ESSAYS ON PHYSICIAN AND PATIENT BEHAVIOUR: ADHERENCE, ADOPTION AND DIFFUSION OF ANTIDIABETIC PHARMACEUTICALS

by

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Biographical Note

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She holds a BSc in Pharmacy from the School of Health Sciences - Polytechnic of Porto (2012) and a MSc in Health Economics and Management from School of Economics and Management - University of Porto (2014). Her MSc dissertation developed a Composite Leading Indicator for the Health Status in Portugal under the supervision of Professor Álvaro Almeida.

In 2015, she enrolled in the Doctoral Programme at the School of Economics and Management - University of Porto (FEP), under the supervision of Professor Nuno Tiago Bandeira de Sousa Pereira.

During the second and third years of her PhD (2017-2018) she worked as a researcher on a project entitled "Health, HIV, Cognitive Ability, and Risk Attitude as Predictors of Success of Small Businesses", which was a part of "The Micro and Small Enterprise Project" led by the University of Pennsylvania.

From 2014 to 2017 she worked as a pharmacist on a community pharmacy in Porto.

Recently, she has become a member of the statutory bodies of the Portuguese Association of Health Economics.

She has been presenting her research in national and international conferences.

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"Das tripas coração".

Abstract

This dissertation proposes to assess the decisions made by patients and physicians in the context of non-communicable diseases (NCDs) for which adherence plays a crucial role in disease management and health outcomes.

The data consider the universe of e-prescriptions associated with pharmaceuticals used to control *Diabetes* in Portugal from January 2015 to October 2019, and it was provided by Serviços Partilhados do Ministério da Saúde, EPE.

We begin our study by providing a brief contextualization on the institutional framework related with the Portuguese National Health System. This works as a transversal approach that introduces the reader about patient pathway, physician's work regime and treatment decision criteria.

The first essay studies the relevance of trust associated to the physician-patient interaction in medication adherence using a fractional regression approach and a two-way fixed effects model. Our findings suggest that the existence of a principal physician increases the adherence levels by 3 to 5pp.

The second essay considers the importance of adherence in improving health outcomes by using a fixed effect ordered logistic approach. Our results suggest that higher levels of adherence increases the probability of controlling diabetes with monotherapeutic schemes (level 1) by 10.4 pp. Furthermore, it decreases the probability of transition to dual therapy (level 2) by 0.9 pp as well as the probability to switch to triple therapy adjustment (level 3) by 9.5 pp.

Finally, the third essay explores the differences in the adoption and diffusion processes of innovations by physicians working in a single establishment (public *vs.* private sector) and those working in both public and private entities. Our findings suggest that the private sector (exclusivity regime) plays an important role on adoption as well as on diffusion. In job-duality regimes, the public sector has a more expressive role of adoption, while private setting play an active role on diffusion.

Resumo

Esta tese propõe estudar as decisões tomadas por médicos e utentes no contexto de doenças não-comunicáveis, onde a adesão à terapêutica tem um papel crucial na manutenção da doença e resultados em saúde.

Os dados utilizados consideram um universo de prescrições eletrónicas contendo fármacos utilizados no controlo da Diabetes em Portugal desde Janeiro de 2015 até Outubro de 2019, sendo estes cedidos pelos Serviços Partilhados do Ministério da Saúde, EPE.

Iniciamos o estudo a providenciar uma contextualização breve da ferramenta institucional do Serviço Nacional de Saúde. Este capítulo funciona como uma abordagem transversal que introduz o leitor sobre o percurso do utente, regimes de trabalho do médico e critérios de decisões terapêuticas.

O primeiro ensaio estuda a importância do processo de confiança associado à interação existente entre médico e utente através de duas abordagens: Fractional Regression Model e Two-way fixed effects model. Os resultados encontrados sugerem que a existência de uma relação entre o medico principal e o utente aumentam os níveis de adesão entre 3 e 5 pontos percentuais.

O Segundo ensaio considera a importância de adesão à terapêutica no melhoraramento dos resultados em saúde utilizando um modelo fixed effect ordered logistic. Os resultados sugerem que niveis mais alto de adesão à terapêutica aumentam a probabilidade de controlar a Diabetes em monoterapia em 10.4 pontos percentuais. Além disso, também diminuem a probabilidade de transitar para níveis superiores de terapêutica, nomeadamente terapia dupla e tripla em 0.9 e 9.5 pontos percentuais, respetivamente.

Por último, o terceiro ensaio explora as diferenças nos processos de adoção e difusão de inovações por medicos que trabalham num único sector (setor público *vs.* privado) e por médicos que trabalham em ambas as entidades. Os resultados sugerem que o setor privado (regime de exclusividade) participam ativamente na adoção e difusão destes fármacos. Em regimes de não-exclusividade, o setor público tem um papel mais expressivo na adoção, enquanto o setor público participa mais ativamente na difusão.

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Acronyms and abbreviations

2FE – Two-Way Fixed Effects

ATC – Anatomical Therapeutic Chemical

ATP – Active Treatment Provider

CNPEM – Código Nacional para a Prescrição Eletrónica de Medicamentos (National Code for the Eletronic Prescription of Pharmaceuticals)

DDD – Defined Daily Dosage

DOT – Duration of Treatment

E-prescription –Electronic Prescription

FRM – Fractional Regression Model

GP – General Practitioner

HHI – Herfindahl-Hirschman Index

ICD – International Common Designation

IRR – Incidence Rate Ratio

MPR – Medication Possession Ratio

NBM – Negative Binomial Model

NCD – Non-Communicable Diseases

NHS – National Health Service

NPI – Non-Pharmacological Interventions

OLS – Ordered Least Squares

PP – Percentage Points

SPMS, EPE – Serviços Partilhados do Ministério de Saúde, Entidade Pública Empresarial

T1DM – Type-1 Diabetes Mellitus

T2DM – Type-2 Diabetes Mellitus

UCP – Usual Care Provider

UCP (per year) – Usual Care Provider (per year)

1 Introduction

The application of a paperless prescription circuit in 2015, which became mandatory in 2016, enhanced safety in prescription and filling, and encouraged better communication and monitoring between health professionals, patients, and institutions. Through this procedure, the prescription, dispensing and selling became electronic for the physician, the patient, and the pharmacy. This opened the opportunity to study and understand better the drivers of prescription by a physician and of treatment adherence by patients.

Prescription drugs are not demanded directly by patients but are requested by a physician on their behalf. For this reason, the physician-patient interaction is an essential part of healthcare economics. The physician considers the patient's best interest, evaluating the set of available options, but his utility function only partly coincides with the utility function of the patient, as his self-interest is also a relevant argument of his utility function (Cutler et al., 2019; Ludwig et al., 2010).

Patients, on the other hand, have the power to decide whether to follow physicians' recommendations. When they don't, they may inadvertently be decreasing their utility, contributing to poorer health outcomes, and triggering avoidable healthcare costs that result from excess hospitalization and visits to the doctor as medical problems evolve into forms that are even more expensive to treat (Wilke et al., 2013).

Physicians can prescribe and monitor the effects of the drugs, while patients have the power to decide how many of the prescribed drugs they buy, where and when.

We propose to study patient's and physician's decisions in the context of non-communicable diseases (NCDs) for which prescription and adherence plays a crucial role in the disease management process and in improving health outcomes. NCDs kill 40 million people each year, the equivalent to 70% of all deaths globally, from which 87% are in high income countries (World Bank, 2013). Most NCDs are chronic conditions whose successful control requires proper diagnosis and adequate therapeutic regimen. We selected *Diabetes Mellitus*, a chronic condition with a worldwide prevalence and availability of new therapeutic alternatives.

In this dissertation, we develop three related topics that aim to add evidence on questions about treatment adherence, job duality, and innovation diffusion.

The first paper aims to evaluate the relevance of trust in medication adherence in the context of treatment of a chronic condition, where this impact may be more acute. More specifically, we aim to answer the following questions: Are patients more prone to higher

medication adherence when the prescriptions come from their principal physicians? Is this effect more evident when the relationship is established through a public provider, where there is less freedom to choose the physician that follows you, or a private one, where the freedom to choose is higher?

The second paper aims to study the importance of adherence in improving health outcomes also in the context of a chronic condition. We answer the following questions: are patients with lower adherence levels more likely to see their health level deteriorate and require more intensive treatment? Is this effect also influenced by the number and type of interaction with the physician, namely number of previous visits and whether the physician works in a public or private setting?

The third and final essay considers the issue of job duality and answers the following question: are there differences in the adoption and diffusion processes of innovations by physicians working in a single establishment (public *vs.* private sector) and those working in both public and private entities?

We apply recent and differentiated inference methods, including fractional response models, ordered logistic models, survival analysis and count models to a panel of patients' prescriptions and dispensing events. The data represent 10% of the universe of e-prescriptions associated with pharmaceuticals used to control *Diabetes* in Portugal, which includes more than 20 million observations that contain a pharmaceutical used to treat Type-1 and Type-2 *Diabetes Mellitus*. The individual prescription data is matched with individual, physician, prescription drug, pharmacy, and geographical characteristics, enabling assessing prescription and dispensing patterns while controlling for a broad range of cofounders.

Each prescription observation contains data on prescription date, dispensing date, cost of the drug to the NHS, price borne by the patient, number of pills, pharmaceutical form, number of packages, dosage, active ingredient, and respective codes (CNPEM and national drug code) and posology. The data is linked to prescriber and patient unique identifiers with information on: i) the patient age, gender, healthcare insurance, geographical location; ii) health provider/prescriber information including medical specialty, workplace, type of care – hospital vs. primary care; iii) and pharmacy information (geographical location).

The thesis is organized as follows.

Section 2 describes the relevant institutional framework within the Portuguese National Health System. This works as an introductory chapter that guides the reader about patient

pathways, clinical guidelines, physician's work regime, and treatment decision criteria. This section is transversal to the following sections.

Section 3, named "Tell me who you consult with, I'll tell you how compliant you are", analyses the relevance of trust associated to the physician-patient interaction in medication adherence.

Section 4, named "Highway to health: primary adherence and health improvement", evaluates the importance of adherence in improving health outcomes.

Section 5, named "Differences in dual-practice prescription of recent hypoglycaemic agents: a private vs. public provider approach", considers the differences in the adoption and diffusion processes of innovations by physicians working in a single establishment (public *vs.* private sector) and those working in both public and private entities.

Conclusions are shown in section 6.

2 Institutional Framework: The Portuguese National Health System

2.1 Public vs. Private Healthcare in a National Health System

Most healthcare systems comprise a combination of public and private provision and financing. The Portuguese health system is no exception. It is characterized by three co-existing and overlapping financing systems: the national health service, a set of special public and private insurance schemes for certain professions or entities (health subsystems) ,[1] and private voluntary health insurance (Brekke and Sogard, 2007; Simões et al., 2017). Consequently, in addition to the NHS, which provides universal coverage for a comprehensive set of services and is predominantly financed through general taxation[2], individuals can benefit from extra layers of insurance coverage from either or even both public and private health subsystems, and private voluntary health insurance, contracted through the employer or on an individual basis. Approximately 16% of the population is covered by a health subsystem, and around 25.8% of the population is covered by individual or group private health insurance (Simões et al., 2017).

In terms of provision, the NHS offers primary care and specialized hospital care. Out-of-pocket payments, including cost-sharing schemes, and direct payments for private sector services, are present. Cost-sharing schemes are present in both the NHS and private financing arrangements, and the most common are co-payments[3] (or user charges). The second take place for those services not covered by statuary pre-payment, including dental care and private ambulatory care (Simões et al., 2017).

Table 2.1 compiles the type of user charge associated to each healthcare setting.

[1] Membership is based on professional or occupational category.

[2] All residents in Portugal are covered by the NHS, irrespective of their socioeconomic, employment or legal status. The NHS is universal, comprehensive, and almost free at point of delivery (according to the Portuguese Constitution, Article 64). The universal and comprehensive nature of the NHS was defined at its inception (1979) and has been kept since then (Simões et al., 2017).

[3] Co-payments are defined as a fixed amount charged for the service. In Portugal, they are mostly noticeable to the population in emergency and outpatient visits.

Table 2.1 - Coverage for Health Services (source: Simões et al., 2017)

Healthcare Setting	Health Service	Type of user charge
Public Healthcare Units	Primary Care	Co-payment
	Specialist Visit (Hospital Care)	Co-payment
	Emergency visits	Co-payment / None[4]
	Prescription Drugs	Co-insurance[5]
	Inpatient stay	None[6]
Private Healthcare Units	Primary Care	Co-payment [a)] / Direct Payment [b)]
	Specialist Visit	Co-payment [a)] / Direct Payment [b)]
	Emergency visits	Co-payment [a)] / Direct Payment [b)]
	Prescription Drugs	Co-insurance
	Inpatient stay	None[c)]/Co-payment[a)]/Direct Payment[b)]

Notes:

a) If health subsystems exist.
b) If health subsystems do not exist, i.e., patient seeks private care and pays out-of-pocket.
c) If NHS agreements are applied.

[4] In case of payment exemptions and pediatric users.
[5] Coinsurance, in which the user pays a fraction of the cost of the service, is in place for pharmaceutical products covered by the NHS and by other health insurance arrangements (subsystems and voluntary health insurance) (Simões et al., 2017).
[6] Co-payment for inpatient stay was removed in 2009. There is no cap in OOP payments (Simões et al., 2017).

2.2 Patient Referral System

The patient preferred contact with the NHS is through the General Practitioner in a primary care unit. The patients access the primary care unit by signing up to any unit of their choice, within a geographical area defined around their residence (*Diário da República, 1.a série—N.o 82—27 de abril de 2017*). A General Practitioner is then assigned to each patient randomly.

Technically, individuals do not have direct access to secondary care provided by the NHS, since they are subject to a gatekeeping process managed by the General Practitioner. The patient gets access to secondary care by being referred to a specialist appointment at the hospital of their residence area [7,8,9,10]. The specialist is also randomly assigned to the patient.

The choice of provider is greater for those insured by a health subsystem or voluntary health insurance. Beneficiaries have the option to use the network of contracted providers, or to simply pay for a service in any provider without contract and later request partial reimbursement of expenses (Simões et al., 2017). Either way, patients can pay directly and visit a private health sector physician. In this alternative, the choice of provider is greater and allowed (Simões et al., 2017).

For the scope of this study, the number of appointments that the patient has access to varies according to their glycaemic control. On primary care, glycaemic control should be done as soon as the patient is diagnosed with Diabetes and, from then on, with 3 to 6 months intervals.[11]

Table 2.2 compiles the patient choice of provider.

[7] Patients often bypass their General Practitioner by visiting emergency departments.

[8] Secondary care is subject to a gate-keeping process, with strict rules for referral both for outpatient appointments and emergency room episodes (Simões et al., 2017).

[9] When referral from the NHS to the network of private contracted providers occurs, beneficiaries can choose to use a provider contracted with the NHS or one contracted with their health subsystem (Simões et al., 2017).

[10] NHS users can be referred to a hospital out of their residence area if waiting times for a given procedure or outpatient consultation are shorter (Decision No. 6170-A/2016, of 9 May).

[11] *Indicadores de Desempenho para as Unidades de Saúde Familiares – Ministério da Saúde*. Clinical therapeutic guidelines available for the Portugal are present at *Norma 052/2011* from *Decreto Regulamentar no 14/2012, de 26 de Janeiro (alínea a) do no 2 do artigo 2o)*.

Table 2.2 – Patient choice of Provider (source: Simões et al., 2017)

Choice of Provider	Is it available?	Applicability
Choice of Primary Care Physician	Yes	Available exclusively in the private sector. In the public sector, the choice is limited to availability of practitioner in the primary care unit related to the patient's residence area.
Direct access to Specialists	Yes	Available exclusively in the private sector. In the public sector, access to specialists requires referral by primary care (or emergency).
Choice of Hospital	Yes	Available exclusively in the private sector. In the public sector, hospital access is related to the patient's residence area.

2.3 Patient Clinical Pathway – Therapeutic Guidelines for Diabetes

The pharmacological approach considered for type-2 *Diabetes Mellitus* (T2DM) is defined in *Norma no. 052/2011 de 27/12/2011 (update at 27/04/2015).*

The use of any drug should consider the equilibrium between efficacy on glycaemia reduction, adverse effects, potential additional benefits, costs, and other concerns such as posology and need of glycaemia monitoring. The patient should participate in the treatment decision and communicate with the physician his concerns and goals.

The baseline approach also considers non-pharmacological interventions (NPI) in all stages of treatment. The pharmacological approach considers three-levels – mono, double and triple therapy. The transition between these levels requires a criteria decision such as the revision period and conditions for admission.

Table 2.3 provides information on the therapeutic decision criteria for Type-2 Diabetes Mellitus.

Table 2.3 - Clinical Guideline criteria decision for T2DM

Non-pharmacological interventions	Healthy food regime, Body Weight Control, Promotion of Physical Activity, Therapeutic Education (applied alone or in combination with therapeutic regime - mono, double or triple).		
Pharmacological Approach	Mono Therapy	Double Therapy	Triple Therapy
Decision Criteria	Decision Criteria: From Mono to Double Therapy Revision period: 3 months. Conditions: If after optimization of NPI and confirmation of therapeutic adherence, the glycaemic control is inadequate (HbA1c≥9%) with monotherapy, a second drug can be considered.	Decision Criteria: From Double to Triple Therapy Revision period: 3 to 6 months. Conditions: If after optimization of NPI and confirmation of therapeutic adherence, the glycaemic control is inadequate (HbA1c≥10% and glyceamia≥300mg/dl) with double therapy, a third drug or insulin can be considered.	

Further details regarding: (i) the pharmaceuticals belonging to ATC level 10, (ii) the drugs allocated to each therapeutic level as well as the conditions required are available on Tables 2.4 and 2.5, respectively[12].

