Older Patients and Geographic Barriers to Pharmacy Access: When Non-adherence Translates to an Increased Use of Other Components of Healthcare

Running title: GEOGRAPHIC BARRIERS TO PHARMACY ACCESS

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Abstract

This study develops and applies a Grossman-style health production model to explain whether geographic barriers can influence non-adherence to prescription drugs, as well as the use of other components of health care, as a potential substitute for drug compliance, and their effect on patients' health. To test the theoretical hypothesis, we used a multivariate probit model estimated by maximum simulated likelihood that considers individual unobserved heterogeneity, which may characterize the relationship between adherence, medical care utilization and health outcome. We used administrative data from Liguria, Italy, the region with the highest rate of individuals over the age of 65 in Europe. Our sample included older individuals affected by cardiovascular diseases, which remain one of the leading causes of death in most OECD countries. Our results showed that not only longer distance to reach drug providers but also "pharmacy desert" negatively influence patients' adherence. According to our results, patients' non-adherence to pharmacological therapy is responsible for an increased probability of patients' post-discharge mortality and the overuse of other medical services, namely hospitalizations and emergency department visits. Non-adherence may thus represent a potential source of waste for the health care system.

Keywords: spline; distance; pharmacy desert; adherence; health production; chronic diseases; multivariate probit

JEL classification: I11; I12; C31.

1. Introduction

The advances in medicine over the last half century have increased life expectancy in the Western world. This has also led to an increase in the incidence of chronic diseases and the number of individuals in need of long-term drug therapy, whose full benefits are not always realized because more than 50% of such patients do not faithfully adhere to prescription-medication regimens (World Health Organization [WHO], 2003).

Non-adherence is most prevalent among patients who require multiple drug therapy, particularly older adults due to a higher number of coexisting diseases. Non-adherence in older patients may be associated with increased emergency-room visits and excess hospitalizations together with suboptimal clinical outcomes that might increase the overall health care costs, placing a significant financial burden on modern health care systems (Atella, Belotti, & Depalo, 2017). According to Cutler and Everett (2010), non-adherence is one of the main sources of waste for the US health care system, with around $100 billion spent each year in avoidable hospitalizations and the total avoidable expenses being approximately $290 billion per year (about 13% of their total health care spending, i.e., 2.3% of their GDP).

Attempts to explain disparities in therapeutic non-compliance have mostly focused on drug affordability and patient-related factors, such as socioeconomic status, health condition, or type of therapy prescribed (Doshi, Zhu, Lee, Kimmel, & Volpp, 2009; Gaynor, Li, & Vogt, 2006; Osterberg & Blaschke, 2005).[1,2] Geographic and environmental contextual factors too, however, may influence the ability to fill prescriptions. Access to pharmacies is a basic but necessary step for ongoing medication access. Travel burden (longer travel time or longer distance in reaching drug providers) and "pharmacy desert" may be important barriers to patients' ability to fill prescriptions, especially for older individuals, even in the absence of economic barriers (Amstislavski, Matthews, Sheffield, Maroko, & Weedon, 2012; Qato et al., 2014).[3]

Geographic barriers may have a direct effect on the demand for drugs and patients' compliance as well as an indirect effect on the demand for other medical services. In responding to geographic barriers, people suffering from chronic illnesses, for instance, might reduce compliance

[1] The duration and complexity of drug regimens may have consequences for adherence to therapy, since the longer and more difficult the treatment is, the greater is the likelihood of discontinuation (Rasmussen et al., 2007).
[2] Higher out-of-pocket costs for medication discourage adherence; people use more drugs when drug prices are lower. However, in a recent study, Doshi et al. (2009) showed that, even among patients whose health insurance plan does not require any cost sharing for medications, non-adherence rate was about 40%.
[3] The term "pharmacy desert" has been coined based on the concept of "food desert" (i.e., a geographic area where residents lack access to healthy foods—especially fresh fruits and vegetables—because of the absence of supermarkets or other stores selling various affordable healthy food options within a convenient travelling distance). Similarly, pharmacy desert here refers to a geographic area that lacks access to a nearby pharmacy and where the availability of most commonly dispensed prescription drugs is poor or they are difficult to obtain (Amstislavski et al., 2012; Qato et al., 2014).

with drug therapies. However, poor compliance could lead to poor health outcomes, which may lead, in turn, to the use of additional medical care services. For example, longer travel time or longer distance to the dispensing pharmacy may cause people to fall out of compliance with their drug therapy for hypertension in favor of other medical services; they may thus be more likely to suffer from heart attacks, strokes, and other complications, leading to a higher number of emergency room visits or to excess hospitalizations (Akinbosoye, Taitel, Grana, Hill, & Wade, 2016; Balkrishnan, Byerly, Camacho, Shrestha, & Anderson, 2001; Encinosa, Bernard, & Dor, 2010; Gaynor et al., 2006; Johnson, Goodman, Hornbrook, & Eldredge, 1997; Sokol, McGuigan, Verbrugge, & Epstein, 2005; Soumerai, Ross-Degnan, Avorn, Mclaughlin, & Choodnovskiv, 1991; Tamblyn et al., 2001). Further, older adults are especially more vulnerable and prone to adverse outcome compared to the rest of the population, and they access EDs and hospitals more often and for more urgent problems than any other age group (Samaras, Chevalley, Samaras, & Gold, 2010).

The above discussion suggests that the first step toward a complete understanding of the effects described requires a complex model that considers the simultaneous relationships between non-adherence to therapy, health status, and medical care service utilization.

Grossman (1972) provided a useful theoretical framework for analyzing this issue. According to his approach, we assumed that prescription drugs can be considered inputs into the health production function together with other medical care services. Drugs and other medical care services are characterized by a certain level of substitutability, the extent of which may vary widely among conditions and even patients. For instance, when patients encounter difficulties in accessing drugs because of geographic barriers (e.g., longer travel time or longer distance to reach drug providers), the opportunity cost of adherence increases, affecting the demand for not only drugs but also substitute services. This may lead patients to the "uneconomic" portions of the health production isoquant, meaning those combinations of inputs that may in fact harm patients and require more medical intervention to maintain the same health status (Folland, Goodman, & Stano, 2013).

