critically revised the manuscript. GC contributed to the interpretation of the results. All authors provided advice at different stages. All authors approved the final version of the manuscript. The

corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. SGC is the guarantor.

**Funding** This work was supported by grants from the Italian Ministry of Education, University and Research ('PRIN' 2017, project 2017728JPK).

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by the Ethics Committee of the University of Milano Bicocca. Protocol title: 'Valutazione dell'aderenza alle terapie farmacologiche per le malattie croniche non trasmissibili tra i migranti irregolari'. Approval No. 748, 29 June 2023. All data were completely and permanently anonymised. All procedures were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This is a retrospective study using data retrieved from databases.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available on reasonable request from the corresponding author.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

## ORCID iDs

Gianfrancesco Fiorini <http://orcid.org/0000-0001-5468-4063>

Giacomo Pellegrini <http://orcid.org/0000-0001-6935-8332>

Giovanni Corrao <http://orcid.org/0000-0002-1034-8444>

## REFERENCES

- World Health Organization. Adherence to long-term therapies: evidence for action. 2003. Available: <https://apps.who.int/iris/handle/10665/42682>
- Walsh CA, Cahir C, Tecklenborg S, *et al*. The association between medication non-adherence and adverse health outcomes in ageing populations: A systematic review and meta-analysis. *Br J Clin Pharmacol* 2019;85:2464–78.
- Mafruhah OR, Huang YM, Lin HW. Impacts of medication non-adherence to major modifiable stroke-related diseases on stroke prevention and mortality: a meta-analysis. *J Neurol* 2023;270:2504–16.
- Hamrahian SM, Maarouf OH, Fülöp T. A critical review of medication adherence in hypertension: barriers and facilitators clinicians should consider. *Patient Prefer Adherence* 2022;16:2749–57.
- Burnier M, Egan BM. Adherence in hypertension. *Circ Res* 2019;124:1124–40.
- Aznar-Lou I, Fernández A, Gil-Girbau M, *et al*. Impact of initial medication non-adherence on use of Healthcare services and sick leave: a longitudinal study in a large primary care cohort in Spain. *Br J Gen Pract* 2017;67:e614–22.
- Cutler RL, Fernandez-Llimos F, Frommer M, *et al*. Economic impact of medication non-adherence by disease groups: a systematic review. *BMJ Open* 2018;8:e016982.
- Brown MT, Bussell J, Dutta S, *et al*. Medication adherence: truth and consequences. *Am J Med Sci* 2016;351:387–99.
- Lemay J, Waheedi M, Al-Sharqawi S, *et al*. Medication adherence in chronic illness: do beliefs about medications play a role? *Patient Prefer Adherence* 2018;12:1687–98.