[12] Further evidence and details are available at *Norma no. 052/2011 de 27/12/2011 (update at 27/04/2015).*

Table 2.4 - Characterization of pharmaceuticals belonging to ATC level 10

Drug	***Pharmaceutical Class***	***Launching***	***Degree of therapeutic Innovation*** [a)]	***DDD*** [b)]	***Average Cost (OOP per drug)*** [c)]	***Average Cost (OOP per class)***	***First Prescription*** [d)]	***Generic Drug***	***Antidiabetic agents (per prescription)***
Metformin	Biguanides	Nov. 27, 1961	No therapeutic innovation	2 g	1,430	1,430	No	Yes	1.101.923 (44.47%)
Glibenclamide	Sulfonylureas	Nov. 10, 1970	No therapeutic innovation	10 mg	1,375	1,655	No	Yes	583.788 (23.56%)
Gliclazide		Feb. 19, 2001		60 mg	2,068				
Glimepiride		Sept. 23, 2013		2 mg	1,803				
Glipizide		Feb. 15, 1972		10 mg	1,372				
Acarbose	α-glucosidase inhibitors	January 16, 1991	No therapeutic innovation	0.3 g	1,559	1,559	No	Yes	92.574 (3.74%)
Alogliptin	Dipeptidyl Peptidase-4 (DPP-4) inhibitors	**Sept. 13, 2013**	**Highly innovative**	**25 mg**	**2,217**	**2,592**	**Yes**	**No**	307.501 (12.41%)
Linagliptin		Aug. 14, 2011		5 mg	2,930		No	No	
Saxagliptin		Oct. 1, 2009		5 mg	2,710		No	No	
Sitagliptin		March 21, 2007		0.1 g	2,329			Yes	
Vildagliptin		Sept. 16, 2007		0.1 g	2,773			Yes	
Pioglitazone	Thiazolidinediones	Oct. 13, 2000	No therapeutic innovation	30 mg	4,062	4,062	No	Yes	24.474 (0.99%)
Nateglinide	Meglitinides	April 3, 2001	No therapeutic innovation	0.36 mg	2,556	2,556	No	No	13.181 (0.53%)
Canagliflozin	Sodium-glucose co-transporter-2 (SGLT2) inhibitors	**Nov. 15, 2013**	**Highly innovative**	**0.2 g**	**3,762**	**3,493**	**Yes**	No	128.287 (5.18%)
Dapagliflozin		Nov. 12, 2012		10 mg	3,280		No		
Empagliflozin		**May 22, 2014**		**17.5 mg**	**3,436**		**Yes**		
Dulaglutide [e)]	Glucagon-like peptide-1 (GLP1) receptor agonists	**Nov. 21, 2014**	**Highly innovative**	**0.16 mg**	**4,655**	**6,265**	**Yes**	No	61.169 (2.47%)
Exenatide [e)]		Nov. 20, 2006		15 mcg	5,454		No		
Liraglutide [e)]		June 30, 2009		1.5 mg	8,687				
Metformin + Alogliptin	Combinations of oral blood glucose lowering drugs	**Sept. 19, 2013**	**Modest therapeutic innovation**	**-**	**3,014**	**3,361**	**Yes**	No	842.223 (33.99%)
Metformin + Canagliflozin		**April 23, 2014**			**4,370**				
Metformin + Dapagliflozin		**Jan. 16, 2014**			**3,725**				
Metformin + Linagliptin		**July 20, 2012**			**3,469**				

Metformin + Pioglitazone		Dec. 11, 2007			2,997			Yes	
Metformin + Saxagliptin		Nov. 24, 2011			3,325			No	
Metformin + Sitagliptin		July 16, 2008			3,167		No	Yes	
Metformin + Vildagliptine		Nov. 14, 2007			3,341			Yes	
Glibenclamide + Metformin		March 9, 2010			1,001			No	
Pioglitazone + Alogliptin		**Sept. 19, 2013**			**2,215**		**Yes**	**No**	
Glimepiride + Pioglitazone		Nov. 12, 2007			3,429		No	No	
Empagliflozin + Metformin		**May 27, 2015**			**6,279**		**Yes**	**No**	
Insulin aspart (soluble)	Insulins and analogues for injection, fast-acting	Sept. 7, 1999	No therapeutic innovation	40 U	0,451	0,520	No	No	440.468 (17.78%)
Insulin glulisine		Sept. 27, 2004			0,656				
Insulin (human, soluble)		June 9, 1995			0,496				
Insulin lispro (soluble)		April 30, 1996			0,476				
Insulin (human, isophanic)	Insulins and analogues for injection, intermediate-acting	Feb. 21, 1997	No therapeutic innovation	40 U	0,701	0,737	No	No	
Insulin (human soluble+isophanic)		Feb. 21, 1997			0,598				
Insulin aspart (soluble+protamine)		Aug. 1, 2000			0,753				
Insulin lispro (soluble+protamine)		April 30, 1996			0,896				
Insulin degludec	Insulins and analogues for injection, long-acting	Jan. 21, 2013	No therapeutic innovation	40 U	0,749	0,926	Yes	No	
Insulin detemir		June 1, 2004			1,035		No		
Insulin glargine		June 9, 2000			0,994				

Notes:

a) The criteria used to classify the degree of therapeutic innovation consider the year of market introduction, the low availability of generic drugs for the group and the observation of the first prescription.
b) Defined daily dosage according to https://www.whocc.no/atc_ddd_index/?code=a10.
c) Out-of-pocket cost for the all period of analysis has into account quarterly variations imposed by the responsible entities.
d) First prescription observed after the period of observation of our sample – January 2015.
e) Injectable, however not considered as an insulin.

Table 2.5 - Therapeutic Guidelines for Diabetes

Revision period: 3 months.
Conditions: If after optimization of NPI and confirmation of therapeutic adherence, the glycaemic control is inadequate (HbA1c≥9%) with monotherapy, we can consider a second drug (check Norma no. 052/2011 de 27/12/2011 (update at

NON-THERAPEUTIC INTERVENTIONS (NPI)	Healthy food regime, Body Weight Control, Promotion of Physical Activity, Therapeutic Education (Applied alone or in combination with therapeutic regime - mono, double or triple)
MONOTHERAPY	Metformin (a) **OR** Sulfonylurea (b) **OR** α-glucosidase inhibitors **OR** DPP4i (c)

	Metformin	**Metformin**	**Metformin**	**Metformin**	**Metformin**	**Metformin**	**Metformin**	**Metformin**
	+	+	+	+	+	+	+	+
DOUBLE THERAPY	Thiazolidinedione	Sulfonylurea	DPP4i	SGLT2i	GLP-1 agonist	α-glucosidase inhibitors	Phenylalanine Derivate	Insulin

	Metformin	**Metformin**	**Metformin**	**Metformin**	**Metformin**	**Metformin**	**Metformin**	**Metformin**
	+	+	+	+	+	+	+	+
	Thiazolidinedione	Sulfonylurea	DPP4i	SGLT2i	GLP-1 agonist	α-glucosidase inhibitors	Phenylalanine Derivate	Insulin
	+	+	+	+	+	+	+	+
		Thiazolidinedione	Thiazolidinedione	Thiazolidinedione	Thiazolidinedione	Thiazolidinedione	Thiazolidinedione	Thiazolidinedione
	Sulfonylurea		Sulfonylurea	Sulfonylurea	Sulfonylurea	Sulfonylurea	Sulfonylurea	-
	DPP4i	DPP4i		DPP4i	-	DPP4i	DPP4i	DPP4i
	SGLT2i	SGLT2i	SGLT2i		SGLT2i	SGLT2i	SGLT2i	SGLT2i
	GLP-1 agonist	GLP-1 agonist	-	GLP-1 agonist		GLP-1 agonist	GLP-1 agonist	GLP-1 agonist
	α-glucosidase inhibitors	α-glucosidase inhibitors	α-glucosidase inhibitors	α-glucosidase inhibitors	α-glucosidase inhibitors		α-glucosidase inhibitors	α-glucosidase inhibitors
	Phenylalanine derivates	Phenylalanine derivates	Phenylalanine derivates	Phenylalanine derivates	Phenylalanine derivates	Phenylalanine derivates		Phenylalanine derivates
TRIPLE THERAPY	Insulin	Insulin	Insulin	Insulin	Insulin	Insulin	Insulin	

Revision period: 3 to 6 months.
optimization of NPI and confirmation of therapeutic adherence, the glycaemic control is inadequate (HbA1c≥10%; glyceamia≥300mg/dl) with double therapy, we can consider a third drug or insulin (check Norma no. 052/2011 de 27/12/2011 (update at 27/04/2015) for further evidence).

a) In monotherapy regimes, Metformin is the first line drug to be implemented together with all non-pharmacological recommendations.
b) Applied when there's intolerance to Metformin or its use is not indicated.
b) Applied when: (i) history of documented hypoglyceamia or (ii) the use of a Sulfonylurea is not indicated.

2.4 Physician Workplace and Work Regimen

The interaction between public and private healthcare provision within the NHS system considers the following sequence of events (Brekke and Sogard, 2007):

1. Legislation on whether or not to allow physicians to work in the private sector, i.e. dual practice;
2. Legislation on the public sector remuneration (wage);
3. Physicians' allocation of their time to the public sector, and if allowed, to the private sector;
4. Patients' demand for public and, if allowed, private medical treatment.

According to the Portuguese Law, physicians who transit to the medical special career terms have a work regimen (*Decreto-Lei n.o 177/2009 de 4 de Agosto*) which defines time allocation as follows:

a) 35 weekly hours, no exclusivity;
b) 35 weekly hours; exclusivity;
c) 42 weekly hours;
d) 35 weekly hours, no exclusivity and permanent availability;
e) 35 weekly hours; exclusivity and permanent availability.

The non-exclusivity regimen allows physicians to practice in more than one workplace, private or public.

2.5 Portuguese Drug Prescription System

In 2011, the government made electronic prescriptions mandatory for physicians with a volume of prescriptions of at least 50 prescriptions per month. Paper prescriptions were allowed, but only if the system failed

In 2015, the government declared the implementation of a paperless prescription circuit (de-materialization). The prescription, dispensing and selling became electronic for physician, patient, and pharmacy. Electronic means were prioritized over paper within the NHS, enhancing the monitorization of prescriptions. It became a compulsory method since 2016, but both materialized electronic and manual prescription still coexist (only for the exemptions mentioned before).

Electronic prescribing aims to increase safety in prescription and filling and promotes better communication and monitoring between health professionals and institutions. It is available under the same rules for both public and private institutions, and for both over the counter and prescription drug. It also gives the patient the authority to decide how many of the prescribed drugs he buys, where and when, since drugs associated to e-prescriptions can be filled at different pharmacies and at different dates.

Physicians are recommended to prescribe by International Common Designation indicating the pharmaceutical form, dosage, package size and posology. Patients have the right to choose any pharmaceutical within the same ICD, pharmaceutical form, dosage, and package size to the ones prescribed.

Each line of prescription contains up to a maximum of:

- 2 packages, in the case of drugs used in short- of intermediary-term treatments. They are valid for 60 straight days from the moment of the date of emission of the prescription.
- 6 packages, in the case of drugs used in long-term treatments. They are valid through 6 months from the moment of the date of emission of the prescription.

The e-prescriptions also contain information regarding the prescribing physician, the patient and the pharmaceutical. Prescriptions can be renewable for long-term treatments, in which antidiabetic medication is included. Renewable and single prescriptions are valid for six months and 30 days from the date on the prescription, respectively.

In Portugal, access to antidiabetic drugs requires a prescription and the government reimburses part of the therapeutic regime. The extent of coverage varies according to the

following categories: A (it included all pharmacological groups and subgroups with a reimbursement rate of 90%), B (reimbursement rate of 69%), C (reimbursement rate of 37%) and D (reimbursement rate of 15%). These rates vary according to the therapeutic indications of the medicine, its use, the prescribing entities, and the increased consumption for patients with certain conditions.

There exists a special regimen for reimbursement which adds 5% for rate A and 15% to rates B, C and D for pensioners whose total annual income is below a predefined amount. It should be highlighted that these reimbursement rates are in place since 2010.

3 Tell me who you consult with, I'll tell you how compliant you are.

Abstract

Adherence to medication is key to ensure recovery from illness, particularly in the context of chronic conditions, that require an effective disease management process to avoid sudden deterioration of the individuals' health and the additional need for care. Higher adherence levels are reached when patients express higher levels of satisfaction, which usually happens when they are treated by physicians they know and trust.

We hypothesize that the physician-patient relationship, the setting where this interaction is established, and the frequency of that interaction impact individual behaviour, more specifically primary adherence with regards to medication for antidiabetic drugs.

We deploy fractional regression methodologies using a panel of patients' prescriptions and dispensing events with the universe of all prescriptions and dispensing in Portugal from January 2015 to October 2019 (N=1,363,778). The individual prescription data is matched with individual, physician, prescription drug, pharmacy and geographical characteristics, allowing for the control of a broad range of cofounders and time-constant physician-specific characteristics.

We estimate an increase in adherence levels when the prescription is issued by the principal physician.

Keywords: Medication Adherence, Prescription Drugs, e-prescription, Diabetes Mellitus, Portugal

JEL Codes: I11, I13, I15

3.1 Introduction

"*The relationship between patients and their primary care provider is widely valued, but how much does it matter for healthcare consumption and health?"*
– (Sabety, 2020).

Many medical goods, such as prescription drugs, are not demanded directly by patients (principal), but are requested by a physician (agent) on their behalf. The physician considers the patient's best interest, evaluating the set of available options, but her utility function only partly coincides with the utility function of the patient, as her self-interest is also a relevant argument of the utility function (Cutler et al., 2019; Ludwig et al., 2010). A stable, trustworthy, and long-lasting agency relationship is important, as it enables physicians to collect and process more information about their patients' medical history and to cater better to their needs.

Patients, on the other hand, have the power to decide whether to follow physicians' recommendations. When they don't, they may inadvertently be decreasing their utility, contributing to poorer health outcomes, and triggering avoidable healthcare costs that result from excess hospitalization and visits to the doctor as medical problems evolve into forms that are even more expensive to treat (Wilke et al., 2013). The decision to adhere to the prescribed treatment is intrinsically related to the level of trust between principal and agent (Dwyer et al., 2012; Lind, 2019; Vermeire et al., 2001). Previous studies have shown that patients express higher levels of satisfaction when treated by physicians they know and trust, leading to higher levels of adherence (Johnson et al., 2016; Lind, 2019).

The study of the relationship involving the patient and the physician has been gaining relevance over the recent years due to its direct impact on the patient's health. However, as mentioned by Sabety (2020), "*researchers still lack strong evidence for whether and to what extent this relationship matters for patients, despite the number of recent and proposed reforms affecting this relationship*".

In our case, this challenge may be addressed by: (i) having access to prescriptions that allow us to study the roles of demand- and supply-side factors in shaping the physician-patient interaction in the process of medication adherence; (ii) observing multiple

interactions between patients and physicians, evaluating the impact of this relationship on medication adherence.

Prescriptions are an output of the patient-physician relationship, but they also translate the implemented therapeutic regime, as well as the patient access to it through the dispensing pattern. When we observe if the prescription is filled, we observe, although incompletely, the patient's decision to proceed or not with the recommended treatment provided by the physician.

In this paper, we evaluate the relevance of trust in medication adherence in the context of the treatment of a chronic condition, where this impact may be more acute (Abulhaj et al., 2013; Alowi and Kani, 2018; Gönül et al., 2001; Socha, 2010; Yağar and Dökme, 2017). More specifically, this study answers the following questions: Are patients more prone to higher medication adherence when the prescriptions come from their principal physicians? Is this effect more evident when the relationship is established through a public provider, where there is less freedom to choose the physician that follows you, or a private one, where the freedom to choose is higher?

To answer these questions, we build on the framework of a physician-patient agency relationship and use a Fractional Regression Model as our principal econometric approach. This model is applied to both cross-sectional and longitudinal samples. The dependent variable is the fraction of the prescribed drugs that is acquired by the patient. The main variable of interest is the nature of the relationship between the physician and the patient, namely whether the prescription is issued by the physician with whom the patient has more interaction with. Other econometric models, such as a standard OLS, Probit model and Two-Way fixed effects model are also used to provide robustness to the results.

We test our hypotheses on a large longitudinal matched physician-prescription-patient dataset for all Portuguese e-prescriptions collected from *Serviços Partilhados do Ministério da Saúde* between January 2015 and October 2019, covering all regions in Portugal. Each selected prescription contained at least one pharmaceutical used to treat Type-1 and Type-2 Diabetes Mellitus. *Diabetes* is a common chronic condition, with a worldwide prevalence and broad availability of therapeutic alternatives. Its successful control requires proper diagnosis and adequate therapeutic regimen. Without them, severe

complications and increasing mortality can emerge, as well as high economic burden for both patients and healthcare system.

We build on Koulayev et al. (2017) two-way fixed effects model to estimate the impact of the principal physician on medication primary adherence while accounting for patient, healthcare system, and treatment characteristics. To the best of our knowledge, no other paper has developed such a comprehensive approach to this topic.

We make some key contributions to the literature. First, we focus on medication primary adherence instead of secondary adherence, a much more widely studied topic. Primary adherence, which measures the first contact of the patient with its therapeutic regime, has been less studied due to data unavailability, but the introduction of electronic prescriptions allowed for a long-term follow-up of patients and their behaviour regarding dispensing procedures, as well as provided information on issued, but not filled, prescriptions. Second, we consider the differentials on adherence by type of provider - public *vs.* private, primary *vs.* hospital care, and general practitioners *vs.* specialists, which overcomes the limited focus of previous studies on primary care physicians (Fadlon and Van Parys, 2020; Kwok, 2019; Sabety, 2020). This is particularly interesting as we expect this to be correlated with trust levels.

Our results are aligned with the findings by Atella et al. (2017), Koulayev et al. (2013), Koulayev et al. (2017) and Orom et al. (2018). We estimate an increase on adherence levels by 3 to 5 percentage points (pp) when the prescription is issued by the principal physician. This positive influence of physicians on patients' health behaviour and on the decision to follow the recommended therapy supports the need for customized interventions and the increase in the number of 'Family Doctors'. That could improve adherence and reduce indirect costs to the health service.

Other finding is that prescriptions coming from the public health setting have lower levels of adherence by 1.2 to 7.2 pp in comparison with those coming from private health setting. More precisely, if the principal physician works in the public sector, then the levels of adherence decrease by approximately 3pp in comparison with main physicians located in the private sector. This is particularly relevant since the Portuguese NHS is mainly public and each patient is usually assigned to a "Family Doctor". In fact, primary care physicians can informally coordinate care and formally manage access to specialists (Kwok, 2019),

guiding the patient and helping him access a multidisciplinary team of experts in order to produce better health outcomes.

Our results have some limitations. First, we do not have any information regarding some sociodemographic features such as the patients' education and income or information on some important doctor-level covariates such as age, gender, or years of experience. Second, we do not have visibility on whether there was a relationship between the patient and the physician prior to our period of analysis.

The study is organized as follows. The next section reviews the literature on medical adherence. Section 3.3 presents the data and the methodological approach. Section 3.4 presents the main results and section 3.5 provides a brief description of the robustness tests. These results are discussed in section 3.6. Section 3.7 concludes.

3.2 Theoretical Background

3.2.1 Definition of Adherence

The terms “adherence” and “compliance” are often used interchangeably to characterize the extent in which a patient decides to follow the prescribed treatment. However, they have different meaning, and the difference relies on how one perceives the relationship between the patient and the healthcare provider (Hugtenburg et al., 2013).

Compliance is known as “the extent to which a person’s behaviour in terms of taking medications, following diets or executing lifestyle changes coincides with medical or health advice” (Vermeire et al., 2001). It is a paternalist approach as the patient passively follows the practitioners’ instructions, and the treatment plan is usually not based on a therapeutic alliance or contract established between patient and physician (Matias, 2019; Osterberg and Blaschke, 2005; Stavropoulou, 2012).

Adherence, on the other hand, “corresponds to the level of commitment to the agreed recommendations coming from a healthcare provider” (Hugtenburg et al., 2013). It implies a more proactive attitude by giving the patient an active role. The patient, after being properly informed by the doctor, can decide whether to follow her recommendations (Lamiraud and Geoffard, 2007; Stavropoulou, 2012). This is the preferred approach to this topic (Hugtenburg et al., 2013).

In the current study, however, we use adherence to refer to patients’ compliance to the prescribed medication as we cannot observe what was the level of the patients’ involvement in the therapeutic decision.

3.2.2 Patient’s Therapy and Medication Adherence: What are the contributing factors?

Adherence is a dynamic, complex, and multidimensional issue, especially when involving chronic conditions management. It comprehends the decision about whether to initiate the treatment, follow the prescribed regimen, and discontinue the adopted pharmacotherapy (Cramer, 2004; García-Pérez et al., 2013; Hugtenburg et al., 2013; Kennedy-Martin et al., 2017; Tang et al., 2017; WHO, 2003)

The World Health Organization considers several factors associated with drug adherence, including characteristics related to patient, healthcare provider, healthcare system, treatment, and socioeconomic related-factors (Atella et al., 2017; Borgsteede et al., 2011; Fernandez-Lazaro et al., 2019; Jacobs et al., 2016; Lam and Fresco, 2015). We group them into three categories of characteristics: (i) patient related (includes demographic and socioeconomic status, sociocultural as well as behavioural factors); (ii) treatment related (considers the therapeutic regimen complexity, polypharmacy, drug perception, duration of the treatment as well as prescription characteristics); and (iii) provision related (comprises the provider-patient relationship, drug costs, access and provision) (Gibson et al., 2011; Jacobs et al., 2016; Karter et al., 2018; Karve et al., 2009; Kirkman et al., 2015; Koulayev et al., 2017; Polonsky and Henry, 2016; Vaidya et al., 2013)

The three categories are interrelated. Examples of this interrelation include a complex therapeutic regimen, lack of communication between patient and physician, patient's belief that the treatment is not necessary, and patient's inability to follow the treatment due to its costs (Hugtenburg et al., 2013).

Previous studies on adherence associated to long-term therapeutic regimens estimated that, on average, 20 to 80% of patients do not adhere to medical therapies (Blackburn et al., 2013; Fischer et al., 2010; Freccero et al., 2016; Gellad et al., 2009; Krueger et al., 2005). Non-adherence levels associated to diabetes range from 7% to 64% (Bloomgarden et al., 2017; Kirkman et al., 2015; Pladevall et al., 2004; Polonsky and Henry, 2016; WHO, 2003). [1] Our data report that 17.86% of the e-prescriptions were never dispensed.