The purpose of this study is threefold. First, we aim to understand whether a potential driver behind non-adherence, such as geographic barriers to pharmacies, measured through travel distance and "pharmacy desert," may contribute to a decreased adherence among older patients. Second, we test whether inadequate drug therapy, because of geographic barriers, may lead older patients to increase their demand for other medical care inputs. Finally, we investigate the mediating role of health in influencing the degree of substitution between drugs and medical care consumption and the potential repercussions that medication non-compliance and overuse of medical services, as a substitute for drugs, might have on patients' health status.

The paper is divided into two parts. The first part provides the theoretical background, describing the relationship between non-adherence to therapy, medical care service utilization, and patients' health status, which is built on the basic concepts of the production of health by Grossman (1972). The second part offers empirical support to the theoretical assumptions. Specifically, in the empirical part of the paper, we use a simultaneous equation model for binary variables. We constructed a joint model of adherence, medical care utilization and health outcome that we estimated by using a recursive multivariate probit model which also takes into account the individuals unobserved heterogeneity which may characterize this relationship.

For the empirical investigation, we used a unique dataset from Liguria, the oldest Italian region, and which has the highest concentration of elderly population in Europe: more than 28.4% of its population is over 65 years and around 5% is over 85 years (Eurostat, 2018). Eurostat projections forecast that the rest of Europe will be characterized by a similar rate of over 65 years in the next 30 years only. Liguria is located in northwest Italy, crossed by the two main Italian mountain ranges, Apennines and Alps, and bordered to the west by France and to the south by the sea. The orographic features of the region mean that a substantial part of the population, even the elderly, lives in mountainous areas where health services may not be easily accessible. Our sample included older individuals affected by cardiovascular diseases (CVDs), which remain one of the leading causes of death in most OECD countries (Johnston, Propper & Shield; Rasmussen, Chong, & Alter, 2007).

According to our results, which also support the theoretical assumptions, geographic barriers are associated with persistent and significant decline of the adherence to the therapy among older adults affected by CVDs. Poor compliance lead to increased use of other components of healthcare, as substitute for with drugs regime, such as hospitalizations and emergency room visits, potentially resulting in worsened health status i.e. a higher probability of post-discharge mortality.

The rest of the paper is organized as follows. Section 2 presents the theoretical background. Section 3 describes the data and variables used in this study. Section 4 explains the empirical strategy, including the estimation method, while the results are discussed in Section 5. Finally, Section 6 summarizes and concludes the paper.

2. Theoretical Background

According to Grossman (1972) consumers actively produce health. The stock of health capital is determined by the production function:

$$H = f(D, M) \tag{2}$$

where D denotes patients' drug consumption and M represents the quantity of all other medical care inputs. Drug consumption and other medical care inputs are characterized by a certain level of substitutability, the extent of which may vary widely among conditions and even patients (Folland et al., 2013). How people choose to "produce" health depends on the price of health-affecting goods and services and their opportunity costs.

The health production function isoquants are assumed to be oval shaped: patients may improve their level of health in those segments of the isoquants that are convex to the origin (i.e., the economic region of production). If patients move on to the "uneconomic" portions of the isoquants, meaning those combinations that should never be selected, then the marginal product of drugs tend to zero (point G in Figure 1). It is also possible that increases in drugs consumption D beyond a given threshold (dashed segment) could even harm the patient and more medical interventions have to be consumed in order to maintain the patient on the same health level. In this region, the isoquant will become positively sloped (point H in Figure 1). Similar logic may apply to the vertical portion of an isoquant with increases in M. The dashed segments of the isoquant can be considered "waste-bearing segments" (see Figure 1).

We assume that geographic barriers in accessing drugs, such as longer travel time, or longer distance to reach the dispensing pharmacy, or pharmacy desert, might increase the cost opportunity of adherence to therapy, leading patients to not follow the recommendations for prescribed treatments. If patients counteract health deterioration by substituting drugs with other medical care inputs, they might move on to the dashed segment of the health production function isoquant.

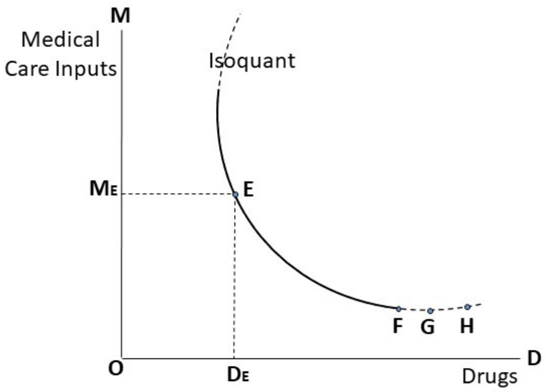

Figure 1: Health Production Function Isoquant

The following provided empirical support to these theoretical assumptions.

3. Data and Variables

For this study, we constructed a new dataset from three different data sources: the Liguria Hospital Discharge Records (HDRs) database (roughly 270,000 accesses per year) containing information about hospitalizations, the Ligurian Emergency Departments (ED) Registry (roughly 630,000 accesses per year) containing information on all visits to ED services, and the Ligurian Pharmaceutical Registry (roughly 15,000,000 records per year) containing information about drug purchases. The HDRs database was used to retrieve patients' year of birth, health status (i.e., presence of multiple chronicity), and socio-demographic information (i.e., gender, date of birth, nationality, educational level, zip code of residence, and marital status). The final dataset was obtained by linking records between the three above-mentioned databases, which was possible due to the presence of a unique patient identification code.