- 10 Gil-Guillen VF, Balsa A, Bernárdez B, *et al.* Medication non-adherence in rheumatology, oncology and cardiology: A review of the literature of risk factors and potential interventions. *Int J Environ Res Public Health* 2022;19:12036.
- 11 Agenzia Italiana del Farmaco. Indicatori per La Valutazione Dell'Aderenza e Della Persistenza al Trattamento Farmacologico. Rome. 2020.
- 12 Uchmanowicz B, Chudiak A, Uchmanowicz I, *et al.* Factors influencing adherence to treatment in older adults with hypertension. *Clin Interv Aging* 2018;13:2425–41.
- 13 Alsofyani MA, Aloufi AO, Al-Qhtani NS, *et al.* Factors related to treatment adherence among hypertensive patients: A cross-sectional study in primary Healthcare centers in Taif city. *J Family Community Med* 2022;29:181–8.
- 14 Pourhabibi N, Mohebbi B, Sadeghi R, *et al.* Determinants of poor treatment adherence among patients with type 2 diabetes and limited health literacy: a scoping review. *J Diabetes Res* 2022;2022:2980250.
- 15 Liu C, Wang D, Liu C, *et al.* What is the meaning of health literacy? A systematic review and qualitative synthesis. *Fam Med Community Health* 2020;8:e000351.
- 16 Osborne RH, Elmer S, Hawkins M, *et al.* Health literacy development is central to the prevention and control of non-communicable diseases. *BMJ Glob Health* 2022;7:e010362.
- 17 World Health Organization. World Report on the Health of Refugees and Migrants. Geneva. Licence: CC BY-NC-SA 3.0 IGO. 2022.
- 18 Istituto per gli Studi di Politica Internazionale (ISPI). Migrazioni in Italia: tutti i numeri. 2020. Available: <https://www.ispionline.it/it/pubblicazione/migrazioni-italia-tutti-i-numeri-24893>
- 19 Fiorini G, Cerri C, Bini S, *et al.* The burden of chronic noncommunicable diseases in undocumented migrants: a 1-year survey of drugs dispensation by a non-governmental organization in Italy. *Public Health* 2016;141:26–31.
- 20 Fiorini G, Franchi M, Pellegrini G, *et al.* Characterizing non-communicable disease trends in undocumented migrants over a period of 10 years in Italy. *Sci Rep* 2023;13:7424.
- 21 Andrade SE, Kahler KH, Frech F, *et al.* Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiol Drug Saf* 2006;15:565–74; .
- 22 Miller TA. Health literacy and adherence to medical treatment in chronic and acute illness: A meta-analysis. *Patient Educ Couns* 2016;99:1079–86.
- 23 Ran X, Chen Y, Jiang K, *et al.* The effect of health literacy intervention on patients with diabetes: a systematic review and meta-analysis. *Int J Environ Res Public Health* 2022;19:13078.
- 24 Lieslehto J, Tiihonen J, Lähteenvuo M, *et al.* Primary nonadherence to antipsychotic treatment among persons with schizophrenia. *Schizophr Bull* 2022;48:655–63.
- 25 Poletti V, Pagnini F, Banfi P, *et al.* The role of depression on treatment adherence in patients with heart failure - a systematic review of the literature. *Curr Cardiol Rep* 2022;24:1995–2008.
- 26 Szabo G, Fornaro M, Dome P, *et al.* A bitter pill to swallow? Impact of affective temperaments on treatment adherence: a systematic review and meta-analysis. *Transl Psychiatry* 2022;12:360.
- 27 Gast A, Mathes T. Medication adherence influencing factors - an (updated) overview of systematic reviews. *Syst Rev* 2019;8:112.
- 28 McGuinness S, Hughes L, Moss-Morris R, *et al.* Adherence to adjuvant endocrine therapy among white British and ethnic minority breast cancer survivors in the United Kingdom. *European J Cancer Care* 2022;31:e13722.
- 29 Patel D, Jalal Z, Guo P. Medicine adherence and associated factors in immigrants and refugees: a systematic review. *Int J Clin Pract* 2022;2022:1993066.
- 30 Shahin W, Kennedy GA, Stupans I. A qualitative exploration of the impact of knowledge and perceptions about hypertension in medication adherence in middle Eastern refugees and migrants. *Explor Res Clin Soc Pharm* 2021;3:100038.
- 31 Alfian SD, Pradipta IS, Hak E, *et al.* A systematic review finds inconsistency in the measures used to estimate adherence and persistence to multiple cardiometabolic medications. *J Clin Epidemiol* 2019;108:44–53.
- 32 Jackevicius CA, Li P, Tu JV. Prevalence, predictors, and outcomes of primary nonadherence after acute myocardial infarction. *Circulation* 2008;117:1028–36.
- 33 Yfantopoulos J, Protopapa M, Chantzaras A, *et al.* Doctors' views and strategies to improve patients' adherence to medication. *Hormones (Athens)* 2021;20:603–11.
- 34 Carroll CL, Feldman SR, Camacho FT, *et al.* Adherence to topical therapy decreases during the course of an 8-week psoriasis clinical trial: commonly used methods of measuring adherence to topical therapy overestimate actual use. *J Am Acad Dermatol* 2004;51:212–6.
- 35 Shinn EH, Broderick G, Fellman B, *et al.* Simulating time-dependent patterns of nonadherence by patients with breast cancer to adjuvant oral endocrine therapy. *JCO Clin Cancer Inform* 2019;3:1–9.
- 36 Gibson TB. A dynamic analysis of medication adherence. *J Manag Care Spec Pharm* 2022;28:1392–9.
- 37 Napolitano F, Napolitano P, Angelillo IF, *et al.* Collaborative Working Group. Medication adherence among patients with chronic conditions in Italy. *Eur J Public Health* 2016;26:48–52.
- 38 Horii T, Momo K, Yasu T, *et al.* Determination of factors affecting medication adherence in type 2 diabetes mellitus patients using a nationwide claim-based database in Japan. *PLoS One* 2019;14:e0223431.
- 39 Dozza A, Krymchantowski AV. Adherence to migraine treatment does not depend on the number of prescribed medications. *Arq Neuropsiquiatr* 2013;71:171–3.
- 40 Kim SJ, Kwon OD, Han EB, *et al.* Impact of number of medications and age on adherence to antihypertensive medications: A nationwide population-based study. *Medicine (Baltimore)* 2019;98:e17825.
- 41 Dilles T, Mortelmans L, Loots E, *et al.* People-centered care and patients' beliefs about medicines and adherence: a cross-sectional study. *Heliyon* 2023;9:e15795.
- 42 Newman PM, Franke MF, Arrieta J, *et al.* Community health workers improve disease control and medication adherence among patients with diabetes and/or hypertension in Chiapas, Mexico: an observational stepped-wedge study. *BMJ Glob Health* 2018;3:e000566.
- 43 Sharma N, Mariam W, Basu S, *et al.* Determinants of treatment adherence and health outcomes in patients with type 2 diabetes and hypertension in a low-income urban agglomerate in Delhi, India: a qualitative study. *Cureus* 2023;15:e34826.
- 44 Baghikar S, Benitez A, Fernandez Piñeros P, *et al.* Factors Impacting adherence to diabetes medication among urban, low income Mexican-Americans with diabetes. *J Immigr Minor Health* 2019;21:1334–41.
- 45 Gandy J, Sawin EM, Zook S, *et al.* Improving adherence to mental health in a low income clinic. *SAGE Open* 2019;9:215824401985101.
- 46 Boutilier JJ, Yoeli E, Rathausser J, *et al.* Can digital adherence technologies reduce inequity in tuberculosis treatment success? Evidence from a randomised controlled trial. *BMJ Glob Health* 2022;7:e010512.
- 47 Schulze LN, Stentzel U, Leipert J, *et al.* Improving medication adherence with telemedicine for adults with severe mental illness. *Psychiatr Serv* 2019;70:225–8.
- 48 Hacker K, Anies M, Folb BL, *et al.* Barriers to health care for undocumented immigrants: a literature review. *Risk Manag Healthc Policy* 2015;8:175–83.
- 49 Onarheim KH, Melberg A, Meier BM, *et al.* Towards universal health coverage: including undocumented migrants. *BMJ Glob Health* 2018;3:e001031.