Non-adherence wastes resources and may lead to severe complications, avoidable hospitalizations and increasing mortality, as well as high economic burden for both the patients and the health service. It also leads to a loss of productivity and absenteeism. Each year, non-adherence costs the EU €1.25bn (Atella et al., 2017; Bussière et al., 2020; Chan et al., 2020; DiMatteo, 2004; Kennedy-Martin et al., 2017; Lublóy et al. 2015; Morillas et al., 2015; Orom et al., 2018; Osterberg and Blaschke, 2005; Roebuck et al. 2011; Stavropoulou, 2011; Stavropoulou, 2012; Tang et al., 2017; Van Dulmen et al., 2007; Zullig et al., 2015).

[1] Poor levels of adherence lead to worse blood glucose levels, higher rates of acute metabolic events, increased risk of hospitalization and mortality, and higher healthcare costs than necessary (Wilke et al., 2013).

Nonadherence can happen in all treatment phases. Patients – the principal decision-maker towards therapeutic adherence - may decide not to collect their medicines from the pharmacy and not initiate treatment (primary nonadherence) (Pladevall et al., 2004), or they may not take their medication as prescribed, do not refill the prescription on time, or discontinue their medication altogether (secondary nonadherence) (Hugtenburg et al., 2013, Lam and Fresco, 2015; Lemstra et al., 2018; Pagès-Puigdemont et al., 2016; Wilke et al., 2013). [2]

Our focus is on primary adherence that we measure by: (1) the rate at which patients collect their newly prescribed medication from pharmacies (patient-level of measurement[3]), or (2) the proportion of prescriptions that were not filled within a stipulated period (prescription-level of measurement). Still, we test the robustness of our findings by also using secondary adherence as our dependent variable.

3.2.3 Physician-Patient Interaction: A trustworthy agency relationship

Physicians play a central role in addressing patients' needs by prescribing medication, screening adherence, and suggesting lifestyle changes (Orom et al., 2018).

The physician-patient interaction embodies an agency relationship, in which healthcare professionals act as agents for patients (principal) and mostly decide and recommend on their behalf what health services/products they need (Folland and Goodman, 2016; Mooney and Ryan, 1993). Motives behind this delegation of power are related with the patients' awareness of their insufficient knowledge about the most appropriate decisions to be made. The best way to resolve this is to rely on an informed agent such as the physician (Folland and Goodman, 2016). This physician-patient interaction can be more

[2] Electronic prescriptions solve the difficulty of capturing primary adherence since they allow us to track patient's behaviour and decisions towards prescriptions over time (Lee et al., 2018; Lemstra et al., 2018).
[3] Measurements made at the patient level can over or underestimate primary adherence (Lemstra et al., 2018).

"doctor-centered"[4] or more "patient-centered"[5], and patients may prefer one interaction style over the other (Krupat et al., 2000).

A perfect agent would make the choices that the principal would make if he had the same information, professional knowledge, and expertise (Blomqvist, 1991; Folland and Goodman, 2016; Gafni and Charles, 2009). But the doctor's and the patient's utility functions are independent (Mooney and Ryan, 1993), i.e., the agent has his own utility function, which he seeks to maximize. The utility functions only partly coincide (Culyer and Newhouse, 2000; Ludwig et al., 2010; McGuire, 2000), which makes the physician an imperfect agent for the patient.

The asymmetry of information in healthcare creates an incentive problem, resulting in more (or less) treatment being "demanded" than would have been the case if the patient had full information and knowledge (Mooney and Ryan, 1993). Another issue is the difference between information and knowledge, i.e., the quantity and quality of information a patient receives and whether he can understand it (Scott and Vick, 1999). For this reason, a good communication between both parties is fundamental.

The larger is the information asymmetry and the patients' vulnerability concerning their health, the more relevant the trust relationship between principal and agent becomes (Shortell et al., 1998). Trust is usually forward-looking and reflects a commitment to an ongoing relationship, being built through repeated interactions (Rowe and Calnan, 2003).[6] Patients tend to visit the physician more often, express higher levels of satisfaction, and are willing to pay more to continue being treated by the providers they trust (Johnson et al., 2016). This leads to higher levels of adherence, reduced adverse clinical outcomes (Johnson et al., 2016), and lower healthcare costs to both patient and health system (Wilke et al., 2013).

[4] This is a more paternalistic approach. Physician is dominant and the medical problem is the central concern to be addressed. She recommends the treatment to the patient and tries to persuade him to accept it, not taking into consideration the patient's opinion in the decision process (Choné and Ma, 2011; Hargis and Castel, 2018; Ito, 2013; Pagès-Puigdemont et al., 2016).

[5] Physicians create a relationship with the patient, who is involved in the decision-making process. The patient is the focal point of treatment. Both parties deliberate or discuss treatment preferences and decide which treatment is preferable. The patient provides information on his needs, values, preferences, lifestyle, beliefs and knowledge about the illness and the treatment alternatives (Choné and Ma, 2011; Hargis and Castel, 2018; Ito, 2013; Pagès-Puigdemont et al., 2016).

[6] Trust in physicians can be divided in two dimensions: (i) trust in the physician's cognitive abilities and technical competence, and (ii) affect based trust such as characteristics of empathy and compassion (Lind, 2019).

Through systematic interactions, patients learn about a physician's competence and become aware of the physician's trustworthy behaviour (Lind, 2019). This constitutes the fundamentals of interpersonal trust, which is often understood as the "optimistic acceptance of a vulnerable situation in which the truster believes the trustee will care for him and act on his best interests" (van der Schee et al., 2006) [7]. This involves a set of beliefs or expectations about a physician behaviour (Dwyer et al., 2012; Lind, 2019; Peter and Bilton, 2018).

Repeated interactions are also potentially beneficial because the physician becomes, over time, more familiar with the patient's disease and medical history, social circumstances, values, and preferences (Culyer and Newhouse, 2000; Saxell, 2014). The physician may thus learn the quality of the patient's match to the drug, enabling her to make better treatment choices (Mooney and Ryan, 1993; Saxell, 2014).

A good match between both parties is a product of the attitudes and orientations that the two participants bring to the relationship (Krupat et al., 2000). By improving communication, enhancing patient involvement, confidence, and trust in the therapeutic process, a good match increases adherence and consistency in behaviours (Atella et al., 2017; Borgsteede et al., 2011; Dwyer et al., 2012; Gellad et al., 2009; Krueger et al., 2005; Lind, 2019; Orom et al., 2018; Schwartz et al., 2017).

Koulayev et al. (2013) show that primary care physicians exert substantive influence on patients' health behaviour. Koulayev et al. (2017) analyse population-level registry data that track patient adherence over time and across different physician–patient pairings to provide the first empirical evidence on the relative importance of patient-level, physician-level, and match-level factors as determinants of patient medication compliance. Their research helps classify the impact of different inputs into the health investment function – compliance with clinical therapy being the most immediate and measurable manifestation of health investment. Another notable finding is that a sizeable component of the variation in patient compliance across doctor–patient pairs cannot be explained by fixed patient-specific or doctor-specific characteristics. Instead, it appears that the quality

[7] Interpersonal trust is characterized by an individual's confidence in the words, actions, and decisions of another person. It includes proper and good means of communication from both parties such as listening, understanding, explaining, and expressing care (empathy) (Dwyer et al., 2012; Lind, 2019). Higher levels of interpersonal trust encourage patients to reveal stigmatized information, accept prescribed changes in risky behaviour, share thoughts and feelings, so disorders can be diagnosed, and the treatment accepted (Lind, 2019).

of the doctor–patient match has a separate and important contribution. This suggests that the process by which patients are matched to doctors in a healthcare system is a significant determinant of the overall level of a patient's medication compliance.

Atella et al. (2017) also show that the physician unobserved heterogeneity is an important determinant of health status, although patient heterogeneity appears to be significantly more important in explaining its variability. Patients can negatively contribute to health outcomes through lack of understanding of their disease, lack of involvement in the decision-making process, lack of adherence to therapy, and lack of medical literacy. On the other hand, physicians may fail to contribute to improve patient health outcomes, as they often do not recognize medication nonadherence in their patients, prescribe complex drug regimens without explaining their benefits and side effects, or do not consider the potential financial burden for patients. Finally, the way patients and physicians interact may help overcome much of these difficulties. This suggests that physicians play a role in shaping patients' health status that goes far beyond the standard determinants of health usually analysed by the clinical and health economic literatures.

Orom et al. (2018) complemented this perspective by showing that the quality of the physician-patient interaction is a significant factor in treatment adherence and therefore is likely to ultimately improve patient outcomes and healthcare efficiency. They consider that greater trust in physicians is associated with improved treatment adherence, lifestyle change, and ultimately better clinical outcomes. Also, a more patient-centred care, where patients are involved in decision making by the physician, is also associated with better adherence.

More recently, Kwok (2019) concludes that primary care physician practice styles can affect healthcare use in the long run showing that patients who switch from a primary care physician whose other patients have low utilization to one whose other patients have high utilization experience increases in long-run utilization of care, whereas patients who switch in the opposite direction experience decreases.

Fadlon and Van Parys (2020) provide evidence on how primary care physicians practice style intensity affects the care that patients receive. They consider that primary care physicians are institutionally positioned to play a central role in healthcare provision and, in most cases, work as patients' principal physician, and may have more continuous interactions with their patients than other types of healthcare providers. They conclude

that the practice styles of primary care physicians could have long-lasting and far-reaching consequences on the quantity and quality of patient healthcare utilization and, hence, potentially on the patient health.

Sabety (2020) follows a similar approach and shows that relationships determine where patients demand care and that the relationship with the primary care physician is moderately important for patients' health.

The study of the relationship involving the patient and the physician is relevant and has been a target of research interest in the recent years due to its direct impact on patient's health. However, as mentioned by Sabety (2020), "*researchers still lack strong evidence for whether and to what extent this relationship matters for patients, despite the number of recent and proposed reforms affecting this relationship*".

3.3 Data and Methodological Issues

3.3.1 Data

Prescriptions are an observable output that emerges from the patient-provider relationship. They reflect the supply side of health provided by physicians and the demand for treatment required by a patient. They also reflect the immediate decision by the patient to proceed or not with the treatment recommended by the physician. The access to this output through large datasets containing patient-provider linkages makes the study of the interaction between the physician and the patient and its impact in adherence possible.

In this study, we use a large longitudinal matched physician-prescription-patient dataset containing e-prescriptions collected by *Serviços Partilhados do Ministério da Saúde* (SPMS) between January 2015 and October 2019, covering all regions in Portugal. [8]

Our data comprise the pharmacological class A10 - Drugs Used in Diabetes: A10A (Insulins and Analogues) and A10B (Blood Glucose Lowering Drugs, excl. Insulins), complemented with information from the Therapeutic Group 8 of the Portuguese Therapeutic Medical Record (subclass 8.4. "*Insulinas, antidiabéticos e glucagon*").[9]

The data are a representative 10% of the universe of e-prescriptions associated with pharmaceuticals used to control *Diabetes*, which comprises more than 20 million observations of the prescriptions that contained any pharmaceutical used to treat Type-1 and Type-2 *Diabetes Mellitus*.

The dataset covers 27,937 physicians, 128,155 patients, 2,477,672 e-prescriptions and 42 different anti-diabetic pharmaceuticals, including oral hypoglycaemic agents and insulins. Prescriptions were selected if: (1) the patients were 18 years or older and (2) if they had been prescribed with anti-diabetic pharmaceuticals within the selected time range.[10]

SPMS provided anonymized information at the prescription level (id number, prescription date, dispensing date, cost of drug for the NHS, price supported by the patient, number of pills, pharmaceutical form, number of packages, dosage, active ingredient, and respective codes (CNPEM and national drug code) and posology). We

[8] E-prescribing data recorded all electronic prescriptions issued, regardless of whether they were eventually filled or not.

[9] Further details can be assessed at https://app10.infarmed.pt/prontuario/frameprimeiracapitulos.html

[10] Dataset does not include other prescriptions for the patient if they did not include antidiabetic drugs at all.

also had access to information on the patient (age, gender, healthcare insurance, geographical location, health insurance), healthcare provider (medical specialty, workplace, type of care – hospital vs. primary care) and pharmacy where the prescription was dispensed (geographical location). Each line of observation corresponds to a single prescription.

We only considered oral hypoglycaemic agents for the purpose of this study. Although we can control for insulin use and dispensing patterns, insulin dosage instructions depend on glycaemic levels that we do not observe (Roebuck et al., 2011). The final panel observes 27,125 physicians, 121,727 patients, 1,363,778 e-prescriptions events and 28 different oral anti-diabetic pharmaceuticals.

The dataset has important attributes. First, it covers an extremely large number of patients and physicians. Second, it provides rich administrative data on physicians' characteristics related to accumulated experience during the observed period. Third, it provides information on pharmacy visits and their translation into medication purchasing patterns. Finally, it allows us to match patients and physicians and provide information on the mechanisms and intensity of their interaction.

Still, the dataset has some limitations. First, there is no information on patients' socioeconomic characteristics or on their demographics such as race/ethnicity, years of education, employment status, number of people in the household and marital status. [11] Second, we have no information on sociodemographic aspects of the physician such as age, gender, place of medical education, level of education and year of graduation from medical school.

3.3.2 Adherence Measure

We focus our attention on primary adherence, a patient-level measurement. Our aim is to determine the rate of dispensed drugs per prescription as follows:

$$share\ dispensed\ drugs_{it} = \frac{\sum dispensed\ drugs_{it}}{\sum total\ prescribed\ drugs_{it}},$$

where i and t index the patient and the date of prescription, respectively.

[11] We inferred some of this information by (i) considering that individuals with the higher level of reimbursement belong to a lower income group, or (ii) using publicly available average household income for each district.

This measure is a fraction that can assume values between 0 (no drug was dispensed) and 1 (all drugs were dispensed). It is an aggregated measure as it adds all drugs that were acquire per prescription even if the acquisition was done through multiple visits to the pharmacy.[12] An alternative measure for primary adherence was also considered to test for the robustness of our findings. In this case, the binary variable assumes the value zero if a prescription is not filled at all and one if at least one drug is dispensed by the pharmacy.[13].

Finally, and considering that most of the previous studies have used secondary adherence as the dependent variable, we also ran all our regressions using secondary adherence as our dependent variable. In this case, secondary adherence is computed according to the following formula:

$$MPR_{it} = \frac{\text{Average of } \sum \text{(days of supply for all medication fills) } or \text{ Duration of Treatment (DoT)}}{N\text{umber of days in specific period}}$$

where i and t index the patient and date of filling, respectively.

Total days' supply or DoT is calculated by taking the stock of drugs in the patient's possession, in milligrams, and dividing it by the defined daily dosage (DDD). The number of days covers the difference between dates of fillings.

There could be situations in which a patient could accumulate leftover stock and have an over-possession ratio ($MPR > 100\%$) in certain moments in time. In those case, we opted to truncate the measure to 1.

3.3.3 Principal Physician Measure

In chronic diseases, the patients need to see a physician regularly to have access to prescriptions and feedback on the disease evolution. The physician with whom the patient maintains a more regular interaction and who guides and adjusts the treatment plan is considered by us to be her principal physician.[14]

[12] Patients can opt to fill the entire prescription immediately, or they can adjust their purchasing pattern to their needs by going to the pharmacy as many times as the number of prescribed packages. With e-prescriptions, patients can get part of the prescribed medicines without the prescription becoming invalid, with the additional benefit of being able to pick the remaining packages when and where they prefer.

[13] The binary variable was considered using a Probit Model.

[14] It reflects the extent to which a patient's visits are concentrated in a single provider or practice group (Pollack et al., 2016).

In our paper, the prescribing physician is classified as the principal physician according to the following alternatives:[15]

1. Usual Care Provider (UCP): We consider the number of interactions between both parties and classify a physician as the principal physician if she is the one with more visits (mode) by that patient over the observed period.[16]
2. Active-Treatment Provider (ATP): The physician is considered the principal physician for a patient due to its guidance and follow-up on the active treatment. This approach uses the long-term relationship by considering the physician who is responsible for the active treatment (according to implemented therapeutic guidelines), i.e, the physician responsible for the higher number of therapeutic choices and changes.
3. Usual Care Provider *per* year (UCP- *per* year): Same approach as the UCP but the measure is considered for each year separately.

We also study the impact of the setting where the relationship happens. In the public system, physicians are randomly assigned to patients. Although this can also happen in the private sector, patients are usually allowed to choose the physician and remain with her if they want. Evidence shows that the patients present higher adherence levels when associated to physicians they know and trust better. In the case of the private sector, they can choose and switch physicians as much as they want until reaching a point where the best fit is achieved. This should make the relationship between physician and patient stronger in the private sector.

[15] As a complementary measure we used a Herfindahl-Hirschman Index (HHI) to reflect the extent an individual's visits during an episode of care are concentrated with a single or group of providers (Pollack et al., 2016). This perspective distinguishes a patient whose care is equally divided across two providers and a patient who interacts almost exclusively with one provider but had a single consultation with an alternate provider (Agha et al., 2017). This index is commonly used in economic analyses of market concentration (Pollack et al., 2016). It considers the order of visits, not just their concentration or dispersion among providers. It equals the fraction of sequential visits pairs at which the same provider is visited, i.e. same provider being visited at both the previous and current visits (Pollack et al., 2016). The results yielded using this variable are presented in appendix 3.10, appendix 3.11 and appendix 3.14, to appendix 3.25.

[16] This is like the Bice-Boxerman Continuity of Care Index which reflects "*the extent to which a given individual's total number of visits for an episode of illness or a specific time period are with a single or group of referred providers*" (Pollack et al., 2016).

3.3.4 Methods

We aim to analyse the impact of trust associated to the physician-patient relationship in the percentage of prescribed medicines that are filled. We do that by considering a Fractional Response Model (FRM).

Other econometric models, such as a standard OLS, Probit Model[17] and Two-Way fixed effects (2FE) Model are also used to verify the robustness of the results. The main variable of interest is the nature of the relationship between the physician and the patient, in particular by evaluating if prescriptions issued by the physician the patient has more interaction with exhibit higher adherence levels.

Our analysis is implemented at the patient-level, meaning that unobserved heterogeneity and its possible correlation with the explanatory variables may occur. The regression model should allow for unobserved time-constant individual effects to be related to individuals' characteristics. The approach considered by Papke and Wooldridge (2008) allows for time-constant unobserved effects that can be correlated with explanatory variables. They suggest the use of a Generalised Estimation Equation (GEE) Model or the new Fractional Probit Regression (FPR) Model to deal with possible within-subject correlation. We adopt the approach by Wooldridge (2019), which extends (Papke and Wooldridge, 2008) to unbalanced panel data.

The following equation describes our object of study:

$$sharedispensed_{it} = \beta_0 + \beta_1 principalphysician_{it} + \beta_2 \boldsymbol{X}_{it} + \varepsilon_i,$$

where i and t index the patient and date of prescription, X_{it} is a set of control variables for patient (gender, age, health insurance, region, income level, disease severity and comorbidities), healthcare system (principal physician measure, physician specialty, health sector – public/private, type of care – primary/hospital care, physician's region, principal physician and health sector interaction, number of other physicians seen by the patient and visits to other physicians), and treatment characteristics (renewable prescription, induce prescription, first-visit, first 6 months of treatment), and ε_i is a random error term assumed to be uncorrelated with the regressors.

When dealing with unbalanced panels we must add to this equation four other components: (i) explanatory variables averages for each i; (ii) time dummies; (iii) time

[17] This approach considers a binary dependent variable, that assumes the value zero if a prescription is not filled at all and one if at least one drug is dispensed by the pharmacy.

averages for each i; and (iv) dummies for the number of total time periods used for each i. Wooldridge (2019) introduces a series of selection indicators for each i, $\{s_{ij1}, \dots, s_{ijT}\}$, where $s_{ji1} = 1$ if period t can be used in the estimation for unit ij. In this case, the information is only used if a full set of data is observed. Therefore, $s_{ij1} = 1$ if and only if (X_{ijt}, y_{ijt}) is fully observed; otherwise $s_{ijt} = 0$.[18]

The baseline model takes the following format:

$$y_{ijt} = X_{ijt}\beta + c_{ij} + u_{ijt}, \qquad t = 1, \dots, T \tag{3.1}$$

where i, j and t denote the patient, the physician, and the date of prescription, respectively, y_{ijt} is the response variable, X_{ijt} is a $1 \times K$ vector that includes a full set of time dummies or other aggregate time variables, and c_i is the unobserved effect. In this study, y_{ijt} is the primary adherence rate and X_{ijt} is a set of control variables for patient, healthcare system and treatment characteristics.