We focused on patients over 65 years suffering from CVDs who represented more than 85% of the initial sample. Indeed, although in recent decades, developed countries have witnessed remarkable improvements in CVD outcomes, CVDs remain one of the leading causes of death in most OECD countries, and prospects for further reduction of their burden are particularly challenging because of the following reasons. First, elderly populations represent the most vulnerable group with a higher baseline cardiovascular risk and propensity for non-adherence to drugs due to complexities in medical regimens. Moreover, lack of adherence to recommended treatments tend to be more common for CVDs, which may often be asymptomatic; hypertension, for instance, which is a well-established risk factor for CVD morbidity and mortality, is also called the "Silent Killer," leaving patients unaware of any risks and feeling fine even without medications until an episode occurs (Johnston, Propper & Shield; Rasmussen, Chong, & Alter, 2007).

Specifically, we included in our sample those patients who have received at least one diagnosis, either primary or secondary, connected to diseases of the circularity system in the period 2013-2016 (around 27% of the initial sample, i.e., 127.119 over 471.657 patients).[4]

We further restricted our sample to patients with a Liguria zip code of residence only: given the tourist vocation of the Liguria region, particularly during the summer season, this filter was useful to avoid the inclusion of patients who occasionally bought drugs or used medical services in Liguria but lived outside the region. Finally, we included only patients whose complete socio-demographic information was available and who are still alive at the beginning of 2017. After applying the aforementioned filters and correcting for missing values, the final sample included 35,898 observations.

Our dependent variables were indicators of patients' health outcome, adherence to therapy, and other medical care service utilization.

The health outcome indicator concerned patients' post-discharge mortality. Data on patients' post-discharge mortality were obtained from the regional population registry containing information on the date of death of Ligurian patients[5]. Specifically, we constructed a binary indicator of death that takes value 1 if the patient died in 2017 or 2018 and 0 otherwise. Most existing studies have focused on patients' in-hospital mortality, since such data are commonly available. We excluded this variable because of its inability to accurately measure treatment-related mortality (Vitikainen, Linna, & Street, 2010). Indeed, in-hospital mortality may be determined by the severity of chronic conditions rather than by medication adherence or hospital-treatment effects. Here, we used a variable measuring long-term overall treatment-related mortality (as done by Farsi & Ridder, 2006).

To the best of our knowledge, there is a lack of a clear consensus on the definition of adherence (see also Atella et al., 2017; DiMatteo, 2004). Even when objective measures of adherence are available, no one method is accepted as the "gold standard" for measuring medication adherence. In the absence of a "gold standard," to assess adherence to therapy, we constructed a binary variable that

[4] The selection of ICD-9-CM codes was carried out by using the Chronic Condition Indicator developed as part of the Healthcare Cost and Utilization Project to classify diagnosis code in 18 categories of chronic conditions. See https://www.hcup-us.ahrq.gov/toolssoftware/chronic/chronic.jsp .

[5] The registry includes information concerning patients deceased for all causes of death (not only for CVDs). Consequently, our model might suffer from measurement error in the dependent variable that implies loss of precision and results biased against zero. Apparently from our results this is not a real problem since our standard errors are relatively low (see Table 5 and 6).

compares the behavior of each patient in terms of drug consumption (source: Pharmaceutical Registry, year 2017) to that of a group of "equal needs" patients.[6] Twelve peer clusters were built to group patients homogenous in terms of age (65-74, 75-84, 85+), gender (male, female), and number of chronic conditions (one chronic condition, multiple chronic condition). The number of observations for each cluster was between 1,310 and 8,006. Non-adherence to therapy was then defined with a binary variable that takes value 1 if patients consume a quantity of drugs specifically targeted to diseases of the circulatory system (Anatomical Therapeutic Chemical [ATC] code C09, WHO Collaborating Centre for Drug Statistics Methodology) lower than the average of his/her group of "equal needs," and 0 otherwise.[7,8,9]

Following previous studies, as indicators of "other medical services," we considered two variables that measure emergency room visits and hospitalizations, respectively. Similar to the indicator of adherence, we constructed two binary indicators for excessive use of the abovementioned health care services that take value 1 if patients' number of hospitalizations/ED visits to any Ligurian hospital in 2017 was higher than the peer group average, and 0 otherwise (sources: HDRs database and ED Registry, year 2017).[10,11]

3.1 Geographic Barriers: Distance and Pharmacy Desert

The main variables of interest proxied for geographic barriers and were mainly based on the concept of distance to the closest dispensing pharmacy and "pharmacy desert" (i.e., areas where the possibility to access pharmacy services is limited or absent [Pednekar & Peterson, 2018; Pednekar, Peterson, & Heller, 2016; Qin, Diniz, & Coleman, 2018]).

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[6] In case of death during 2017, the quantity of drugs purchased was weighted for the effective number of days of life. This is obtained by dividing each variable by the number of days of life and by multiplying it with 365.

[7] We selected the ATC code equal to C09 since, in our sample, drugs belonging to this category are the most consumed by the group of patients under investigation. See also Huber, Szucs, Rapold, and Reich (2013), Liu et al. (2017), Gama et al. (2017).

[8] We also ran a sensitivity analysis with a different measure of adherence. We evaluated adherence on the two ATC categories of drugs most consumed by the population under investigation (ATC C09 "Agents acting on the renin-angiotensin system" and ATC C07 "beta blocking agents"). The sensitivity analysis confirmed that the results are robust. For the sake of brevity, we did not include these results in the paper, but they are available from the authors on request.

[9] The cross-sectional nature of the design might pose some interpretive problems: "low-adherence" may depend on the fact that some patients received short-term therapy or started drug therapy late in the analysis period. However, given the chronic nature of CVDs, it is likely that most patients were continuing medication users and that their treatment had started before the analysis period began.