We are interested in estimating β, allowing for correlation between c_i and the history of covariates $\{X_{ijt}: t = 1, \dots, T\}$.

With unbalanced panels, the key assumption is most easily stated as

$$E\left(u_{ijt} \middle| \mathrm{X}_{ij}, c_{ij}, s_{ij}\right) = 0, \ t = 1, \dots, T, \tag{3.2}$$

where $\mathrm{X}_{ij} = (\mathrm{X}_{ij1}, \mathrm{X}_{ij2}, \dots, \mathrm{X}_{ijT})$ and $\mathrm{s}_{ij} = (\mathrm{s}_{ij1}, \mathrm{s}_{ij2}, \dots, \mathrm{s}_{ijT})$ are the histories of the covariates and selection indicators, respectively. This assumption implies that observing a data point in any period cannot be systematically related with the idiosyncratic errors, u_{ijt}. It is a version of strict exogeneity of selection (along with strict exogeneity of the covariates) conditional on c_{ij}. It also allows for the selection s_{ijt} at period t to be arbitrarily correlated with (X_{ij}, c_{ij}), that is, with the observable covariates and the unobserved heterogeneity.

Combining the previous two equations, we get

$$E\left(y_{itj} \middle| \mathrm{X}_{ij}, c_{ij}, s_{ij}\right) = E\left(y_{ijt} \middle| \mathrm{X}_{ij}, c_{ij}\right) = X_{ijt}\beta + c_{ij} \tag{3.3}$$

The fixed effects (within) estimator on the unbalanced panel is generally consistent under (3.3), provided there is sufficient time variation in the covariates and the selected sample is not "too small". To characterize the FE estimator on the unbalanced panel, we must multiply Eq. (3.1) by the selection indicator to get:

[18] s_{ijt} indicates if we have a "complete case" for unit i in period t.

$$s_{ijt}y_{ijt} = s_{ijt}X_{ijt}\beta + s_{ijt}c_{ijt} + s_{ijt}u_{ijt}, \qquad t = 1, \dots, T \tag{3.4}$$

Averaging this equation across t for each i gives,

$$\overline{y_{ij}} = \overline{X_{ij}}\beta + c_{ij} + \overline{u_{ij}}, \ t = 1, \dots T, \tag{3.5}$$

where $\overline{y_{ij}} = T_{ij}^{-1}\sum_{r=1}^{T} s_{ijr}y_{ijr}$ is the average of the selected observations and $T_i = \sum_{r=1}^{T} s_{ijr}$ is the number of time periods observed for unit i and j.

If we now multiply (3.5) by s_{it} and subtract from (3.4), we remove c_{ij} and get:

$$s_{ijt}\left(y_{ijt} - \overline{y_{ij}}\right) = s_{ijt}\left(X_{ijt} - \overline{X_{ij}}\right)\beta + s_{ijt}\left(u_{ijt} - \overline{u_{ij}}\right) \tag{3.6}$$

As a computational point, note that the time averages of y_{ijt} and X_{ijt} are computed exclusively for time periods where data exist on the full set of variables (X_{ijt}, y_{ijt}): s_{ijt} is defined as a complete cases indicator.[19]

The 2FE model was used in complement to the FRM. It has become widely used as a default method for estimating causal effects applied to panel data. It decomposes the adherence effects into a share explained by changes on the patients' decision and the share explained by changes in physicians' practice style.

We examine the variation in the ratio of dispensed drugs per unit of time, y_{it}, observed for individual i at date t, expressed as a function of patient heterogeneity (permanent unmeasured differences among the individuals), physician heterogeneity (permanent differences among the healthcare provider), and measured time-varying characteristics. Due to the matched patient and physician and the longitudinal nature of our data, we control for both measured and unmeasured heterogeneity in the patients and health professionals.

We consider the statistical decomposition of adherence into patient and physician effects to address some concerns: (i) the basis of inter-physician adherence differentials and how

[19] Further details are available in Papke and Wooldridge (2008) and Wooldridge (2019).

this disparity is related with the physician–patient interaction,[20] and (ii) the relation between physician–healthcare sector and adherence.[21]

Koulayev et al. (2017) apply the 2FE model to the doctor–patient setting, while Simonsen et al. (2017) apply the 2FE model to measure patient and practice fixed-effect. Kwok (2019) also considers this approach to capture time-invariant patient characteristics and primary care physicians practice styles.

These models present advantages: (i) they are able to adjust for changes in patient outcomes due to switching between physicians,[22] and (ii) they provide higher efficiency of estimates of factors related to the match value and factors related to time variation in adherence rates.[23] This model places higher demand on the quality of the data since it requires a panel dataset with sufficient amount of doctor switching in order to identify both doctors' and patients' adherence styles (Koulayev et al., 2017).

Following Koulayev et al. (2017), we combine a model of adherence that takes the following format:

$$y_{ijt} = \delta_i + \gamma_j + \sigma_{ij} + \varepsilon_{ijt} \tag{3.7}$$

where y_{ijt} is the outcome variable, δ_i if the patient fixed-effect component, γ_j is the physician fixed-effect component and ε_{ijt} is the deviation of compliance with refill t from the average compliance within the patient-physician match σ_{ij}.

Equation (3.7) becomes equation (3.8) when using a match-specific variable X_{ijt} to explain a portion of the match-specific component σ_{ij}:

---

[20] Within a connected group of patients and physicians, identification can be determined by using conventional methods for the analysis of covariance. Connecting patients and physicians requires that some of the individuals are associated to multiple physicians. When a group of patients and physicians is connected, the group contains all the patients seen by any of the physicians in the group and all the physicians at which any of the patients ever consulted with. From an economic perspective, connected groups of patients and physicians show the real mobility of care within the economy. From a statistical perspective, connected groups of patients and physicians allow for a precise statement of identification restrictions on the patient and physician effects.

[21] Further details are available in Abowd et al. (1999) and Abowd et al. (2002) that explore this methodology in the firm-worker context. These papers are the baseline contributions to health economics applications.

[22] Multi-level models miss those changes and may come to erroneous conclusions regarding the relative contributions of patient-level and doctor-level factors to the total variation (Koulayev et al., 2017).

[23] This occurs because all observed and unobserved patient-level factors are accounted for by the patient fixed effect. In contrast, multi-level models do not allow for such a regressor as it cannot be identified within their structure (because outcomes of patient A across doctors B and C are assumed to be independent) (Koulayev et al., 2017).

$$y_{ijt} = \delta_i + \gamma_j + \beta X_{ijt}, + \eta_{ijt} \tag{3.8}$$

The estimation of Equation (3.8) includes both patient and physician fixed effects, whose estimates are denoted by $\hat{\delta}_i$ and $\hat{\gamma}_j$. With that, the other parameters in Equation (3.7) can be expressed as:

$$\hat{\sigma}_{ij} = \frac{1}{T_{ij}} \sum (y_{ijt} - \hat{\delta}_i + \hat{\gamma}) \tag{3.9}$$

$$\hat{\varepsilon}_{ijt} = y_{ijt} - \hat{\sigma}_{ij} - \hat{\gamma}_j$$

The decision to follow physicians' treatment advice depends on both physician- and patient-level factors, that are constant over time, and on contextual variables. The latter include the level of knowledge between physician and patient, patient knowledge about their own medical condition and the implemented therapeutic scheme, and other potentially unobservable time-varying characteristics (Gellad et al., 2009; Haynes et al., 2002; Koulayev et al., 2017; Krueger et al., 2005).

For this reason, our empirical model relies on the following identity:

$$y_{ijt} = c + \beta_1 P_{it} + \beta_2 D_j + \beta_3 X_{ijt} + \varepsilon_{ijt_i} \tag{3.10}$$

where i, j and t denote the patient, the physician, and the date of filling, respectively, and y_{ijt} is our outcome variable – medication possession ratio – for a particular refill.

The main variable of interest for this model is the nature of the relationship between the physician and the patient, in particular whether the prescription is issued by the physician with whom the patient has more interaction within that year.

The set of explanatory variables includes patient's characteristics (P_{it}), healthcare system attributes such as the physician-specific fixed effects (D_j) and a set of controls variables (X_{ijt}) that include match-specific variables such as the classification of whether the prescription was provided by the principal physician or not (Koulayev et al., 2017).[24]

[24] Further details are available in Papke and Wooldridge (2008) and Wooldridge (2019).

3.4 Results

3.4.1 Descriptive Statistics

We start by showing descriptive statistics for the whole sample and then for specific subgroups.[25] Table 3.1 provides statistics on patients, healthcare, and treatment characteristics. Between January 2015 and October 2019, a total of 1,363,778 e-prescriptions from 27,125 physicians were assigned to 121,727 patients.

Adherence levels[26] consist of approximately 69% of the total drugs available on a prescription are filled by the patient, and when we consider the universe of filled vs. non-filled prescriptions, we have a level of non-adherence of 17.9%.

Patients are key decision-makers in the adherence process. They are mainly located in the Norte region (32.5%), followed by Lisboa e Vale do Tejo (25.6%) and Centro (23.6%), matching the most populated areas in Portugal. An average of 52.1% of patients prescribed with oral antidiabetic medication is women. The mean age of the patients is 68.50 years, varying from 18 to 110 years old. Approximately 60% of our sample corresponds to patients aged between 60 and 80 years old, which matches the demographics of the disease.

A major part of prescriptions is exclusively covered by the national health service insurance (91.1%) and approximately 35% of individuals present lower levels of co-payment possibly due to lower levels of income.

Our sample contains 27,125 physicians and approximately 83.4% are General Practitioners, followed by Internal Medicine physicians (6.5%) and Endocrinologists (3.0%). Prescriptions usually come from the public (81.2%) primary care sector (69.9%). Patients tend to have consultations with approximately more than 3 physicians, other than its principal physician and visit a physician an average of 11.6 times during the observed five years.

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[25] Appendix 3.1, appendix 3.2 present the statistics regarding the patient characteristics for the public and private sector; and statistics on adherence levels associated with the patient characteristics for the public and private sector, respectively.
Appendix 3.3 and appendix 3.4 present the statistics regarding the healthcare characteristics divided by public and private sector; and statistics on adherence levels associated with the healthcare characteristics divided by public and private sector, respectively.
Appendix 3.5 and appendix 3.6 present the statistics regarding the treatment characteristics for public and private health sector and statistics on adherence levels associated with treatment characteristics for public and private health sector, respectively.

[26] Appendix 3.7 presents the statistics on adherence levels for the complete sample as well as divided by public and private sectors.

The selected period includes a total of 1,363,778 prescriptions containing oral hypoglycaemic agents evenly distributed across all years. They reflect the therapeutic approach and can contain up to 6 pharmaceuticals, with each prescription containing an average of 1.38 drugs. Each patient has 2.1 health comorbidities besides Diabetes.
Of all prescriptions, 54.3% are renewable prescriptions and 43.1% contain at least one induced drug, i.e., drugs that must be purchased according to physician's choice.

Table 3.1 - Statistics regarding to adherence levels, patient, healthcare, and treatment characteristics

Variable	Description	Mean	Std. Dev.
	Adherence Levels		
Share Dispensed Drugs (Fraction)	Share of dispensed drug per prescription	0.689	0.394
Dispensed Prescription (Binary)	= 1 if prescription contains at least one filled drug, 0 otherwise	0.821	0.383
	Patient's characteristics		
Patient Gender	= 1 for females, 0 otherwise	0.521	0.500
Patient Age	Patient's Age	68.492	11.941
Insurance Type	= 1 for NHS, 0 otherwise	0.911	0.285
Lower Income	= 1 if lower income, 0 otherwise	0.353	0.478
	Healthcare characteristics		
Physician Specialty	= 1 if General Practitioner	0.834	0.372
	= 2 if Endocrinologist	0.030	0.170
	= 3 if Internal Medicine	0.065	0.247
	= 4 if Other	0.071	0.257
Public Workplace	= 1 for physician working in the public healthcare sector, 0 otherwise	0.812	0.391
Primary Care	= 1 if Primary Care, 0 otherwise	0.699	0.459
Other physicians	Physicians seen by patient (besides principal physician)	2.913	2.528
Number of Visits	Number of visits made by patient to any physician	11.597	10.065
	Treatment characteristics		
Number of Antidiabetic Drugs	Number of antidiabetic drugs (per patient)	1.388	0.665
Level of Comorbidities	Number of other comorbidities (per patient)	2.115	1.294
Renewable Prescription	= 1 if Renewable Prescription; 0 otherwise	0.543	0.498
Induced Prescription	= 1 if prescription contains drugs that are specifically selected by the physician (patient doesn't have the opportunity to choose); 0 otherwise	0.431	0.495
Number of Observations		1,363,778	

In terms of adherence, Table 3.2 shows that it is slightly lower for women (68.1%) than men (69.7%), and it increases as patients get older, becoming more stable for patients 60 years or older. This may be related with the existence of caregivers that are responsible to fill the prescription on the patient's behalf.

Prescriptions covered by NHS insurance exhibit higher adherence levels (69.2%) than those associated with complementary health insurance (65.7%), whether subsystems or voluntary.

Table 3.2 - Statistics about adherence levels associated to patient's characteristics

Variable	Description	N	Mean	Std. Dev.
Patient Gender	= 1 if female	710,141	0.681	0.399
	= 0 otherwise	653,637	0.697	0.389
Patient Age (10-year interval)	= 1 if < 20 years old	507	0.561	0.422
	= 2 if 20 – 29	3,958	0.561	0.432
	= 3 if 30 – 39	14,937	0.609	0.424
	= 4 if 40 – 49	65,830	0.643	0.405
	= 5 if 50 – 59	214,676	0.669	0.395
	= 6 if 60 – 69	396,991	0.693	0.389
	= 7 if 70 – 79	409,526	0.700	0.391
	= 8 if 80 – 89	227,770	0.698	0.399
	= 9 if >= 90 years old	29,583	0.710	0.403
Insurance Type	= 1 for NHS	1,242,076	0.692	0.393
	= 0 otherwise	121,702	0.657	0.409
Lower Income	= 1 if lower income	481,724	0.706	0.392
	= 0 otherwise	882,054	0.680	0.395

Note:
The 4th column shows the mean of adherence levels.

Table 3.3 shows us the influence of the healthcare characteristics. Adherence presents higher values for General Practitioners (70.4%) and lower values for Endocrinologists (58.8%). The public sector (69.2%) and primary care units (71.5%) also present higher adherence rates than the private sector (67.4%) and hospital care units (62.8%). As the number of appointments with other physicians increases, the level of adherence tends to decrease. On the contrary, the higher the number of appointments with the physician that issues the prescription, the higher is the patient's compliance level.

Table 3.3 - Statistics regarding the adherence levels associated to healthcare characteristics

Variable	Description	N	Mean	Std. Dev.
Physician Specialty	General Practitioner	1,136,825	0.704	0.388
	Endocrinologist	40,468	0.588	0.398
	Internal Medicine Physician	89,154	0.616	0.411
	Other Specialty	97,331	0.622	0.427
Public Workplace	= 1 for physician working in the public healthcare sector	1,107,279	0.692	0.388
	= 0 otherwise	256,499	0.674	0.420
Primary Care	= 1 if Primary Care	952,818	0.715	0.378
	= 0 otherwise	410,955	0.628	0.424
Other physicians	Other Physicians = 0	219,197	0.680	0.400
	Other Physicians = 1-3	688,565	0.696	0.391
	Other Physicians = 4-6	332,746	0.688	0.394
	Other Physicians = 7-9	95,211	0.676	0.398
	Other Physicians >=10	28,059	0.644	0.409
Number of Visits	Number of Visits = 1-2	106,725	0.370	0,.427
	Number of Visits = 2-5	253,019	0.553	0.426
	Number of Visits = 5-10	346,692	0.720	0.374
	Number of Visits = 10-15	262,018	0.773	0.342
	Number of Visits = 15-20	165,301	0.778	0.340
	Number of Visits = 20-25	96,075	0.776	0.343
	Number of Visits = 25-30	55,404	0.775	0.347
	Number of Visits >=30	78,544	0.786	0.347

Note:
The 4th column shows the mean of adherence levels.

Table 3.4 provides us details on adherence levels determined by treatment characteristics. Adherence decreases slightly as the patient's condition worsens, but the impact of other concomitant health conditions seems to be higher. Renewable prescriptions present an adherence of 79.2%, while non-renewable only have an adherence level of 56,6%/. Induced/Locked[27] and non-induced/non-locked prescriptions show adherence levels of approximately 69%.

[27] By induced/locked prescription, we mean that prescription contains drugs that are specifically selected by the physician. For this reason, the patient does not have the opportunity to choose the drug that best suits amongst the ones with the same active ingredient, him during the pharmacy visit.

Table 3.4 - Statistics regarding the adherence levels associated to treatment characteristics

Variable	Description	N	Mean	Std. Dev.
Diabetes Severity	Therapeutic guideline = 1	659,359	0.690	0.403
	Therapeutic guideline = 2	468,882	0.691	0.393
	Therapeutic guideline = 3	235,537	0.682	0.371
Level of Comorbidities	0	164,032	0.708	0.401
	1	315,652	0.699	0.393
	2	348,508	0.694	0.391
	3	270,906	0.685	0.391
	4	264,680	0.663	0.397
Renewable Prescription	= 1 if Renewable Prescription	740,570	0.792	0.286
	= 0 otherwise	623,208	0.566	0.464
Induced Prescription	= 1 if prescription contains drugs that are specifically selected by the physician	587,117	0.686	0.390
	= 0 otherwise	776,661	0.691	0.398

Note:
The 4th column shows the mean of adherence levels.

The agency relationship between the patient and the physician is the focal point of our study. As mentioned on section 3.3, we use multiple ways of measuring the interaction between the patient and the physician.

Table 3.5 provide us details on the adherence levels for the several measures of principal physician.[28] It shows that approximately 70% of the prescriptions in our sample are associated to the patient's principal physician Adherence levels for the measures UCP, ATP and UCP-per year are quite consistent, with a share of approximately 70% of the prescription being dispensed, in comparison with the 65% of adherence for non-principal physicians.

[28] Appendix 3.8 and appendix 3.9 present the statistics regarding the agency relationship between patient and physician divided by public and private sector; and statistics on adherence levels associated with the agency relationship between patient and physician for the public and private sector, respectively.

Table 3.5 - Statistics regarding the adherence levels associated to the agency relationship between patient and physician

Variable	Description	N	Mean	Std. Dev.
Usual Care Provider	= 1 if principal physician (for a specific patient)	918,157 (67.3%)	0.704	0.388
	= 0 otherwise	445,621	0.658	0.404
Active-Treatment Provider	= 1 if principal physician (for a specific patient)	925,507 (67.9%)	0.704	0.389
	= 0 otherwise	438,271	0.658	0.404
Usual Care Provider (Year)	= 1 if principal physician (for a specific patient, for a specific year)	1,003,422 (73,6%)	0.696	0.392
	= 0 otherwise	360,356	0.668	0.401
Second Principal Physician	= 1 if second principal physician (for a specific patient)	161,523 (11.8%)	0.666	0.401
	= 0 otherwise	1,202,255	0.692	0.393

Note:
The 4th column shows the mean of adherence levels.

Table 3.6 exhibits some statistics related to the patient clinical pathway. Ideally, patients start their therapeutic journey in monotherapy with no associated comorbidities. This is called the baseline condition. Then patients usually follow a well-defined trajectory after entering the healthcare system. Although they can interact with more than one physician, they are subject to the same therapeutic guidelines that shape the decisions of all physicians.[29]

A patient can be prescribed mono, dual, or triple therapy. Monotherapeutic works as a proxy for first prescription/first consult, and it allows us to verify the baseline adherence. Not all patients are first observed at this stage of treatment. In our sample, the prescriptions we can clearly identify as first prescriptions amount to 74,846. These first prescriptions present a baseline adherence of 44.4%, that increase up to 70.3% in subsequent prescriptions. The first six months of therapy have an average adherence of 47.8%, which also increases to 71.6% after this period.[30]

This element is also helpful to characterize the patient pathway through the health system. Most patients enter the system through the public (79.0%), and the primary-care (66.3%) sectors. They are frequently associated to a General Practitioner (78.9%), also called as

[29] See Chapter 2, Section 2.3: Patient Clinical Pathway – Therapeutic Guidelines for Diabetes.
[30] The first six months of treatment are only available for patients with a first prescription. It corresponds to a period of 6 months after the first prescription.