[10] The value of 1 in our analysis denotes a "not optimal" behavior (i.e., non-adherence or excessive use of health care services). This should capture the idea that patients might select the "uneconomic" portion of the health production function isoquant.

[11] Again, in accordance with the measure of non-adherence, in case of death during 2017, the number of ED visits and hospitalizations were weighted for the effective number of days of life.

For each patient, the distance to the closest community pharmacy was estimated by using zip codes. The travel distance (in km) was estimated using Bing maps, a Microsoft Cloud Service[12]. To model the effect of distance, first, we included in the model the distance to the closest pharmacy and its quadratic term that allowed for non-linearity. Then, a piecewise-polynomial function was fitted. We employed a restricted cubic spline as regressor where knot locations were determined according to Harrell's (2001) procedure by using the *mkspline* function of STATA 15.[13]

Pharmacy desert was measured through a "pharmacy desert index" constructed as the first component resulting from a Principal Component Analysis (PCA) that included the following variables: number of pharmacies in the zip code of residence; number of pharmacies within 20 km from the centroid of the zip code of residence; living within a zip code with no pharmacy; living in a rural municipality. We also standardized the index to lie on a continuous scale between 0 (lowest difficulties in accessing drugs) to 1 (highest difficulties in accessing drugs) to aid in interpretation (see Table A1 in the Appendix for details).

In addition, we included an indicator of means of transportation (i.e., the possession of a private car). This information was deducted from the ED Registry, where it was reported if patients reached ED by their own means of transportation. According to Wang (2016), a private car may influence individuals' ability to access health care services and procure medications.[14]

The other independent variables in the model, together with the dependent variables and the indicators of geographic barriers to pharmacy access, are listed in Table 1. We considered the following variable categories: demographics (patients' age, gender, and whether patients are foreign-born), patients' health status at the beginning of the observation period (whether patients suffer from multiple chronicity), distance to other health care providers, and socio-economic variables (years of education completed and patients' marital status).

Among the socioeconomic variables, patients' level of education, in particular, may play a pivotal role here. A higher level of education tends to positively influence health literacy (i.e., patients' ability to understand the consequences of adherence to therapy and medical care utilization and to recognize that their behavior may influence the efficacy of the therapy [DiMatteo, 2004]).

Among the control variables, drug prices were not included. In fact, the therapeutic regimes considered in our study concerned drugs belonging to the so-called "class A" category that are reimbursed by the Italian National Health Services (NHS) and dispensed directly through hospital pharmacies (Distribuzione Diretta—DD) or by territorial pharmacies (Distribuzione per conto—

[12] To ease the interpretation of the coefficients the distance variables have been rescaled using a min-max normalization.
[13] A restricted cubic spline is a smooth, piecewise polynomial function that evaluates the association of a variable with an outcome without assuming any association a priori (Desquilbet & Mariotti, 2010).
[14] The mode of travel (i.e., how people travel) should also be considered as a proxy for difficulties and potential barrier to reach health care facilities (Wang, 2016).

DPC) (see Folino-Gallo, Montilla, Bruzzone, & Martini, 2008). In Italy, the price of "class A" drugs is fixed and regulated at the central level by the National Regulatory Authority (Agenzia Italiana per il Farmaco—AIFA).

Table 1: Description of the variables included in the system of simultaneous equations

Variable name	Description
Post-discharge mortality	Dummy variable = 1 if the patient died during 2017-2018
Male	Dummy variable = 1 if the patient is male
Age class	64-74 years
	75-84 years
	85+ years
Multiple chronicity	Dummy variable = 1 if the patient suffers from more than one chronicity
Foreign	Dummy variable = 1 if foreign-born patients
Married	Dummy = 1 if the patient is married
Educational level	Number of years of education completed
Non-adherence to therapy	Dummy = 1 if the patient consumes less drugs than expected
Excessive use of hospitalizations	Dummy = 1 if the patient has more hospitalizations than expected
Excessive use of emergency department (ED) services	Dummy = 1 if the patient has more ED visits than expected
Distance to hospital	Distance to the closest hospital (in km)
Rural municipality	Dummy variable = 1 if the patient lives in a municipality with a low level of urbanization
Own means of transportation	Dummy = 1 if the patient accesses EDs during 2017 only using his/her own means of transportation
Distance to pharmacy	Distance to the closest pharmacy (in km)
No pharmacy	Dummy variable = 1 if the patient has no pharmacies in his/her zip code of residence
Pharmacy desert index	First component resulting from a Principal Component Analysis (PCA) including the following variables: number of pharmacies in the zip code of residence; number of pharmacies within 20 km from the centroid of the zip code of residence; living within a zip code with no pharmacy; living in a rural municipality.

4. Estimation Strategy

To investigate the relationship between patients' adherence to therapy, medical care service utilization, and patients' mortality, we employed a simultaneous equation model for binary variables. We identified two classes of dependent variables: individual health behaviors, namely drug consumption and medical care utilization, and health outcome (i.e., post-discharge mortality). In the medical care utilization equation, the adherence to therapy indicator is included as an explanatory variable. The inclusion of this indicator allowed us to test whether patients treat medical service utilization as a substitute for compliance with therapy. In the post-discharge mortality equation, health behaviors (adherence and medical care utilization) were included as regressors.

The potential endogeneity that may arise with the inclusion of the drug consumption and medical care utilization variables as regressors into the health outcome equation, and the inclusion of drug consumption into the medical care utilization equation, was corrected by using a recursive multivariate probit model that considers that the risk of mortality and drug consumption and medical care utilization depend on individual unobservable heterogeneity.[15] The equation for adherence to therapy was modelled as a reduced-form equation. The post-discharge mortality and medical care utilization equations were structural equations.

Therefore, we constructed and estimated a system of three equations with one reduced-form and two structural equations. One of the two structural equations was represented by the post-discharge mortality equation, and the other one by one of the two medical care utilization services: ED visits and hospitalizations. Thus:

$$\begin{gathered} y_{1i}^{*} = \beta_1' x_{1i} + \varepsilon_{1i} = \delta_1 y_{2i} + \delta_2 y_{3i} + \alpha_1' z_{1i} + \varepsilon_{1i} \\ y_{2i}^{*} = \beta_2' x_{2i} + \varepsilon_{2i} = \gamma_2 y_{3i} + \alpha_2' z_{2i} + \varepsilon_{2i} \\ y_{3i}^{*} = \beta_3' x_{3i} + \varepsilon_{3i} = \alpha_3' z_{3i} + \varepsilon_{3i} \end{gathered} \tag{3}$$

where x_{li} (with l = 1, 2, 3) and z_{hi} (with h = 1, 2, 3) are vectors of exogenous variables, β_l and α_h are parameter vectors, and δ_o (with o = 1, 2) and γ_2 are scalar parameters. ε_{hi} are the error terms distributed as multivariate normal, each with a mean zero and a variance covariance matrix Σ. Σ has values of 1 on the leading diagonal and correlations $\rho_{jk} = \rho_{kji}$ on off-diagonal elements (where ρ_{jk} is the covariance between the error terms of equation j and k).

In the above setting, the exogeneity condition is stated in terms of the correlation coefficients, which can be interpreted as the correlation between the unobservable explanatory variables of the different equations. All equations in (3) can be estimated separately as a single probit model only in the case of independent error terms (i.e., the coefficient ρ_{jk} is not significantly different from zero).[16]

The parameters of the first and second equations are not identified if z_{3i} includes all variables in z_{1i} and z_{2i}. The estimation of the above-described multivariate probit model requires some considerations for the identification of the model parameters. Maddala (1983) proposed that at least one of the reduced-form exogenous variables (z_{3i}) is not included in the structural equations as an explanatory variable. Following Maddala's approach, we imposed exclusion restrictions. For the reduced form, we used the distance to the closest dispensing pharmacy and the "pharmacy desert index," assuming they only have an indirect effect on health and medical care access through the

[15] The multivariate probit model with endogenous dummies belongs to the general class of simultaneous equation models (Maddala, 1983). See Cappellari and Jenkins (2003) for more on the estimation of the multivariate probit model, and Balia and Jones (2008), Di Novi (2010), and Di Novi (2013) for applications that use the multivariate probit model to estimate a recursive system similar to the one used here.

[16] The STATA software provides the statistic $z=\hat{\rho}/S_{\hat{\rho}}$ to test the hypothesis H_0: $\rho_{jk} = 0$. If the error terms are independent, the Maximum Simulated Likelihood estimation is equivalent to the separate Maximum Likelihood probit estimation.

adherence to therapy variable. Moreover, the medical care access equation includes an indicator of distance to the nearest health care provider (either hospital or ED).

As stated earlier, the main variables of interest were entered in the adherence to therapy equation and included the distance to the closest supplier and the "pharmacy desert index," which are proxies of geographic barriers, which is the focus of our analysis.

The estimation of the multivariate probit was performed using the STATA 15 software, which applies the method of Simulated Maximum Likelihood estimation (see Cappellari & Jenkins, 2003).

5. Results

Table 2 shows a simple descriptive analysis, presenting sample means and standard deviations for the variables used in the models (49% male; mean age: 80 years). Noteworthily, according to our definition of non-adherence to therapy, more than 50% of the sample was non-adherent (reflecting the results reported by WHO, 2003). Around 24% of the sample accessed hospitals, and around 27% accessed EDs more than the peer group average. The rate of post-discharge mortality in our sample was around 18%.

Table 2: Descriptive statistics: Patients' socio-demographic characteristics

Variable Name	Mean	Standard Deviation
Post-discharge mortality	0.1824	0.3862
Male	0.4931	0.5
Age class: 64-74	0.2698	0.4439
Age class: 75-84	0.4323	0.4954
Age class: 85+	0.2978	0.4573
Multiple chronicity	0.7340	0.4419
Foreign	0.0073	0.0851
Married	0.7037	0.4566
Educational level	7.434	3.160
Non-adherence to therapy	0.5471	0.4978
Excessive use of hospitalizations	0.2431	0.4290
Excessive use of EDs	0.2670	0.4424
Distance to hospital	5.7811	8.7670
Rural municipality	0.0762	0.2653
Pharmacy desert	0.6981	0.2225
Own means of transportation	0.1219	0.3272
Distance to pharmacy	4.5218	7.0451
No pharmacy	0.5909	0.4917

According to Table 3, as expected, post-discharge mortality was higher for patients who were not adherent to therapy (23% against 12%; see also Table A2 in the Appendix for further details). ED visits and hospitalizations were slightly higher for those who were not adherent to therapy (28% against 25%, and 26% vs. 22%, respectively).

Table 3: Adherence, post-discharge mortality, and excessive use of other medical services

Dependent Variables	**Adherent**	**Non-Adherent**
Post-discharge mortality	12.06%	23.36%
Excessive use of hospitalization	21.84%	26.36%
Excessive use of EDs	24.92%	28.17%

The geographic accessibility of pharmacies varies substantially across Liguria. Figure A1, in the Appendix, shows the pharmacy density in each specific zip code. A higher distance to pharmacy and pharmacy desert decrease pharmacy access, thereby limiting patients' ability to fill and adhere to prescribed medications. According to Table 4, the indicators of pharmacy desert, especially living in a zip code with no pharmacy, seem to influence the likelihood of being adherent to therapy more than the other indicators of geographic barriers to pharmacy access.