Family Doctors, which shows that our data are aligned with the defined clinical pathway in Portugal.[31]

Table 3.6 - Statistics on the Patient Clinical Pathway

Variable	Description	N	Mean	Std. Dev.
	Baseline Adherence			
First Prescription	= 1 if the prescription matches the first contact between the patient and physician and contains monotherapy	74,846	0.444	0.442
	= 0 otherwise	1,288,932	0.703	0.387
Physician Specialty	General Practitioners	74,846	0.790	0.408
	Endocrinologist	74,846	0.048	0.213
	Internal Medicine	74,846	0.065	0.246
	Other Specialties	74,846	0.098	0.297
Healthcare Setting	Public	74,846	0.790	0.407
	Private	74,846	0.663	0.473
First 6 months	= 1 adherence the first 6 months of treatment	154,861	0.478	0.441
	= 0 otherwise	1,208,917	0.716	0.379

Note:
The 4th column shows the mean of adherence levels.

3.4.2 Regressions

Table 3.7 shows the estimation results yielded by the different adopted econometric approaches. Due to the large number of control variables, we present the estimates associated with the variables of interest[32] – UCP, ATP, UCP-year, healthcare setting (public *vs.* private), interaction between the principal physician and the health setting variables, number of physicians seen by the patient (other than the principal physician) and the frequency of interaction with the physician that issues the prescription (number of visits) – reported for the OLS, the Fractional Response, and the 2-way Fixed Effects Models. [33]

[31] See Chapter 2, Section 2.2 – Patient Referral System.
[32] We have also computed the results using OLS, Probit Model and FRM for the variable HHI. Results follow the same direction of the UCP, ATP, with UCP-per year with HHI also promoting a positive effect on adherence levels (for further detail please consider Appendix 3.10).
[33] We also considered a Probit Model with a binary dependent variable. Results show that UCP, ATP, UCP-per year, and HHI have a positive effect on adherence levels (for further detail please consider Appendix 3.11).

Results are presented in terms of marginal effects (dy/dx), which give the change in percentage points (pp) in the dependent variable given by a one-unit change in the explanatory variable, *ceteris paribus*.

The principal physician, measured as the Usual Care Provider, Active Care Provider, or the Usual Care Provider (per year), have a positive influence on primary adherence. They have the capacity to increase adherence in approximately 2.6pp to 5.4pp, in comparison to other physicians that the patient might see. Considering that our baseline adherence is 44,4%, that is a relevant increase. However, we also observe that the increase in adherence shrinks as we consider physician-fixed effects (FRM – longitudinal) and effects for both physician and patient (2FE). In the latter, the increase becomes only 1.6pp, which is, nevertheless, still relevant. This finding may suggest that an important part of the positive impact on adherence is related to the patient-physician match.

That conclusion is supported by the observation that the more contacts they have, whether by number of interactions (all time or year) or by the course of the therapeutic, the more likely a trustworthy relationship emerges. Physicians can provide more specific treatment and patients are more predisposed to consider and follow their recommendations.

Our estimates also show that public-origin prescriptions decrease the levels of primary adherence by approximately 1.2pp to 5.4pp, in comparison with private-origin prescriptions. Furthermore, when the principal physician is located at the public health sector, there is a negative influence on primary adherence that offsets the initial positive impact. In fact, when this occurs, we have a decrease on adherence of approximately 1.9pp to 3.8pp, in comparison with privately located principal physicians.

Although the principal physician presents a positive influence on adherence, the possible access barriers for some population, namely reported unmet needs for medical care due to costs, distance and long waiting times, seem to influence negatively adherence compromising better health outcomes. Potentially more relevant, patients cannot choose their physician in the public sector, which can undermine the level of trust between the pair. Efforts should be made to improve this relationship on the public sector.

Results on the importance of relationship are complemented by considering the number of physicians seen by the patient other than the principal physician. In comparison with the principal physician, seeing up to three other physicians decreases the effect on adherence by approximately 1.6 to 2.4pp. If the patient sees up to six physicians, the

effect on adherence decreases by 3.3 to 4.9pp. When they see up to nine physicians the effect on adherence decreases by 5 to 6.6pp. If the patient sees more than ten physicians other than the principal physician, the effect on adherence decreases by 8 to 9.2pp.

This suggests a decreasing pattern regarding trusting in physicians other than its principal. Although he might see other providers, the patient lacks trust on them, so the levels of adherence also decrease.

When considering the number of visits made to the physician, we see that the more visits (interactions) they have, the higher the willingness to comply with therapeutics, in comparison with one visit (reference category).

Adherence levels start to increase from 20 to 21.4pp (up to five visits) reaching a plateau around 25 visits, where adherence levels increase from 1.1 to 41.9pp. Adherence levels remain stable when the number of visits is higher than 25, i.e., adherence levels tend to increase from 1.7 to 43pp if they have up to 30 visits and 4.2 to 46.1pp when the number of visits is higher than 30.

This shows a small but increasing impact on adherence levels in early stages of the interaction between both parties, which tends to stabilize in the long run, which suggests that a trusting relationship takes time to be built and it requires an effort between the patient and the physician.

The control variables considered in the models described above work the way we would expect and are aligned with the previous evidence provided by the literature.

The available data allow us to apply distinct methods using different outcome measures and get a stronger sense of the results. Although results are consistent, they vary quantitatively from method to method and according to the way of measuring the physician-patient relationship. Still, the results are consistent throughout the different methodologies, adding robustness to the analysis.

Further discussion of these results is developed in Section 3.5.

Table 3.7 - Determinants of primary adherence considering the physician-patient interaction. Dependent Variable: Share Dispensed Drugs (Fractional)

	OLS - Coefficients			FRM - Marginal Effects: Cross-Sectional (a)			FRM - Marginal Effects: Longitudinal (a) (b)			2FE
UCP	0.053***			0.051***			0.029***			
	(0.002)			(0.002)			(0.003)			
ATP		0.054***			0.052***			0.029***		
		(0.002)			(0.002)			(0.003)		
UCP - year			0.037***			0.049***			0.026***	0.016***
			(0.002)			(0.002)			(0.002)	(0.002)
public	-0.054***	-0.053***	-0.058***	-0.049***	-0.048***	-0.043***	-0.034***	-0.034***	-0.044***	-0.012***
	(0.002)	(0.002)	(0.003)	(0.002)	(0.002)	(0.002)	(0.002)	(0.002)	(0.002)	(0.003)
*UCP * Public*	-0.038***			-0.035***			-0.029***			
	(0.002)			(0.002)			(0.003)			
*ATP * Public*		-0.039***			-0.036***			-0.029***		
		(0.002)			(0.002)			(0.003)		
*UCP - year * Public*			-0.036***			-0.042***			-0.025***	-0.019***
			(0.003)			(0.002)			(0.002)	(0.002)
other_physicians (1-3)	-0.017***	-0.018***	-0.024***	-0.016***	-0.016***	-0.019***	0.011***	0.011***	0.003	
	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.002)	(0.002)	(0.002)	
other_physicians (4-6)	-0.036***	-0.036***	-0.049***	-0.033***	-0.034***	-0.039***	0.009***	0.009***	0.001	
	(0.001)	(0.001)	(0.0015)	(0.001)	(0.001)	(0.001)	(0.004)	(0.004)	(0.004)	
other_physicians (7-9)	-0.053***	-0.054***	-0.066***	-0.050***	-0.051***	-0.057***	0.005	0.005	-0.0003	
	(0.002)	(0.001)	(0.002)	(0.001)	(0.002)	(0.001)	(0.006)	(0.006)	(0.006)	
other_physicians (>10)	-0.083***	-0.084***	-0.092***	-0.080***	-0.080***	-0.087***	-0.008	-0.008	-0.005	
	(0.002)	(0.002)	(0.003)	(0.002)	(0.002)	(0.002)	(0.009)	(0.009)	(0.009)	
nvisits (2-5)	0.200***	0.200***	0.187***	0.202***	0.202***	0.202***	-0.014***	-0.014***	-0.014***	0.214***
	(0.002)	(0.002)	(0.002)	(0.002)	(0.002)	(0.002)	(0.002)	(0.002)	(0.002)	(0.002)
nvisits (5-10)	0.335***	0.335***	0.315***	0.335***	0.335***	0.337***	-0.009***	-0.009***	-0.010***	0.355***
	(0.002)	(0.002)	(0.002)	(0.002)	(0.002)	(0.002)	(0.002)	(0.002)	(0.002)	(0.002)

nvisits (10-15)	0.387***	0.386***	0.365***	0.387***	0.387***	0.388***	0.0002	0.0002	-0.001	0.413***
	(0.002)	(0.002)	(0.002)	(0.002)	(0.002)	(0.002)	(0.003)	(0.003)	(0.003)	(0.002)
nvisits (15-20)	0.406***	0.406***	0.385***	0.404***	0.404***	0.406***	0.007**	0.007**	0.006*	0.434***
	(0.002)	(0.002)	(0.002)	(0.002)	(0.002)	(0.002)	(0.003)	(0.003)	(0.003)	(0.002)
nvisits (20-25)	0.419***	0.419***	0.396***	0.415***	0.415***	0.416***	0.011***	0.011***	0.010***	0.446***
	(0.002)	(0.002)	(0.003)	(0.002)	(0.002)	(0.002)	(0.0004)	(0.0004)	(0.004)	(0.002)
nvisits (25-30)	0.430***	0.430***	0.403***	0.423***	0.423***	0.425***	0.017***	0.017***	0.016***	0.456***
	(0.002)	(0.002)	(0.003)	(0.002)	(0.002)	(0.002)	(0.004)	(0.004)	(0.004)	(0.002)
nvisits (>30)	0.461***	0.461***	0.424***	0.448***	0.449***	0.450***	0.042***	0.042***	0.042***	0.482***
	(0.002)	(0.002)	(0.001)	(0.002)	(0.002)	(0.002)	(0.005)	(0.005)	(0.005)	(0.002)
R-squared	0.200	0.200	0.202							0.420
Number of Observations	1,363,778	1,363,778	1,363,778	1,363,778	1,363,778	1,363,778	1,363,778	1,363,778	1,363,778	1,343,582

Notes:
Dependent Variable: Share Dispensed Drugs (Fractional)
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
(a). Regression includes control variables for: (i) patient sociodemographic characteristics (age, gender, patient location (region), health insurance); (ii) health sector characteristics (type of care, specialty, patient-physician interactions (visits)); and (iii) treatment characteristics (condition severity, comorbidities, time, and type of prescription).
(b). This also includes control variables for: (i) averages of the explanatory variables for each i; (ii) time dummies (week); (iii) time averages for each i; and (iv) dummies for the number of total time periods used for each i.

3.5 Robustness Checks

To reinforce the validity of our results we perform the same regressions for different sample restrictions and use different measures for same of the variables.

I. Secondary Adherence Measure

As previously mentioned, most of the previous studies have used secondary adherence as the dependent variable. For this reason, we complement our approach using secondary adherence as our dependent variable. Results are shown in Table 3.8 and suggest that the levels of secondary adherence tends to increase by 2.2 to 3.6pp in the presence of a principal physician. Consequently, we may conclude that our findings are not driven by the use of an alternative measure for adherence, although the impact seems to be slightly higher when primary adherence is used.

Table 3.8 - Determinants of secondary adherence. Dependent Variable: Medication Possession Ratio

	OLS - Coefficient	FPM – Marginal Effects: Cross Sectional (a)	FPM – Marginal Effects: Longitudinal (b)
ATP	0.036***	0.035***	0.022 ***
	(0.002)	(0.002)	(0.002)
public	-0.023***	-0.023***	-0.024***
	(0.002)	(0.002)	(0.002)
*ATP * public*	-0.008***	-0.008***	-0.014***
	(0.002)	(0.002)	(0.003)
R-Squared	0.265	-	-
Number of Observations	1,559,183	1,559,183	1,559,183

Notes:
Dependent Variable: Share Dispensed Drugs (Fractional)
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
(a). Regression includes control variables for: (i) patient sociodemographic characteristics (age, gender, patient location (region), health insurance); (ii) health sector characteristics (type of care, specialty, patient-physician interactions (visits)); and (iii) treatment characteristics (condition severity, comorbidities, time, and type of prescription).
(b). This also includes control variables for: (i) averages of the explanatory variables for each i; (ii) time dummies (week), (iii) time averages for each i and (iv) dummies for the number of total time periods used for each i.

II. Changes in the Principal Physician Measure

a. Second Principal Physician

We use a "*placebo test*" to the impact of the principal physician by computing the regressions using the Second Principal Physician, i.e., the second physician that the patient interacts more often. This seems to be a good alternative since approximately 86% of patients in our dataset have access to more than one physician.

Results are shown in Table 3.9 and suggest that the levels of adherence tend to decrease by 2.2 to 4.5pp when considering the interaction with the second principal physician as an explanatory variable. [34] This enhances the importance of the first principal physician as well as the necessity and importance of this agency relationship for policy purposes.

Table 3.9 - Determinants of primary adherence considering the second principal physician-patient interaction. Dependent Variable: Share Dispensed Drugs (Fractional)

	OLS - Coefficient (a)	FRM – Marginal Effects Cross Sectional (a)	FRM – Marginal Effects Longitudinal (a) (b)
second UCP	-0.045***	-0.044***	-0.022***
	(0.002)	(0.002)	(0.003)
public	-0.083***	-0.074***	-0.047***
	(0.001)	(0.001)	(0.002)
*second UCP * public*	0.028***	0.025***	0.016***
	(0.002)	(0.002)	(0.003)
R-Squared	0.200	-	-
Number of Observations	1,363,778	1,363,778	1,363,778

Notes:
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
(a). Regression includes controls variables for: (i) patient sociodemographic characteristics (age, gender, patient location (region), health insurance); (ii) health sector characteristics (type of care, specialty, patient-physician interactions (visits)) and (iii) treatment characteristics (condition severity, comorbidities, time, and type of prescription).
(b). This also includes controls variables for: (i) averages of the explanatory variables for each i; (ii) time dummies (week), (iii) time averages for each i, and (iv) dummies for the number of total time periods used for each i.

[34] Results from the Probit Model are available in Appendix 3.12 and are consistent with the approach considered on Table 3.9, showing a negative effect of a second principal physician on adherence levels of 2.3 pp.

b. Exclusion of observations that do not belong to the Principal Physician

By restricting our sample to the Principal Physician – UCP and ATP – we are allowed to study the impact of the healthcare sector where the relationship occurs. Results are presented on Table 3.10 and suggest that, when restricting our sample to principal physicians, the public health sector presents a negative impact of 2.8 to 9.5pp towards adherence levels. [35] Once more, this estimate alludes to the lower trust level that may be developed towards physicians in the public sector that are not chosen by the patient.

Table 3.10 - Determinants of primary adherence considering a sample of principal physician-patient interaction. Dependent Variable: Share Dispensed Drugs (Fractional)

	OLS - Coefficient (a)		FPM – Marginal effects Cross Sectional (a)		FPM – Marginal Effects Longitudinal (a) (b)	
public (UCP)	-0.095***		-0.083***		-0.028***	
	(0.002)		(0.002)		(0.006)	
public (ATP)		-0.096***		-0.084***		-0.031***
		(0.002)		(0.002)		(0.006)
R-Squared	0.201	0.200	-	-	-	-
Number of Observations	918,157	925,507	918,157	925,507	918,157	925,507

Notes:
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
(a). Regression includes controls variables for: (i) patient sociodemographic characteristics (age, gender, patient location (region), health insurance); (ii) health sector characteristics (type of care, specialty, patient-physician interactions (visits)) and (iii) treatment characteristics (condition severity, comorbidities, time, and type of prescription).
(b). This also includes controls variables for: (i) averages of the explanatory variables for each i; (ii) time dummies (week), (iii) time averages for each i and (iv) dummies for the number of total time periods used for each i.

[35] Results from the Probit Model are available on Appendix 3.13 and are consistent with the approach considered on Table 3.10, showing a decrease of 3.8pp on adherence levels related to patients treated in the public sector.

III. Changes on Patient's Measures

a. Exclusion of patients aged 70 and over.

In Portugal, approximately 2% of people aged 65 and over received long-term care in 2017 (OECD, 2019). This means that prescription drugs and pharmacy visits may be associated with the presence of a caregiver responsible for the patient which may fill the prescription in the name of the patient. This may introduce some bias on the adherence pattern due to the involvement of a third part. Results are presented on Table 3.11. [36] When restricting our sample to individuals aged 70 or under, we keep seeing the positive influence of the principal physician ranging from 1.5 to 4.1pp, while maintaining a negative outcome yielded by the public health setting.

[36] Results achieved when using the measure HHI show a positive impact on adherence levels of 3.2 to 9.2pp. The public setting decreases adherence by 3.2 to 5.7pp (for further details please consider Appendix 3.14). Results from the Probit Model are consistent with the approach on Table 3.13, showing an increase of 1.3 to 3.6pp on adherence levels when associated to a principal physician as well as a decrease in the adherence levels of 2.5pp to 4.1pp when the prescription comes from the public setting (for further details please consider Appendix 3.15).

Table 3.11 - Determinants of primary adherence considering a sample of individuals aged 70 or under. Dependent Variable: Share Dispensed Drugs (Fractional)

	OLS - Coefficient (a)			FPM – Marginal Effects: Cross Sectional (a)			FPM – Marginal Effects: Longitudinal (a) (b)		
UCP	0.041***			0.039***			0.015***		
	(0.002)			(0.002)			(0.004)		
ATP		0.040***			0.038***			0.015***	
		(0.002)			(0.002)			(0.004)	
UCP - year			0.037***			0.035***			0.011***
			(0.002)			(0.003)			(0.003)
public	-0.062***	-0.062***	-0.058***	-0.056***	-0.056***	-0.052***	-0.033***	-0.032***	-0.033***
	(0.002)	(0.002)	(0.003)	(0.002)	(0.002)	(0.002)	(0.003)	(0.003)	(0.003)
*UCP * public*	-0.033***			-0.029***			-0.019***		
	(0.002)			(0.002)			(0.004)		
*ATP * public*		-0.033***			-0.029***			-0.019***	
		(0.002)			(0.002)			(0.004)	
*UCP – year * public*			-0.036***			-0.033***			-0.013***
			(0.003)			(0.003)		*UCP*	0.041***
R-Squared	0.202	0.202	0.202	-	-	-	-	-	-
Number of Observations	696,899	696,899	696,899	696,899	696,899	696,899	696,899	696,899	696,899

Notes:
Dependent Variable: Share Dispensed Drugs (Fractional)
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
(a). Regression includes controls variables for: (i) patient sociodemographic characteristics (age, gender, patient location (region), health insurance); (ii) health sector characteristics (type of care, specialty, patient-physician interactions (visits)) and (iii) treatment characteristics (condition severity, comorbidities, time and type of prescription).
(b). This also includes controls variables for: (i) averages of the explanatory variables for each i; (ii) time dummies (week), (iii) time averages for each i and (iv) dummies for the number of total time periods used for each i.

IV. Changes on Healthcare System Measures

a. Separating Public and Private Samples.

By isolating the presence of a Principal Physician in each one of the healthcare sectors we aim to study its impact on adherence. This is considered as a cross-test to assess the existence of differences on adherence levels related to the principal physician as well as the healthcare sector where this relationship occurs. In the private sector, there is more freedom to choose physicians and so we would expect main physician to have a higher effect on adherence.

Results are exhibited in Table 3.12. [37] The first six lines of the table correspond to a sample of the public health setting while the remaining six lines correspond to a sample of the private health setting.

As expected, the principal physician presents a smaller effect on adherence on the public health setting. In this sector, increases in adherence to treatment prescribed by the principal physician ranges between 0.8 to 1.7pp while in the private sector it range between 3.7 to 3.9pp.

The effect of the principal physician on the public health setting becomes negative (0.3pp) when we consider a longitudinal approach and remove non-observable, time-constant physician specific characteristics, but remains positive in the private sector (between 1.7 to 2.2pp).