Table 4: Adherence to therapy and pharmacy accessibility

	Adherent	**Non-Adherent**
Average distance to the closest pharmacy in km (*standard deviation in parenthesis*)	4.61 (7.29)	4.45 (6.97)
Living in a municipality with a low level of urbanization (%)	7.61%	7.63%
Number of pharmacies within 20 km from the centroid of the zip code of residence (*standard deviation in parenthesis*)	14.90 (16.47)	14.68 (16.52)
Average number of pharmacies in the zip code of residence (*standard deviation in parenthesis*)	3.40 (6.29)	3.26 (6.00)
Living within a zip code with no pharmacy (%)	58.6%	59.5%

Table 5 shows coefficients for the structural post-discharge mortality and excessive use of hospitalization equations estimated in the full recursive model, using the multivariate probit under alternative specifications of equation (3).

With specific reference to the reduced-form equation for non-adherence to therapy, Model 1 referred to the baseline specification of equation (3), in which the regressors included demographics not used to construct the cluster of "equal needs" (i.e., whether patients are foreign-born) and socio-economic variables (i.e., years of education completed and patients' marital status).[17] The main variables of interest, which proxy geographic barriers to reach the closest dispensing pharmacy, were based on the following variables: distance to the closest pharmacy (*distance to pharmacy*) and distance to the closest pharmacy squared (*distance to pharmacy squared*), and living in a zip code with no pharmacy (*no pharmacy*) that relies on the concept of "pharmacy desert." The model also included, among regressors, an indicator of the possession of a private car (*own means of transportation*).

With reference to the structural equation for excessive use of hospitalizations, in Model 1, again, geographic barriers to hospital access were proxied with distance to the closest hospital (*distance to hospital*) and distance to the closest hospital squared (*distance to hospital squared*). Among the controls, we again included the possession of a private car, whether patients were foreign-born, and socio-economic variables. In the structural equation for excessive use of hospitalizations, we also included the binary indicators for non-adherence to therapy, to test the potential substitutability of drug consumption with other medical care services.

Models 2 and 3 tested the robustness of the baseline results. Model 2 included restricted cubic splines for distance to the closest pharmacy and hospital.[18] Model 3 included, in the non-adherence equation, the "pharmacy desert index" that was constructed by using the PCA based on the following variables: number of pharmacies in the zip code of residence; number of pharmacies within 20 km from the centroid of the zip code of residence; living within a zip code with no pharmacy; and living in a rural municipality (see Section 3.1). In Model 3, the structural equation for hospital access included—among the indicators of geographic barriers, together with the indicator of distance and distance squared—the variable *rural municipality* to capture the rural-urban gap in access to health care services (i.e., we assumed that rural patients face greater geographic barriers to health care than their urban counterparts

[17] The variable *foreign* was not used to form clusters that reflect "equal needs" because the percentage of individuals who were born outside Italy was particularly low: 0.73% of the entire sample.

[18] The STATA command *mkspline* created the restricted cubic splines. We used the option *nknots* that specifies the number of knots that are to be used for the restricted cubic spline, unless the knot locations are specified. The number of knots must be between 3 and 7. We opted for 3 knots determined based on the lowest Akaike information criterion. *mkspline* automatically created two variables named spline 1 and spline 2. We then fit the regression model that includes the two spline terms (Orsini & Greenland, 2011).

In all three models showed in Table 5, the structural equation for patients' post-discharge mortality was estimated by including the following among the regressors: demographics (patients' age, gender, and whether patients are foreign-born), whether patients suffered from multiple chronic conditions, and socio-economic variables (years of education completed and patients' marital status). The structural equation for patients' post-discharge mortality also included, among the controls, the binary indicators for non-adherence to therapy and excessive use of hospitalizations.

The estimates in Table 5 show that the different specifications provide a consistent picture. Starting from Model 1, the coefficient for distance was negative, while the coefficient for distance squared was positive; both are statistically significant. The significance of the quadratic term for distance indicates that the relationship between patients' non-compliance with drug therapy and distance to the closest pharmacy was non-linear. The sign of the two coefficients suggests that for low values of distance, the relationship between distance and non-compliance may be negative, but for high values of distance, the relationship becomes positive; longer distance to reach drug providers contributes to poor adherence. The positive coefficient for the variable measuring the absence of pharmacies in the zip code of residence confirms that older adults living in a place characterized by the absence of pharmacies may experience greater difficulty in accessing medications. These results are also supported by the sign of the coefficient of the splines (Model 2) (with reference to distance) and the "pharmacy desert index" (Model 3). Finally, the availability of a private car reduced the probability of patients' non-compliance with drug therapy in Models 1-3; transportation barriers are often cited as barriers to health care access that may lead to missed or delayed care and medication use (Syed, Gerber, & Sharp, 2013).[19] Models 1-3 show that treatment adherence also differed by patients' socioeconomic status. According to previous studies, adherence to medical recommendations tends to be higher among married patients.[20] A higher level of education also had a negative effect on patients' non-compliance with drug regimes. As mentioned earlier, education may contribute to an increase in the level of health literacy, which in turn may positively influence older patients' understanding of their health condition and medical treatment, favoring adherence (see DiMatteo, 2004).

Adherence to prescribed treatment is essential for the successful treatment of older patients and is an important component of health care. According to our theoretical model, barriers to drug access may increase the opportunity costs of medication adherence, resulting in decreased utilization of medications, while simultaneously increasing the use of other medical care services. Indeed, it is plausible that consumers substitute hospitalizations for medications. This may happen because

[19] We found that geographic barriers, specifically longer distance to the closest hospital, also negatively affect access to hospital and reduce the probability of excessive use of hospitalizations.
[20] This result is also consistent with the marriage protection hypothesis, which assumes that "married individuals engage in low-risk activities, share resources, and enjoy caring from each other" (Hu & Wolfe, 2002).

patients experience more adverse health events as a result of decreased drug consumption, thereby leading to an increased use of inpatient care with a potential negative effect on patients' health and waste of health care system resources (Gaynor et al., 2006).

Our empirical results support this hypothesis; accordingly, travel burden, measured through longer distance to the closest dispensing pharmacy and "pharmacy desert" (which affect access to pharmacies), was associated with a persistent and significant decline of adherence among older adults affected by CVDs. According to our results, patients substitute non-adherence with a higher use of hospital services. However, non-adherence and excessive use of hospitalizations negatively affect patients' health by increasing the likelihood of post-discharge mortality, arguably leading patients to the hypothetical "uneconomic" portions of the health production isoquant, which eventually harms patients requiring more medical interventions to maintain the same health status (Folland et al., 2013).

These results are robust under different specifications of Models 1-3.

Table 5: Multivariate probit estimation: Post-discharge mortality and excessive use of hospitalizations[*]

		Model (1)	**Model (2)**	**Model (3)**
Post-discharge mortality	Male	0.2582***	0.2582***	0.2589***
		(0.018)	(0.018)	(0.019)
	Age_65_74	-1.2557***	-1.2557***	-1.2536***
		(0.027)	(0.027)	(0.027)
	Age_75_84	-0.7580***	-0.7580***	-0.7664***
		(0.020)	(0.020)	(0.020)
	Multiple chronicity	0.3696***	0.3696***	0.3682***
		(0.021)	(0.021)	(0.021)
	Educational level	-0.0111***	-0.0111***	-0.0105***
		(0.003)	(0.003)	(0.003)
	Foreign	-0.0715	-0.0715	-0.0926
		(0.116)	(0.116)	(0.124)
	Married	-0.0981***	-0.0981***	-0.0988***
		(0.019)	(0.019)	(0.020)
	Non-adherence to therapy	0.3994***	0.4002***	0.3739***
		(0.035)	(0.035)	(0.035)
	Excessive use of hospitalizations	1.0123***	1.0127***	1.0106***
		(0.044)	(0.044)	(0.044)
	_cons	-1.1590***	-1.1596***	-1.1474***
		(0.038)	(0.038)	(0.039)
Non-adherence to therapy	Educational level	-0.0085***	-0.0086***	-0.0079***
		(0.002)	(0.002)	(0.002)
	Foreign	0.1581*	0.1557*	0.2074*
		(0.079)	(0.079)	(0.086)
	Married	-0.1253***	-0.1244***	-0.1213***
		(0.015)	(0.015)	(0.015)
	Distance to pharmacy	-0.6346***		-0.2320*
		(0.150)		(0.113)
	Distance to pharmacy squared	0.6433**		0.1400
		(0.196)		(0.160)
	Own means of transportation	-0.1209***	-0.1214***	-0.1108***
		(0.020)	(0.020)	(0.021)
	Spline 1		-1.5329***	
			(0.331)	

	Spline 2		2.8531***	
			(0.685)	
	No pharmacy	0.0922***	0.1436***	
		(0.020)	(0.027)	
	Pharmacy desert index			0.0853*
				(0.034)
	_cons	0.2717***	0.2718***	0.2298***
		(0.021)	(0.021)	(0.029)
Excessive use of hospitalizations	Educational level	0.0010	0.0011	0.0007
		(0.002)	(0.002)	(0.002)
	Foreign	-0.1217	-0.1223	-0.0773
		(0.088)	(0.088)	(0.093)
	Married	-0.0195	-0.0188	-0.0191
		(0.016)	(0.016)	(0.016)
	Distance to hospital	0.2794*		0.2671*
		(0.112)		(0.113)
	Distance to hospital squared	-0.5074**		-0.4618*
		(0.196)		(0.198)
	Non-adherence to therapy	0.1371**	0.1382**	0.2131***
		(0.045)	(0.045)	(0.047)
	Own means of transportation	0.2212***	0.2212***	0.2251***
		(0.022)	(0.022)	(0.022)
	Rural municipality			-0.059^{+}
				(0.03)
	Spline 1		0.4134*	
			(0.2083)	
	Spline 2		-1.8011*	
			(0.914)	
	_cons	-0.8054***	-0.8076***	-0.8411***
		(0.035)	(0.036)	(0.036)
	rho21	-0.0057	-0.0061	0.0095
		(0.019)	(0.019)	(0.019)
	rho31	0.0374	0.0372	0.0364
		(0.023)	(0.023)	(0.023)
	rho32	0.0084	0.0075	-0.0387
		(0.027)	(0.027)	(0.028)
	N	35,898	35,898	34,719

[*]Standard errors in parentheses. $p < 0.10$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. In Model 3, the number of observations is 34,719 instead of 35,898 because of missing values in the variable "rural."

We re-ran the model using patients' excessive use of EDs instead of hospitalizations as the outcome of one of the two structural equations in the recursive multivariate probit model. This also allowed us to check to what extent our results were sensitive to the measure of health care access chosen.

Table 6 presents the results for the system in which the post-discharge mortality and excessive use of EDs equations are structural equations. The results are consistent with the previous model and support the theoretical assumptions again; geographic barriers (measured as before with longer distance and "pharmacy desert") may translate into poor adherence, which in turn may lead to an increased use of other components of health care, such as emergency room visits, potentially resulting in worsened health status and a higher probability of mortality.