[37] Results achieved when using the measure HHI confirm a positive impact on adherence levels of 4.7 to 4.9 pp on the public setting and 6.9 to 8.6 pp on the private setting (for further details please consider Appendix 3.16). Results from the Probit Model are consistent with the approach on Table 3.12, showing an increase of 0.3 to 1.9pp on adherence levels when associated to a principal physician on the public sector. When the principal physician is in the private sector, the increase in the level of adherence is high, of about 1.8pp to 4.2pp (for further details please consider Appendix 3.17).

Table 3.12 - Determinants of primary adherence considering a sample for public and private health setting. Dependent Variable: Share Dispensed Drugs (Fractional)

	OLS - Coefficient (a)		FPM – Marginal Effects: Cross Sectional (a)		FPM – Marginal Effects: Panel (a) (b)	
UCP (public)	0.017***		0.017***		-0.003***	
	(0.001)		(0.001)		(0.001)	
ATP (public)	0.016***		0.016***		-0.003***	
	(0.001)		(0.001)		(0.001)	
UCP – year (public)	0.008***		0.008***		-0.001	
	(0.001)		(0.001)		(0.001)	
UCP (private)		0.039***		0.039***		0.022***
		(0.002)		(0.002)		(0.003)
ATP (private)		0.039***		0.039***		0.021***
		(0.002)		(0.002)		(0.003)
UCP – year (private)		0.037***		0.037***		0.017***
		(0.002)		(0.0019)		(0.002)
R-Squared	0.216	0.149	-	-	-	-
Number of Observations	1,107,279	256,499	1,107,279	256,499	1,107,279	256,499

Notes:
Dependent Variable: Share Dispensed Drugs (Fractional)
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
(a). Regression includes controls variables for: (i) patient sociodemographic characteristics (age, gender, patient location (region), health insurance); (ii) health sector characteristics (type of care, specialty, patient-physician interactions (visits)) and (iii) treatment characteristics (condition severity, comorbidities, time, and type of prescription).
(b). This also includes controls variables for: (i) averages of the explanatory variables for each i; (ii) time dummies (week), (iii) time averages for each i and (iv) dummies for the number of total time periods used for each i.

b. Divide the analysis between General Practitioners and Specialists.

Approximately 83.36 % of the prescription episodes presented in our sample are associated to a General Practitioner, while the remaining 16.64% is associated to a Specialist. By isolating General Practitioners and Specialists, we are providing further input on supply-side factors and consider the differentials of adherence towards these two categories of providers.

Results [38] from a sample of e-prescriptions from General Practitioners are presented on Table 3.13 and results [39] from a sample of e-prescriptions from Specialists are presented on Table 3.14.

General Practitioners as principal physicians present a positive effect on adherence levels, increasing it from 2.6 to 4.9pp. When the principal physician has a medical specialty, the effect towards primary adherence keeps presenting positive results that can range from 1.9 to 5pp.

In both cases, the public health setting as well as its interaction with the principal physician keep showing a negative effect on primary adherence.

[38] Restricting our sample to GPs: Results achieved when using the measure HHI prove a positive impact on adherence levels of 6.2 to 8.9pp, respectively. The public setting decreases adherence by 0.6 to 0.7pp (for further details please consider Appendix 3.18).
Results from the Probit Model are consistent with the approach on Table 3.13, showing an increase of 1.2 to 2.7pp on adherence levels when associated to a principal physician that is a General Practitioner (for further details please consider Appendix 3.19).

[39] Restricting our sample to Specialists: Results achieved when using the measure HHI prove a positive impact on adherence levels of 6.3 to 10.1pp, respectively. The public setting decreases adherence by 3.1 to 5pp (for further details please consider Appendix 3.20).
Results from the Probit Model are consistent with the approach on Table 3.14, showing an increase of 2.4 to 5.2pp on adherence levels when associated to a principal physician that has a specialty (for further details please consider Appendix 3.21).

Table 3.13 - Determinants of primary adherence considering a sample of General Practitioners. Dependent Variable: Share Dispensed Drugs (Fractional)

	OLS - Coefficient (a)			FPM – Marginal Effects: Cross Sectional (a)			FPM – Marginal Effects: Longitudinal (a) (b)		
UCP	0.047***			0.046***			0.031***		
	(0.002)			(0.002)			(0.004)		
ATP		0.049***			0.047***			0.031***	
		(0.002)			(0.002)			(0.004)	
UCP - year			0.043***			0.042***			0.026***
			(0.002)			(0.002)			(0.003)
public	-0.008**	-0.007*	-0.005	-0.009**	-0.009**	-0.006	0.0043	0.005	0.0067
	(0.004)	(0.004)	(0.004)	(0.004)	(0.004)	(0.004)	(0.006)	(0.006)	(0.006)
*UCP * public*	-0.029***			-0.026***			-0.036***		
	(0.002)			(0.002)			(0.004)		
*ATP * public*		-0.031***			-0.028***			-0.036***	
		(0.002)			(0.002)			(0.004)	
*UCP – year * public*			-0.032***			-0.029***			-0.026***
			(0.002)			(0.002)			(0.003)
R-Squared	0.208	0.208	0.208	-	-	-	-	-	-
Number of Observations	1,136,825	1,136,825	1,136,825	1,136,825	1,136,825	1,136,825	1,136,825	1,136,825	1,136,825

Notes:
Dependent Variable: Share Dispensed Drugs (Fractional)
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
(a). Regression includes controls variables for: (i) patient sociodemographic characteristics (age, gender, patient location (region), health insurance); (ii) health sector characteristics (type of care, specialty, patient-physician interactions (visits)) and (iii) treatment characteristics (condition severity, comorbidities, time and type of prescription).
(b). This also includes controls variables for: (i) averages of the explanatory variables for each i; (ii) time dummies (week), (iii) time averages for each i and (iv) dummies

for the number of total time periods used for each i.

Table 3.14 - Determinants of primary adherence considering a sample of Specialists. Dependent Variable: Share Dispensed Drugs (Fractional)

	OLS - Coefficient (a)			FPM – Marginal Effects: Cross Sectional (a)			FPM – Marginal Effects: Longitudinal (a) (b)		
UCP	0.050***			0.049***			0.021***		
	(0.003)			(0.003)			(0.005)		
ATP		0.049***			0.048***			0.019***	
		(0.003)			(0.003)			(0.004)	
UCP - year			0.049***			0.049***			0.019***
			(0.003)			(0.003)			(0.004)
public	-0.049***	-0.048***	-0.042***	-0.048***	-0.047***	-0.041***	-0.033***	-0.032***	-0.029***
	(0.002)	(0.002)	(0.003)	(0.002)	(0.002)	(0.003)	(0.004)	(0.004)	(0.004)
*UCP * public*	-0.062***			-0.063***			-0.017***		
	(0.003)			(0.003)			(0.006)		
*ATP * public*		-0.062***			-0.063***			-0.020***	
		(0.003)			(0.003)			(0.006)	
*UCP – year * public*			-0.066***			-0.067***			-0.030***
			(0.003)			(0.003)			(0.005)
R-Squared	0.141	0.140	0.140	-	-	-	-	-	-
Number of Observations	226,953	226,953	226,953	226,953	226,953	226,953	226,953	226,953	226,953

Notes:
Dependent Variable: Share Dispensed Drugs (Fractional)
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
(a). Regression includes controls variables for: (i) patient sociodemographic characteristics (age, gender, patient location (region), health insurance); (ii) health sector characteristics (type of care, specialty, patient-physician interactions (visits)) and (iii) treatment characteristics (condition severity, comorbidities, time and type of prescription).
(b). This also includes controls variables for: (i) averages of the explanatory variables for each i; (ii) time dummies (week), (iii) time averages for each i and (iv) dummies for the number of total time periods used for each i.

V. Changes on Treatment Measures

a. Exclusion of the first prescription and the first six months of therapy.

First prescriptions as well as the first six months of therapy introduce a short-term perspective on prescriptions. Chronic conditions, such as diabetes, require a long-term follow-up with regular prescriptions and visits to the physician. Our data consider that the initial period of prescription presents lower values of adherence, which can be related with the patient-provider long-term relationship. For this reason, we decided to exclude these observations and check the effect on the principal physician estimated coefficient.

Results [40] from a sample of e-prescriptions that excludes first-time prescriptions are presented on Table 3.15 and results [41] from a sample of e-prescriptions that excludes the first 6 months of treatment are presented on Table 3.16. Regression results show us the same direction of effect on adherence.

When excluding first-time prescriptions, the principal physicians present a positive effect on adherence levels, increasing it from 2.9pp to 5.5pp. When excluding the first 6 months, the effect towards primary adherence keeps presenting positive results that can range from 2.9pp to 5.8pp.

In both cases, the public health setting as well as its interaction with the principal physician keep showing a negative effect on primary adherence.

[40] Removing first prescriptions from our sample: Results achieved when using the measure HHI prove a positive impact on adherence levels of 6.9 to 10.7pp. The public setting decreases adherence by 2.5 to 5.7pp (for further details please consider Appendix 3.22).
Results from the Probit Model are consistent with the approach on Table 3.15, showing an increase of 2 to 4.1pp on adherence levels when associated to a principal physician after the first prescription (for further details please consider Appendix 3.23).

[41] Removing first 6 months of prescriptions from our sample: Results achieved when using the measure HHI prove a positive impact on adherence levels of 6.9 to 11.7pp. The public setting decreases adherence by 3.4 to 5.8pp (for further details please consider Appendix 3.24). Results from the Probit Model are consistent with the approach on Table 3.16, showing an increase of 2.2 to 4.7pp on adherence levels when associated to a principal physician after the first six months of treatment (for further details please consider Appendix 3.25).

Table 3.15 - Determinants of primary adherence excluding first-time prescriptions. Dependent Variable: Share Dispensed Drugs (Fractional)

	OLS - Coefficient (a)			FPM – Marginal Effects: Cross Sectional (a)			FPM – Marginal Effects: Longitudinal (a) (b)		
UCP	0.055***			0.052***			0.029***		
	(0.002)			(0.002)			(0.003)		
ATP		0.055***			0.053***			0.029***	
		(0.002)			(0.002)			(0.003)	
UCP - year			0.029***			0.021***			0.027***
			(0.002)			(0.001)			(0.002)
public	-0.059***	-0.058***	-0.026***	-0.052***	-0.052***	-0.026***	-0.036***	-0.035***	-0.033***
	(0.002)	(0.002)	(0.002)	(0.002)	(0.002)	(0.001)	(0.002)	(0.002)	(0.002)
*UCP * public*	-0.038***			-0.035***			-0.029***		
	(0.002)			(0.002)			(0.003)		
*ATP * public*		-0.039***			-0.036***			-0.029***	
		(0.002)			(0.002)			(0.003)	
*UCP – year * public*			-0.027***			-0.018***			-0.026***
			(0.002)			(0.002)			(0.002)
R-Squared	0.186	0.186	0.251	-	-	-	-	-	-
Number of Observations	1,288,932	1,288,932	1,288,932	1,288,932	1,288,932	1,288,932	1,288,932	1,288,932	1,288,932

Notes:
Dependent Variable: Share Dispensed Drugs (Fractional)
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
(a). Regression includes controls variables for: (i) patient sociodemographic characteristics (age, gender, patient location (region), health insurance); (ii) health sector characteristics (type of care, specialty, patient-physician interactions (visits)) and (iii) treatment characteristics (condition severity, comorbidities, time and type of prescription).
(b). This also includes controls variables for: (i) averages of the explanatory variables for each i; (ii) time dummies (week), (iii) time averages for each i and (iv) dummies for the number of total time periods used for each i.

Table 3.16 - Determinants of primary adherence excluding first 6 months of prescriptions. Dependent Variable: Share Dispensed Drugs (Fractional)

	OLS - Coefficient (a)			FPM – Marginal Effects: Cross Sectional (a)			FPM – Marginal Effects: Longitudinal (a) (b)		
UCP	0.058***			0.056***			0.029***		
	(0.002)			(0.002)			(0.003)		
ATP		0.059***			0.057***			0.0293***	
		(0.002)			(0.002)			(0.003)	
UCP - year			0.057***			0.055***			0.028***
			(0.002)			(0.002)			(0.002)
public	-0.061***	-0.060***	-0.054***	-0.053***	-0.053***	-0.047***	-0.036***	-0.035***	-0.033***
	(0.002)	(0.002)	(0.002)	(0.002)	(0.002)	(0.002)	(0.002)	(0.002)	(0.003)
*UCP * public*	-0.039***			-0.037***			-0.029***		
	(0.002)			(0.002)			(0.003)		
*ATP * public*		-0.041***			-0.038***			-0.029***	
		(0.002)			(0.002)			(0.003)	
*UCP – year * public*			-0.048***			-0.044***			-0.027***
			(0.002)			(0.002)			(0.002)
R-Squared	0.175	0.175	0.175	-	-	-	-	-	-
Number of Observations	1,208,917	1,208,917	1,208,917	1,208,917	1,208,917	1,208,917	1,208,917	1,208,917	1,208,917

Notes:
Dependent Variable: Share Dispensed Drugs (Fractional)
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
(a). Regression includes controls variables for: (i) patient sociodemographic characteristics (age, gender, patient location (region), health insurance); (ii) health sector characteristics (type of care, specialty, patient-physician interactions (visits)) and (iii) treatment characteristics (condition severity, comorbidities, time and type of prescription).
(b). This also includes controls variables for: (i) averages of the explanatory variables for each i; (ii) time dummies (week), (iii) time averages for each i and (iv) dummies for the number of total time periods used for each i.

3.6 Discussion

Therapeutic non-adherence is a worldwide concern. It hinders treatments' effectiveness for many conditions, increasing mortality, and the economic burden for health systems (Fischer et al., 2011; McGovern et al., 2016).

This study contributes to a better understanding of the drivers of primary adherence. In particular, the study analyses the role of the principal physician on primary adherence while controlling for patient, healthcare sector, and treatment characteristics.

There is a considerable proportion of people with Type-2 diabetes (T2DM) that do not take their medication as prescribed. McGovern et al. (2016) show that only 67–85% of the prescribed oral medication doses are taken, and Khan and Socha-Dietrich (2018) estimate that only 50 to 70% of individuals take their medications regularly. In our case, we estimate that the average share of dispensed drugs per prescription is 68,8%, with 17,86% of prescriptions not being filled at all.

T2DM is more frequent in adults. It occurs when the body becomes resistant to insulin or doesn't produce enough insulin. It affects 95.92% of our full database and is treated mainly by the use of oral hypoglycaemic agents (82.22% use it exclusively and 8.31% in combination with insulin (Bloomgarden et al., 2017; Gaviria-Mendoza et al., 2018)).

Patients wouldn't have access to proper treatment and advice if the interaction between them and the physician didn't exist. The physician influence on health outcomes extends beyond the choice of clinical therapy. They also promote patient adherence behaviour (Krueger et al., 2005; Gellad et al., 2009). This influence is assessed by studying this pairing scheme for a sufficiently long period to provide meaningful measures of patient adherence and trust.

This study adds to the literature by considering the study of primary adherence, and by filling the gaps presented by Kwok (2019), Fadlon and Van Parys (2020) and Sabety (2020), namely by not being limited to primary-care physicians, and by providing input on supply-side factors such as the influence of healthcare sector – public *vs.* private as well as primary- *vs.* hospital care.

We do it by implementing a fractional regression model approach that considers the filled fraction of prescribed drugs as the dependent variable and uses a set of control variables for patient, healthcare system, and treatment characteristics as explanatory variables. Our main variables of interest are the effect of the principal physician, the effect of the setting

where the interaction takes place (public *vs.* private health sector) as well as the number of visits between both parties.

Our main result suggests a positive relationship between the existence of a principal physician and primary adherence. This follows the same direction as the existing literature that considers that patients become more involved in the therapeutic process and more motivated to make healthy decisions in the presence of a principal physician. In particular, it may increase adherent and consistent behaviours (Atella et al., 2017; Arab et al., 2014; Borgsteede et al., 2011; Orom et al., 2018; Schwartz et al., 2017). The random process by which patients are assigned to physicians and physicians to patients in the public sector hinders potential endogeneity concerns, but also makes it trickier for trust to be developed. Following Orom et al. (2018), the better the quality of the physician-patient interaction, the more significant is the treatment adherence and, therefore, more likely is to ultimately improve patient outcomes and healthcare efficiency. Polinski et al. (2014) and Lee et al. (2018) state that "*poor patient-physician communication caused patients' distrust in the healthcare provider*" which will increase nonadherence. This result reinforces the importance of a proper agency relationship on individual medication adherence.

Efforts should be made to provide a proper match between these two relevant players. Greater trust in a particular physician improves treatment adherence, leads to lifestyle changes, and ultimately better clinical outcomes, namely the reduction of unnecessary hospitalizations which translates into significant excess costs (Orom et al., 2018).

Patients interact with other physicians, so to understand the level of trust and confidence on a particular physician and relationship, we included the effect of other physicians that the patient may consult with, as well as the number of visits to the healthcare system. Although a principal physician is good for the patient in terms of treatment stability and confident relationship, other physicians that the patient consult with introduce a factor of increasing knowledge to the patient who becomes more aware of different interactions, perspectives, and methods of dealing with him (Cutler et al., 2019). Nevertheless, we must bear in mind that the more physicians he interacts with, the less confidence level will be achieved in a relationship. An increasing number of visits to the healthcare system also reveals an increasing number of interactions between the physician-patient pair. This enhances the importance of the existence of a long-run agency-relationship between the

patient and the physician that could bring positive aspects for both but also to the health system.

The health setting where this interaction takes place also matters. Our analysis shows a negative influence on adherence of the public setting, with this effect being accentuated when we interact the principal physician and public healthcare sector. The literature does not provide any information regarding the influence of the healthcare sector on primary adherence, which means that the discussion will take into consideration the perceptions on the results based on the Portuguese NHS context.

The National Health Service [42] provides universal coverage and a broad range of benefits (Simões et al., 2017). Approximately half of the population is exempt and on the past few years, reforms were focused in improving access to care and tackling shortages in the health workforce.

According to Section 1 – subsection 1.2, patients are only allowed to choose the physician in specific cases, mainly on the private sector. For this reason, it can happen that when the patient is allowed to switch physician and choose the one who he feels most comfortable with, he will be more likely to adhere and proceed with therapeutics (Simões et al., 2017).

As such, we reinforce the need of working in the direction of providing and building a strong and valuable relationship between the patient and the provider.

The study of the different factors involved on adherence is a matter of great concern that requires study to provide evidence to decision-makers and improve patient health outcomes.

[42] Available at https://ec.europa.eu/health/sites/health/files/state/docs/2019_chp_pt_english.pdf (accessed at January 25, 2020)

3.7 Concluding Remarks

The aim of this study is to provide additional evidence on what extent the patient is more prone to higher adherence levels when associated to her principal physician. The setting where this relationship is established (public vs. private health provider) also matters and we were also able to test where this effect is more evident.

Adherence rate is defined as patients who do fill the prescribed medication according to the Portuguese prescription rules (primary non-adherence) and we expressed it as the rate of filled medication amongst the prescribed within a prescription episode. Approximately 82.1% of prescriptions contain at least one drug that was dispensed and the average adherence rate for the selected period is 68.9%.

We build on the framework of a physician-patient agency relationship and use a Fractional Regression Model as our principal econometric approach, while considering a large longitudinal matched physician-prescription-patient dataset for all Portuguese e-prescriptions containing information on prescription and dispensing, for the period between January 2015 and October 2019 for all regions in Portugal.

We provide key contributions to the current literature on the field of physician-patient relationship. Our study provides evidence of an increase on adherence levels when the prescription is issued by the principal physician. Adherence can also be influenced by the setting where this interaction is established. The public health setting as well as the presence of the principal physician in the public health setting, provided by the interaction between the two variables, presents a negative impact on adherence levels.

The positive influence of the principal physician on patients' health behaviour and the decision to follow the recommended therapy supports the need for customized interventions and the increase in the number of 'Family Doctors' within the NHS.

These strategies should also be focusing their attention on the public health setting due to their negative impact on adherence and since most interactions are happening in this location.

An increase on the number of 'Family Doctors' would introduce several benefits to the NHS. First, it would reduce the number of patients that are not assigned to a specific physician. This would give the opportunity to increase the follow-up levels and introduce long-term relationships. Second, it would reduce the ratio of patients per physician leading to higher levels of attention given to the patient on each interaction. This would

give more time per visit as well as it would improve communication and trust levels within the interaction.

The suggested benefits were able to improve adherence as well as reduce indirect costs to the health service, such as worse health outcomes and unnecessary hospitalizations.

3.8 Appendix

Appendix 3.1 - Statistics regarding the patient characteristics for the public and private sector

		PUBLIC			PRIVATE			DIFFERENCE	
Variable	Description	N	Mean	Std. Dev.	N	Mean	Std. Dev.	diff = mean(priv.) - mean(pub.)	
Patient Gender	=1 for females, 0 otherwise	1,107,279	0.517	0.500	256,499	0.539	0.498	0.022	***
Patient Age	Patient's Age	1,107,279	68.144	11.499	256,499	69.993	13.585	1.850	***
Insurance Type	=1 for NHS, 0 otherwise	1,107,279	0.926	0.261	256,499	0.844	0.363	-0.082	***
Lower Income	=1 if lower income, 0 otherwise	1,107,279	0.373	0.483	256,499	0.270	0.444	-0.103	***

Notes:
*** p<0.01, ** p<0.05, * p<0.1

Appendix 3.2 - Statistics on adherence levels associated with the patient characteristics for the public and private sector

		PUBLIC			PRIVATE			DIFFERENCE	
Variable	Description	N	Mean	Std. Dev.	N	Mean	Std. Dev.	diff = mean(priv.) - mean(pub.)	
Patient Gender	=1 if female	571,921	0.684	0.392	138,220	0.670	0.424	-0.014	***
	=0 otherwise	535,358	0.701	0.383	118,279	0.678	0.415	-0.024	***
Patient Age (10-year interval)	=1 if < 20 years old	308	0.539	0.425	199,000	0.596	0.417	0.057	*
	=2 if 20 – 29	2,359	0.551	0.428	10,599	0.574	0.437	0.023	*
	=3 if 30 – 39	10,487	0.616	0.417	40,450	0.593	0.441	-0.023	***
	=4 if 40 – 49	52,932	0.646	0.400	120,898	0.628	0.425	-0.018	***
	=5 if 50 – 59	179,021	0.673	0.390	350,655	0.650	0.418	-0.022	***
	=6 if 60 – 69	335,394	0.697	0.384	610,597	0.672	0413	-0.026	***
	=7 if 70 – 79	340,376	0.706	0.385	690,150	0.673	0.419	-0.033	***
	=8 if 80 – 89	169,113	0.698	0.390	580,657	0.697	0.423	-0.001	-
	=9 if >= 90 years old	17,289	0.696	0.393	120,294	0.731	0.415	0.036	***
Insurance Type	=1 for NHS	1,025,601	0.695	0.387	216,475	0.679	0.419	-0.015	***
	=0 otherwise	81,678	0.665	0.401	40,024	0.642	0.424	-0.023	***
Lower Income	=1 if lower income	412,528	0.706	0.387	69,196	0.708	0418	0.002	-
	=0 otherwise	694,751	0.685	0.388	187,303	0.661	0.420	-0.024	***

Notes:
*** p<0.01, ** p<0.05, * p<0.1

Appendix 3.3 - Statistics regarding the healthcare characteristics divided by public and private sector

		PUBLIC			PRIVATE			DIFFERENCE	
Variable	Description	N	Mean	Std. Dev.	N	Mean	Std. Dev.	diff = mean(priv.) - mean(pub.)	
Physician Specialty	=1 if General Practitioner	1,107,279	0.895	0.306	256,499	0.567	0.495	-0.328	***
	=2 if Endocrinologist	1,107,279	0.016	0.124	256,499	0.090	0.286	0.075	***
	=3 if Internal Medicine	1,107,279	0.052	0.223	256,499	0.121	0.327	0.069	***
	=4 if Other	1,107,279	0.037	0.188	256,499	0.221	0.415	0.184	***
Primary Care	=1 if Primary Care, 0 otherwise	1,107,279	0.858	0.349	256,499	0.011	0.102	-0.847	***
Other physicians	Physicians seen by patient (besides principal physician)	1,107,279	2.938	2.490	256,499	2.806	2.682	-0.131	***
Number of Visits	Number of visits made by patient to any physician	1,107,279	11.004	9.170	256,499	14.154	12.942	3.149	***

Notes:
*** p<0.01, ** p<0.05, * p<0.1

Appendix 3.4 - Statistics on adherence levels associated with the healthcare characteristics divided by public and private sector

		PUBLIC			PRIVATE			DIFFERENCE	
Variable	Description	N	Mean	Std. Dev.	N	Mean	Std. Dev.	diff = mean(priv.) - mean(pub.)	
Physician Specialty	General Practitioner	991,319	0.704	0.384	145,506	0.700	0.417	-0.004	***
	Endocrinologist	17,340	0.568	0.397	23,128	0.604	0.398	0.036	***
	Internal Medicine Physician	58,015	0.599	0.407	31,139	0.648	0.418	0.049	***
	Other Specialty	40,605	0.587	0.421	56,726	0.648	0.430	0.061	***
Primary Care	=1 if Primary Care	950,100	0.715	0.377	2,718	0.659	0.432	-0.057	***
	=0 otherwise	157,179	0.555	0422	253,781	0.674	0.420	0.119	***
Other physicians	Other Physicians = 0	169,862	0.687	0.390	49,335	0.658	0.432	-0.028	***
	Other Physicians = 1-3	561,211	0.698	0.386	127,354	0.686	0.415	-0.012	***
	Other Physicians = 4-6	277,458	0.693	0.389	55,288	0.665	0.419	-0.028	***
	Other Physicians = 7-9	77,399	0.678	0.395	17,812	0.666	0.415	-0.011	***
	Other Physicians >=10	21,349	0.647	0.404	6,710	0.636	0.427	-0.011	*
Number of Visits	Number of Visits = 1-2	85,646	0.364	0.421	21,079	0.394	0.452	0.030	***
	Number of Visits = 2-5	210,718	0.563	0.420	42,301	0.505	0.452	-0.058	***
	Number of Visits = 5-10	292,671	0.733	0.363	54,021	0.654	0.422	-0.079	***
	Number of Visits = 10-15	219,734	0.780	0.333	42,284	0.734	0385	-0.046	***
	Number of Visits = 15-20	134,001	0.781	0.333	31,300	0.764	0.366	-0.016	***
	Number of Visits = 20-25	74,343	0.774	0.340	21,732	0.786	0.353	0.012	***
	Number of Visits = 25-30	40,655	0.767	0.347	14,749	0.797	0.348	0.030	***
	Number of Visits >=30	49,511	0.763	0.354	29,033	0.825	0.332	0.062	***

Notes:
*** p<0.01, ** p<0.05, * p<0.1

Appendix 3.5 - Statistics regarding the treatment characteristics for public and private health sector

		PUBLIC			PRIVATE			DIFFERENCE	
Variable	Description	N	Mean	Std. Dev.	N	Mean	Std. Dev.	diff = mean(priv.) - mean(pub.)	
Diabetes Severity	Number of antidiabetic drugs (per patient)	1,107,279	1.402	0.671	256,499	1.327	0.634	-0.076	***
Level of Comorbidities	Number of other comorbidities (per patient)	1,107,279	2.140	1.286	256,499	2.007	1.321	-0.133	***
Renewable Prescription	=1 if Renewable Prescription; 0 otherwise	1,107,279	0.598	0.490	256,499	0.307	0.461	-0.291	***
Induced Prescription	=1 if prescription contains drugs that are specifically selected by the physician; 0 otherwise	1,107,279	0.451	0.498	256,499	0.341	0.474	-0.110	***

Notes:
*** p<0.01, ** p<0.05, * p<0.1

Appendix 3.6 - Statistics on adherence levels associated with treatment characteristics for public and private health sector

		PUBLIC			PRIVATE			DIFFERENCE	
Variable	Description	N	Mean	Std. Dev.	N	Mean	Std. Dev.	diff = mean(priv.) - mean(pub.)	
Diabetes Severity	Therapeutic guideline = 1	528,593	0.693	0.396	130,766	0.678	0.428	-0.015	***
	Therapeutic guideline = 2	378,352	0.695	0.387	90,530	0.675	0.417	-0.020	***
	Therapeutic guideline = 3	200,334	0.687	0.367	35,203	0.653	0.392	-0.034	***
Level of Comorbidities	0	125,892	0.717	0.394	38,140	0.677	0.424	-0.040	***
	1	253,682	0.703	0.387	61,970	0.683	0.419	-0.020	***
	2	285,466	0.697	0.385	63,042	0.680	0.418	-0.016	***
	3	224,177	0.687	0.386	46,729	0.673	0.417	-0.014	***
	4	218,062	0.666	0.391	46,618	0.649	0.421	-0.017	***
Renewable Prescription	=1 if Renewable Prescription	661,911	0.795	0.285	78,659	0.765	0.298	-0.291	***
	=0 otherwise	445,368	0.540	0.463	177,840	0.633	0.458	-0.031	***
Induced Prescription	=1 if prescription contains drugs that are specifically selected by the physician	499,654	0.689	0.386	87,463	0.669	0.413	-0.020	***
	=0 otherwise	607,625	0.696	0.390	169,036	0.676	0.423	-0.020	***

Notes:
*** p<0.01, ** p<0.05, * p<0.1

Appendix 3.7 - Statistics on adherence levels by public and private sector.

		PUBLIC			PRIVATE			DIFFERENCE	
Variable	Description	N	Mean	Std. Dev.	N	Mean	Std. Dev.	diff = mean(priv.) - mean(pub.)	
Share Dispensed Drugs (Fraction)	Share of dispensed drug per prescription	1,107,279	0.692	0.388	256,499	0.674	0.420	-0.019	***
Dispensed Prescription (Binary)	= 1 if prescription contains at least one filled drug, 0 otherwise	1,107,279	0.833	0.373	256,499	0.773	0.419	-0.059	***
First Prescription (Baseline Adherence)	= 1 if prescription corresponds to the first contact between the patient and the physician	59,130	0.442	0.437	15,716	0.451	0.460	0.009	**
	= 0 otherwise	1,048,149	0.707	0.380	240,783	0.688	0.413	-0.019	***
First 6 months	= 1 if prescriptions correspond to the first 6 months of treatment	121,650	0.484	0.435	33,211	0.455	0.461	-0.029	***
	= 0 otherwise	985,629	0.718	0.374	223,288	0.706	0.403	-0.012	***

Notes:
*** p<0.01, ** p<0.05, * p<0.1

Appendix 3.8 - Statistics regarding the agency relationship between patient and physician divided by public and private sector

		PUBLIC			PRIVATE			DIFFERENCE	
Variable	Description	N	Mean	Std. Dev.	N	Mean	Std. Dev.	diff = mean(priv.) - mean(pub.)	
Usual Care Provider	=1 if principal physician (for a specific patient), 0 otherwise	1,107,279	0.679	0.467	256,499	0.649	0.477	-0.030	***
Active-Treatment Provider	=1 if principal physician (for a specific patient), 0 otherwise	1,107,279	0.684	0.465	256,499	0.656	0.475	-0.027	***
Usual Care Provider (Year)	=1 if principal physician (for a specific patient, for a specific year), 0 otherwise	1,107,279	0.738	0.440	256,499	0.725	0.446	-0.013	***
Second Principal Physician	=1 if second principal physician (for a specific patient), 0 otherwise	1,107,279	0.112	0.316	256,499	0.145	0.352	0.032	***
Interaction Usual Care Provider-Public	=1 if principal physician works in public sector, 0 otherwise	1,107,279	0.679	0.467	256,499	0.000	0.000	-0.679	***
Interaction Active-Treatment Provider - Public	=1 if principal physician works in public sector, 0 otherwise	1,107,279	0.684	0.465	256,499	0.000	0.000	-0.684	***
Usual Care Provider (Year) - Public	=1 if principal physician (year) works in public sector, 0 otherwise	1,107,279	0.738	0.440	256,499	0.000	0.000	-0.738	***
Interaction Second Principal Physician - Public	=1 if second principal physician works in public sector, 0 otherwise	1,107,279	0.112	0.316	256,499	0.000	0.000	-0.112	***

Notes:
*** p<0.01, ** p<0.05, * p<0.1

Appendix 3.9 - Statistics on adherence levels associated with the agency relationship between patient and physician for the public and private sector

		PUBLIC			PRIVATE			DIFFERENCE	
Variable	Description	N	Mean	Std. Dev.	N	Mean	Std. Dev.	diff = mean(priv.) - mean(pub.)	
Usual Care Provider	=1 if principal physician (for a specific patient)	751,739	0.707	0.382	166,418	0.692	0.416	-0.015	***
	=0 otherwise	355,540	0.662	0.399	90,081	0.640	0.424	-0.022	***
Active-Treatment Provider	=1 if principal physician (for a specific patient)	757,135	0.706	0.382	168,372	0.692	0.416	-0.014	***
	=0 otherwise	350,144	0.662	0.399	88,127	0.638	0.425	-0.024	***
Usual Care Provider (Year)	=1 if principal physician (for a specific patient, for a specific year)	817,396	0.699	0.001	186,026	0.686	0.001	-0.013	***
	=0 otherwise	289,883	0.674	0.001	70,473	0.642	0.002	-0.033	***
Second Principal Physician	=1 if second principal physician (for a specific patient)	124,400	0.671	0.394	37,123	0.650	0.421	-0.021	***
	=0 otherwise	982,879	0.695	0.387	219,376	0.678	0.419	-0.018	***

Notes:
*** p<0.01, ** p<0.05, * p<0.1

Appendix 3.10 – Determinants of primary adherence considering the physician-patient interaction. Dependent Variable: Share Dispensed Drugs (Fractional) – Complementary approach

	OLS - Coefficient	FPM – Marginal Effects: Cross Sectional (a)	FPM – Marginal Effects: Panel (a) (b)
HHI	0.104***	0.101***	0.069***
	(0.002)	(0.002)	(0.006)
public	-0.051***	-0.046***	-0.032***
	(0.002)	(0.002)	(0.002)
*HHI * public*	-0.058***	-0.054***	-0.073***
	(0.002)	(0.002)	(0.006)
Observations	1,363,778	1,363,778	1,363,778

Notes:
Dependent Variable: Share Dispensed Drugs (Fractional)
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
(a). Regression includes controls variables for: (i) patient sociodemographic characteristics (age, gender, patient location (region), health insurance); (ii) health sector characteristics (type of care, specialty, patient-physician interactions (visits)) and (iii) treatment characteristics (condition severity, comorbidities, time, and type of prescription).
(b) Regression includes controls variables for: (i) averages of the explanatory variables for each i; (ii) time dummies (week), (iii) time averages for each i and (iv) dummies for the number of total time periods used for each i. We also control for physician and location (region).

Appendix 3.11 - Determinants of primary adherence considering the physician-patient interaction. Dependent Variable: Dispensed Drugs (Binary) – Complementary approach

	Probit – Marginal Effects (a)			
UCP	0.019***			
	(0.001)			
ATP		0.019***		
		(0.001)		
UCP - year			0.021***	
			(0.001)	
HHI				0.039***
				(0.002)
public	-0.026***	-0.026***	-0.023***	-0.025***
	(0.001)	(0.001)	(0.001)	(0.001)
*UCP * public*	-0.014***			
	(0.001)			
*ATP * public*		-0.015***		
		(0.001)		
*UCP - year * public*			-0.018***	
			(0.001)	
*HHI * public*				-0.019***
				(0.002)
Observations	1,363,778	1,363,778	1,363,778	1,363,778

Notes:
Dependent Variable: Share Dispensed Drugs (Fractional)
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
(a). Regression includes controls variables for: (i) patient sociodemographic characteristics (age, gender, patient location (region), health insurance); (ii) health sector characteristics (type of care, specialty, patient-physician interactions (visits)) and (iii) treatment characteristics (condition severity, comorbidities, time, and type of prescription).

Appendix 3.12 - Robustness Check IIa: Determinants of primary adherence considering the second principal physician-patient interaction. Dependent Variable: Share Dispensed Drugs (Fractional) – Complementary approach

	Probit Model – Marginal Effects (a)
second UCP	-0.024***
	(0.0018)
public	-0.036***
	(0.001)
*second UCP * public*	0.011***
	(0.002)
Observations	1,363,778

Notes:
Dependent Variable: Dispensed Prescription (Binary)
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
a). Regression includes controls variables for: (i) patient sociodemographic characteristics (age, gender, patient location (region), health insurance); (ii) health sector characteristics (type of care, specialty, patient-physician interactions (visits)) and (iii) treatment characteristics (condition severity, comorbidities, time and type of prescription).

Appendix 3.13 - Robustness Check IIb: Determinants of primary adherence considering a sample of principal physician-patient interaction. Dependent Variable: Dispensed Drugs (Binary) – Complementary approach

	Probit Model– Marginal Effects (a)	
public (UCP)	-0.038***	
	(0.002)	
public (ATP)		-0.038***
		(0.002)
Observations	918,157	925,507

Notes:
Dependent Variable: Dispensed Prescription (Binary)
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
a). Regression includes controls variables for: (i) patient sociodemographic characteristics (age, gender, patient location (region), health insurance); (ii) health sector characteristics (type of care, specialty, patient-physician interactions (visits)) and (iii) treatment characteristics (condition severity, comorbidities, time and type of prescription).

Appendix 3.14 - Robustness Check IIIa.1: Determinants of primary adherence considering a sample of individuals aged 70 or under. Dependent Variable: Share Dispensed Drugs (Fractional) – Complementary approach

	OLS - Coefficient (a)	FPM – Marginal Effects: Cross Sectional (a)	FPM – Marginal Effects: Longitudinal (a) (b)
HHI	0.092***	0.089***	0.032***
	(0.003)	(0.003)	(0.008)
public	-0.053***	-0.048***	-0.031***
	(0.002)	(0.002)	(0.003)
*HHI * public*	-0.064***	-0.059***	-0.048***
	(0.003)	(0.003)	(0.008)
R-Squared	0.203	-	-
Observations	696,899	696,899	696,899

Notes:
Dependent Variable: Share Dispensed Drugs (Fractional)
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
(a). Regression includes controls variables for: (i) patient sociodemographic characteristics (age, gender, patient location (region), health insurance); (ii) health sector characteristics (type of care, specialty, patient-physician interactions (visits)); and (iii) treatment characteristics (condition severity, comorbidities, time, and type of prescription).
(b). This also includes controls variables for: (i) averages of the explanatory variables for each i; (ii) time dummies (week), (iii) time averages for each i; and (iv) dummies for the number of total time periods used for each i.

Appendix 3.15 - Robustness Check IIIa.2: Determinants of primary adherence considering a sample of individuals aged 70 or under. Dependent Variable: Dispensed Drugs (Binary) – Complementary approach

	Probit Model – Marginal Effects (a)			
UCP	0.013***			
	(0.002)			
ATP		0.013***		
		(0.002)		
UCP - year			0.015***	
			(0.002)	
HHI				0.036***
				(0.003)
public	-0.030***	-0.029***	-0.028***	-0.025***
	(0.002)	(0.002)	(0.002)	(0.002)
*UCP * public*	-0.013***			
	(0.002)			
*ATP * public*		-0.014***		
		(0.002)		
*UCP - year * public*			-0.015***	
			(0.002)	
*HHI * public*				-0.030***
				(0.003)
Observations	696,899	696,899	696,899	696,899

Notes:
Dependent Variable: Dispensed Prescription (Binary)
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
(a). Regression includes controls variables for: (i) patient sociodemographic characteristics (age, gender, patient location (region), health insurance); (ii) health sector characteristics (type of care, specialty, patient-physician interactions (visits)) and (iii) treatment characteristics (condition severity, comorbidities, time and type of prescription).