Table 6: Multivariate Probit Estimation - Post-discharge Mortality and Excessive use of ED Services Model*

		Model (1)	Model (2)	Model (3)
Post-discharge mortality	Male	0.2027***	0.2027***	0.2055***
		(0.018)	(0.018)	(0.018)
	Age_65_74	-1.1553***	-1.1554***	-1.1481***
		(0.026)	(0.026)	(0.026)
	Age_75_84	-0.6450***	-0.6450***	-0.6525***
		(0.019)	(0.019)	(0.019)
	Multiple chronicity	0.3887***	0.3886***	0.3826***
		(0.020)	(0.020)	(0.021)
	Educational level	-0.0077**	-0.0077**	-0.0074*
		(0.003)	(0.003)	(0.003)
	Foreign	-0.1167	-0.1167	-0.1151
		(0.112)	(0.112)	(0.119)
	Married	-0.0978***	-0.0978***	-0.0986***
		(0.019)	(0.019)	(0.019)
	Non-adherence to therapy	0.4355***	0.4363***	0.4006***
		(0.035)	(0.035)	(0.036)
	Excessive use of hospitalizations	0.6021***	0.6032***	0.5413***
		(0.037)	(0.037)	(0.037)
	_cons	-1.1362***	-1.1370***	-1.0962***
		(0.039)	(0.039)	(0.039)
Non-adherence to therapy	Educational level	-0.0085***	-0.0086***	-0.0079***
		(0.002)	(0.002)	(0.002)
	Foreign	0.1582*	0.1558*	0.2073*
		(0.079)	(0.079)	(0.086)
	Married	-0.1252***	-0.1244***	-0.1213***
		(0.015)	(0.015)	(0.015)
	Distance to pharmacy	-0.6372***		-0.2315*
		(0.150)		(0.113)
	Distance to pharmacy squared	0.6465***		0.1401
		(0.196)		(0.160)
	Own means of transportation	-0.1224***	-0.1230***	-0.1111***
		(0.020)	(0.020)	(0.021)
	Spline 1		-1.5384***	
			(0.331)	
	Spline 2		2.8642***	
			(0.685)	
	No pharmacy	0.0924***	0.1439***	
		(0.021)	(0.028)	
	Pharmacy desert index			0.0858*
				(0.035)
	_cons	0.2719***	0.2720***	0.2295***
		(0.021)	(0.021)	(0.029)
Excessive use of emergency services	Educational level	-0.0091***	-0.0090***	-0.0093***
		(0.002)	(0.002)	(0.002)
	Foreign	0.0501	0.0501	0.0485
		(0.086)	(0.086)	(0.092)
	Married	0.0016	0.0015	-0.0038
		(0.016)	(0.016)	(0.016)

Distance to hospital	0.1471		0.1612
	(0.112)		(0.113)
Distance to hospital squared	-0.3560^{+}		-0.3615^{+}
	(0.196)		(0.198)
Non-Adherence to therapy	0.1424**	0.1432**	0.1528**
	(0.045)	(0.045)	(0.047)
Own means of transportation	1.1237***	1.1240***	1.1216***
	(0.021)	(0.021)	(0.021)
Rural municipality			0.005
			(0.03)
Spline 1		-0.0672	
		(0.209)	
Spline 2		0.1246	
		(0.921)	
_cons	-0.8007***	-0.7948***	-0.7986***
	(0.036)	(0.036)	(0.036)
rho21	-0.0153	-0.0158	0.0055
	(0.019)	(0.019)	(0.019)
rho31	0.1674***	0.1668***	0.2045***
	(0.020)	(0.020)	(0.020)
rho32	-0.0043	-0.0049	-0.0079
	(0.027)	(0.027)	(0.028)
N	35,898	35,898	34,719

*Standard errors in parentheses. $p < 0.10$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. In Model 3, the number of observations is 34,719 instead of 35,898 because of missing values in the variable “rural.”

As mentioned previously, we estimated the three equations together using the recursive multivariate probit specification. The multivariate probit allowed us to test for unobserved heterogeneity whose effect was captured by the correlation between the error terms from the single equation models. By simultaneously estimating all three equations, and considering the correlation in the error terms for the three equations, we could control for the effect of unobserved factors. Tables 5 and 6 show the correlation for the full recursive models. The null hypothesis of exogeneity was rejected in one case, i.e., in the ED model.[21]

The correlation parameter between the patients’ post-discharge mortality and excessive use of EDs equations indicates whether and how unobservable factors jointly affect ED utilization and health outcomes. According to our results, there exists a positive and statistically significant correlation between the disturbance of the post-discharge mortality equation and the excessive use of Eds equation. The positive coefficient supports the evidence that the frequency of ED visits among older patients increases dramatically as death approaches.

[21] The statistically significant correlation coefficients suggest that the null hypothesis of three univariate probit model or the hypothesis of independence across the error terms of the three latent equations can be rejected, and that the multivariate probit model is a better model for the observed data. Conversely, the null hypothesis cannot be rejected for the hospitalization model: as a consequence single probit models run of the three dependent variables lead to results consistent with those obtained using the multivariate probit (see Table A3 in the Appendix)

6. Conclusions

This paper developed and applied a Grossman-style health production model to test whether geographic barriers affect non-adherence to prescription drugs as well as the use of other components of health care, as a potential substitute for drug compliance, with possible detrimental effects on patients' health. We focused on a specific population group: older adults affected by CVDs.

According to our results, the difficulty in accessing drugs because of geographic barriers (measured through distance between patients' residence and the closest pharmacy, and several proxies of "pharmacy desert") negatively influences patients' adherence to drug regimes. The structural equation for patients' hospitalizations and ED visits clearly identified non-adherence as a determinant of overuse of other medical services. The structural equation for post-discharge mortality provided evidence that non-adherence to pharmacological therapy and excessive use of other medical services positively affect the probability of worsening in terms of health outcome with a potential waste of health care system resources.

As health care costs continue to rise, to reduce the financial burden on the health care systems, policymakers must determine ways to contain the growth of expenditure. A possible strategy is improving patient medication adherence, for instance, by reducing geographic barriers to pharmacies, especially for older patients. It is recommended to provide financial incentives to locate pharmacies in "pharmacy deserts" and to develop and implement complementary policies promoting greater engagement and education with older patients to demonstrate the importance of proper medication use and to motivate behavior changes that improve adherence.

Relatively few existing studies have examined the association between non-adherence, health care use, and health outcome; the potential net economic return when drug therapy is driven by improved adherence is often missed in the public debate. An increased understanding of this relationship in elderly populations presents an opportunity to examine a highly prevalent and modifiable (amenable to behavioral intervention) potential contributor to aging health care costs.

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