Appendix 3.16 - Robustness Check IVa.1: Determinants of primary adherence considering a sample for public and private health setting. Dependent Variable: Share Dispensed Drugs (Fractional) – Complementary approach

	OLS - Coefficient (a)		FPM – Marginal Effects: Cross Sectional (a)		FPM – Marginal Effects: Panel (a) (b)	
HHI (public)	0.047***		0.049***		-0.013***	
	(0.001)		(0.001)		(0.002)	
HHI (private)		0.085***		0.086***		0.069***
		(0.003)		(0.0032)		(0.007)
R-Squared	0.217	0.150	-	-	-	-
Observations	1,107,279	256,499	1,107,279	256,499	1,107,279	256,499

Notes:
Dependent Variable: Share Dispensed Drugs (Fractional)
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
(a). Regression includes controls variables for: (i) patient sociodemographic characteristics (age, gender, patient location (region), health insurance); (ii) health sector characteristics (type of care, specialty, patient-physician interactions (visits)) and (iii) treatment characteristics (condition severity, comorbidities, time and type of prescription).
(b). This also includes controls variables for: (i) averages of the explanatory variables for each i; (ii) time dummies (week), (iii) time averages for each i and (iv) dummies for the number of total time periods used for each i.

Appendix 3.17 - Robustness Check IVa.2: Determinants of primary adherence considering a sample for public and private health setting. Dependent Variable: Dispensed Drugs (Binary) – Complementary approach

	Probit Model – Marginal Effects (a)	
UCP (public)	0.005***	
	(0.001)	
ATP (public)	0.005***	
	(0.001)	
UCP - year (public)	0.003***	
	(0.001)	
HHI (public)	0.019***	
	(0.001)	
UCP (private)		0.018***
		(0.002)
ATP (private)		0.019***
		(0.002)
UCP - year (private)		0.021***
		(0.002)
HHI (private)		0.042***
		(0.003)
Observations	1,107,279	256,499

Notes:
Dependent Variable: Dispensed Prescription (Binary)
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
(a). Regression includes controls variables for: (i) patient sociodemographic characteristics (age, gender, patient location (region), health insurance); (ii) health sector characteristics (type of care, specialty, patient-physician interactions (visits)) and (iii) treatment characteristics (condition severity, comorbidities, time and type of prescription).

Appendix 3.18 - Robustness Check IVb.1: Determinants of primary adherence considering a sample of General Practitioners. Dependent Variable: Share Dispensed Drugs (Fractional) – Complementary approach

	OLS - Coefficient (a)	FPM – Marginal Effects: Cross Sectional (a)	FPM – Marginal Effects: Longitudinal (a) (b)
HHI	0.089***	0.088***	0.062***
	(0.003)	(0.003)	(0.007)
public	-0.006	-0.007	0.0083
	(0.004)	(0.004)	(0.006)
*HHI * public*	-0.041***	-0.038***	-0.077***
	(0.003)	(0.003)	(0.008)
R-Squared	0.209	-	-
Observations	1,136,825	1,136,825	1,136,825

Notes:
Dependent Variable: Share Dispensed Drugs (Fractional)
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
(a). Regression includes controls variables for: (i) patient sociodemographic characteristics (age, gender, patient location (region), health insurance); (ii) health sector characteristics (type of care, specialty, patient-physician interactions (visits)) and (iii) treatment characteristics (condition severity, comorbidities, time, and type of prescription).
(b). This also includes controls variables for: (i) averages of the explanatory variables for each i; (ii) time dummies (week), (iii) time averages for each i and (iv) dummies for the number of total time periods used for each i.

Appendix 3.19 - Robustness Check IVb.2: Determinants of primary adherence considering a sample of General Practitioners. Dependent Variable: Dispensed Drugs (Binary) – Complementary approach

	Probit Model – Marginal Effects (a)			
UCP	0.013***			
	(0.002)			
ATP		0.014***		
		(0.002)		
UCP - year			0.012***	
			(0.002)	
HHI				0.027***
				(0.002)
public	0.0004	0.002	0.001	0.0008
	(0.003)	(0.003)	(0.003)	(0.003)
*UCP * public*	-0.006***			
	(0.002)			
*ATP * public*		-0.008***		
		(0.002)		
*UCP - year * public*			-0.0073***	
			(0.002)	
*HHI * public*				-0.008***
				(0.002)
Observations	1,136,825	1,136,825	1,136,825	1,136,825

Notes:
Dependent Variable: Dispensed Prescription (Binary)
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
(a). Regression includes controls variables for: (i) patient sociodemographic characteristics (age, gender, patient location (region), health insurance); (ii) health sector characteristics (type of care, specialty, patient-physician interactions (visits)) and (iii) treatment characteristics (condition severity, comorbidities, time, and type of prescription).

Appendix 3.20 - Robustness Check IVb.3: Determinants of primary adherence considering a sample of Specialists. Dependent Variable: Share Dispensed Drugs (Fractional) – Complementary approach

	OLS - Coefficient (a)	FPM – Marginal Effects: Cross Sectional (a)	FPM – Marginal Effects: Longitudinal (a) (b)
HHI	0.101***	0.099***	0.063***
	(0.004)	(0.005)	(0.011)
public	-0.050***	-0.049***	-0.031***
	(0.002)	(0.002)	(0.004)
*HHI * public*	-0.084***	-0.083***	-0.040***
	(0.005)	(0.005)	(0.014)
R-Squared	0.141	-	-
Observations	226,953	226,953	226,953

Notes:
Dependent Variable: Share Dispensed Drugs (Fractional)
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
(a). Regression includes controls variables for: (i) patient sociodemographic characteristics (age, gender, patient location (region), health insurance); (ii) health sector characteristics (type of care, specialty, patient-physician interactions (visits)) and (iii) treatment characteristics (condition severity, comorbidities, time, and type of prescription).
(b). This also includes controls variables for: (i) averages of the explanatory variables for each i; (ii) time dummies (week), (iii) time averages for each i and (iv) dummies for the number of total time periods used for each i.

Appendix 3.21 - Robustness Check IVb.4: Determinants of primary adherence considering a sample of Specialists. Dependent Variable: Dispensed Drugs (Binary) – Complementary approach

	Probit Model – Marginal Effects (a)			
UCP	0.025***			
	(0.002)			
ATP		0.024***		
		(0.002)		
UCP - year			0.029***	
			(0.003)	
HHI				0.052***
				(0.004)
public	-0.031***	-0.030***	-0.025***	-0.032***
	(0.002)	(0.002)	(0.003)	(0.002)
*UCP * public*	-0.034***			
	(0.003)			
*ATP * public*		-0.034***		
		(0.003)		
*UCP – year * public*			-0.039***	
			(0.003)	
*HHI * public*				-0.038***
				(0.005)
Observations	226,953	226,953	226,953	226,953

Notes:
Dependent Variable: Dispensed Prescription (Binary)
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
(a). Regression includes controls variables for: (i) patient sociodemographic characteristics (age, gender, patient location (region), health insurance); (ii) health sector characteristics (type of care, specialty, patient-physician interactions (visits)) and (iii) treatment characteristics (condition severity, comorbidities, time, and type of prescription).

Appendix 3.22 - Robustness Check Va.1: Determinants of primary adherence excluding first-time prescription. Dependent Variable: Share Dispensed Drugs (Fractional) – Complementary approach

	OLS - Coefficient (a)	FPM – Marginal Effects: Cross Sectional (a)	FPM – Marginal Effects: Longitudinal (a) (b)
HHI	0.107***	0.105***	0.069***
	(0.002)	(0.002)	(0.006)
public	-0.057***	-0.049***	-0.034***
	(0.002)	(0.002)	(0.002)
*HHI * public*	-0.059***	-0.054***	-0.072***
	(0.002)	(0.002)	(0.006)
R-Squared	0.187	-	-
Observations	1,288,932	1,288,932	1,288,932

Notes:
Dependent Variable: Share Dispensed Drugs (Fractional)
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
(a). Regression includes controls variables for: (i) patient sociodemographic characteristics (age, gender, patient location (region), health insurance); (ii) health sector characteristics (type of care, specialty, patient-physician interactions (visits)) and (iii) treatment characteristics (condition severity, comorbidities, time, and type of prescription).
(b). This also includes controls variables for: (i) averages of the explanatory variables for each i; (ii) time dummies (week), (iii) time averages for each i and (iv) dummies for the number of total time periods used for each i.

Appendix 3.23 - Robustness Check Va.2: Determinants of primary adherence excluding first-time prescription. Dependent Variable: Dispensed Drugs (Binary) – Complementary approach

	Probit Model – Marginal Effects (a)			
UCP	0.020***			
	(0.001)			
ATP		0.020***		
		(0.001)		
UCP - year			0.021***	
			(0.001)	
HHI				0.041***
				(0.002)
public	-0.029***	-0.028***	-0.026***	-0.028***
	(0.001)	(0.001)	(0.001)	(0.001)
*UCP * public*	-0.014***			
	(0.001)			
*ATP * public*		-0.015***		
		(0.001)		
*UCP - year * public*			-0.018***	
			(0.002)	
*HHI * public*				-0.020***
				(0.002)
Observations	1,288,932	1,288,932	1,288,932	1,288,932

Notes:
Dependent Variable: Dispensed Prescription (Binary)
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
(a). Regression includes controls variables for: (i) patient sociodemographic characteristics (age, gender, patient location (region), health insurance); (ii) health sector characteristics (type of care, specialty, patient-physician interactions (visits)) and (iii) treatment characteristics (condition severity, comorbidities, time, and type of prescription).

Appendix 3.24 - Robustness Check Va.3: Determinants of primary adherence excluding first 6 months of prescriptions. Dependent Variable: Share Dispensed Drugs (Fractional) – Complementary approach

	OLS - Coefficient (a)	FPM – Marginal Effects: Cross Sectional (a)	FPM – Marginal Effects: Longitudinal (a) (b)
HHI	0.117***	0.114***	0.069***
	(0.002)	(0.002)	(0.006)
public	-0.058***	-0.045***	-0.034***
	(0.002)	(0.002)	(0.002)
*HHI * public*	-0.064***	-0.059***	-0.072***
	(0.002)	(0.002)	(0.006)
R-Squared	0.176	-	-
Observations	1,208,917	1,208,917	1,208,917

Notes:
Dependent Variable: Share Dispensed Drugs (Fractional)
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
(a). Regression includes controls variables for: (i) patient sociodemographic characteristics (age, gender, patient location (region), health insurance); (ii) health sector characteristics (type of care, specialty, patient-physician interactions (visits)) and (iii) treatment characteristics (condition severity, comorbidities, time and type of prescription).
(b). This also includes controls variables for: (i) averages of the explanatory variables for each i; (ii) time dummies (week), (iii) time averages for each i and (iv) dummies for the number of total time periods used for each i.

Appendix 3.25 - Robustness Check Va.4: Determinants of primary adherence excluding first 6 months of prescriptions. Dependent Variable: Dispensed Drugs (Binary) – Complementary approach

	Probit Model - Margins dydx(*) (a)			
UCP	0.022***			
	(0.001)			
ATP		0.022***		
		(0.001)		
UCP - year			0.025***	
			(0.001)	
HHI				0.047***
				(0.002)
public	-0.029***	-0.029***	-0.026***	-0.028***
	(0.001)	(0.001)	(0.001)	(0.001)
*UCP * public*	-0.014***			
	(0.001)			
*ATP * public*		-0.015***		
		(0.001)		
*UCP - year * public*			-0.019***	
			(0.002)	
*HHI * public*				-0.023***
				(0.002)
Observations	1,208,917	1,208,917	1,208,917	1,208,917

Notes:
Dependent Variable: Dispensed Prescription (Binary)
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
(a). Regression includes controls variables for: (i) patient sociodemographic characteristics (age, gender, patient location (region), health insurance); (ii) health sector characteristics (type of care, specialty, patient-physician interactions (visits)) and (iii) treatment characteristics (condition severity, comorbidities, time and type of prescription).

4 Highway to health: primary adherence and health improvement

Abstract

Adherence to medication is key to ensure recovery from illness, particularly in the context of chronic conditions in which an effective disease management is essential to prevent sudden deterioration of the individuals' health and additional need for care.

We hypothesize that patients with lower levels of adherence are more likely to see their health level deteriorate and require more intensive treatment. We are also interest in knowing whether the number and type of interaction with the physician, namely number of previous visits and whether the physician works in a public or private setting, influence clinical outcomes.

We use a Fixed Effects Ordered Logit Model using a panel of patients' prescriptions and dispensing events within the universe of all prescriptions and dispensing in Portugal from January 2015 to October 2019 (N=1,363,778). The individual prescription data are matched with individual, physician, prescription drug, pharmacy, and geographical characteristics, enabling controlling for a broad range of cofounders.

We estimate that primary adherence to the prescribed medication increases the probability of controlling diabetes with monotherapeutic schemes, while decreasing the probability of transition to dual and triple therapy schemes.

Keywords: Medication Adherence, Prescription Drugs, Therapeutic Guidelines, Disease Severity, e-prescription, Diabetes Mellitus, Portugal

JEL Codes: I11, I13, I15

4.1 Introduction

"*Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments*" – R. Brian Haynes (2001) (Barnes et al., 2017)

Adherence to therapeutics is essential to achieve better outcomes. Patients tend to adhere to therapeutic regimens when they have some tangible sense that the prescribed medication contributes to positive and relatively immediate outcomes (Polonsky and Henry, 2016). Adherence rates are typically higher among patients with acute conditions when compared with those of patients with chronic conditions. Long-term adherence among patients with chronic conditions is disappointingly low, dropping most dramatically after the first six months of therapy (Osterberg and Blaschke, 2005), which represents a complex problem for health systems.

Many medical goods, such as prescription drugs are not demanded directly by patients (principal) but are requested on their behalf by a physician (agent). The physician acts on the patient's best interest, considering the available options. But the agent's and the principal's utility functions only partly coincide, as the professional's self-interest is also a relevant argument of his utility function (Cutler et al., 2015; Ludwig et al., 2010).

Patients are the central point of therapeutic decisions. They are the key decision-makers in the adherence process, having the power to decide whether to follow the physician's recommendations. The more firmly the patients believe that the prescribed medication is necessary and likely to increase their utility, the more adherent they are likely to be (Polonsky and Henry, 2016). When they decide not to comply with the treatment recommendation, patients may be inadvertently decreasing their own utility by contributing to poorer health outcomes and by triggering avoidable healthcare costs due to unnecessary hospitalization and visits to the doctor as medical problems evolve into forms that are even more expensive to treat (Wilke et al., 2013).

We study the importance of adherence in improving health outcomes in the context of the management of a chronic condition, diabetes. Diabetes is a common chronic condition, with a worldwide prevalence and with a significant number of available therapeutic alternatives. To be properly managed, it requires proper diagnosis and a therapeutic regimen that is adequate to the stage of the disease. If either of these fails, it can lead to severe complications, increased mortality, and a higher economic burden for patients and

the health system (Bussière et al., 2020; Kennedy-Martin et al., 2017; Lublóy et al., 2015; Morillas et al., 2015; Zahid et al., 2018; Zullig et al., 2015).

Diabetes is also a disease that has clearly defined clinical pathways and guidelines for treatment. The pharmacological approach considers three-levels – mono, double, and triple therapy. The transition between these levels requires the fulfilment of specific criteria. Although patients can interact with more than one physician, they are subject to the same therapeutic guidelines that conduct the physicians' decisions. Consequently, patients follow a pre-defined trajectory within the health system according to the referred criteria and the disease evolution, which facilitates the establishment of a relationship between transition across therapies and health status.

This study aims to answer the following questions: are patients with lower adherence levels more likely to see their health level deteriorate and require more intensive treatment? Is this effect also influenced by the number and type of interaction with the physician, namely number of previous visits and whether the physician works in a public or private setting?

To answer these questions, we use a Fixed Effects Ordered Logit Model as our principal econometric approach. This model is applied to both cross-sectional and longitudinal samples. The dependent variable is an ordered categorical variable represented by the three levels of clinical guidelines, and we include patients' fixed effects. Our main variables of interests are the primary adherence level, i.e., the filled fraction of prescribed drugs, the setting where the interaction takes place (public *vs.* private health sector), and the number of interactions between patient and physician.

We rely on a large longitudinal matched physician-prescription-patient dataset for all Portuguese e-prescriptions collected from Serviços Partilhados do Ministério da Saúde between January 2015 and October 2019 that contained at least one pharmaceutical used to treat Type-1 and Type-2 Diabetes Mellitus. This is a relevant database as prescriptions reflect the implemented therapeutic regime, as well as the patient decision to follow it observed based on the dispensing pattern. Overall, we analyse a sample of 27,125 physicians, 121,727 patients, 1,363,778 e-prescriptions and 28 different oral anti-diabetic pharmaceuticals, from all regions in Portugal.

This study makes some key contributions to the literature. First, we estimate the impact of primary adherence on disease progression while accounting for characteristics at the patient, healthcare system and treatment levels. Second, our attention goes towards medication primary adherence instead of secondary adherence, which has been the most

widely studied measure so far, but that may be a noisier measure of adherence. Primary adherence has the advantage of being a more objective measure of patients' compliance. The reason it has not been as used as secondary adherence is data unavailability, but the introduction of electronic prescriptions helps overcome that limitation.

Our results show that primary adherence to the prescribed medication increases the probability of controlling Diabetes with monotherapeutic schemes (level 1) by 10.4 percentage points. Furthermore, it decreases the probability of transition to dual therapy (level 2) by 0.9 percentage points. The effect of primary adherence is more expressive when patients are required to switch to triple therapy adjustment (level 3), i.e, the higher the adherence pattern, the lower is the probability of reaching higher levels of medication complexity (9.5 percentage points).

The fact that higher adherence hinders disease progression supports the need for customized interventions that incentivize compliance, with the subsequent impact on health and costs.

Other interesting finding that comes out of this study is the negative influence of the public health setting on disease progression. The public sector induces an improvement of the disease control while avoiding its progression in comparison with the private health setting. In fact, patients located at the public sector present higher probability of about 2.3 percentage points of staying monotherapy. Staying in this health setting decreases the probability of transitioning to dual therapy (level 2) by 0.2 percentage points and to triple therapy (level 3) by 2.1 percentage points. This is particularly relevant since the Portuguese NHS is majorly public.

The number of visits to the physician also play a noteworthy result. The more interactions they have the more likely it is for the patient to be associated to a more complex therapeutic regime. This not strange in the sense that physicians require more interaction about patients to produce better informed decisions.

Our results have some limitations. First, our database has limited information regarding some sociodemographic features such as the patients' education and income. Second, we lack information on some important doctor-level covariates such as age, gender or years of experience that could help us to better characterize the physician's influence on adherence.

The study is organized as follows. The next section reviews the literature on treatment adherence. Section 4.3 presents the data and the methodological approach. Section 4.4

presents the main results and section 4.5 provides a brief description of the robustness tests. These results are then discussed in section 4.6 and section 4.7 concludes.

4.2 Theoretical Background

4.2.1 Definition of Adherence

Non-adherence to prescribed therapeutic is a complex and dynamic problem. The terms "adherence" and "compliance" are often used interchangeably to characterize the extent in which a patient decides to follow the prescribed treatment. However, the meaning is slightly different, and the difference relies on how one perceives the patient-provider relationship (Hugtenburg et al., 2013).

Compliance is known as "the extent to which a person's behaviour in terms of taking medications, following a diet or changing lifestyle coincides with medical or health advice" (Vermeire et al., 2001). It is a paternalist approach as the patient passively follows the practitioners' instructions. The treatment plan is usually not based on a therapeutic alliance or contract established between the patient and the physician (Matias, 2019; Osterberg and Blaschke, 2005; Stavropoulou, 2012).

Adherence, on the other hand, is the preferred term (Hugtenburg et al., 2013). It "corresponds to the level of commitment to the agreed recommendations coming from a healthcare provider" (Hugtenburg et al., 2013) and it implies a more proactive attitude, as it assumes that the patient has a more active role. The patient, after being properly informed by the doctor, can decide whether to follow her recommendations (Lamiraud and Geoffard, 2007; Stavropoulou, 2012).

In the current study we use adherence to refer to patients' compliance to the prescribed medication as we cannot observe the patient's involvement level in the therapeutic decision.

4.2.2 Patient's Therapy and Medication Adherence: What are the contributing factors on Adherence and its effect on disease progression?

Adherence is a dynamic, complex, and multidimensional issue, especially when involving chronic conditions. It may occur at the initiation of the treatment, implementation of the prescribed regimen, and possible discontinuation of the pharmacotherapy (Cramer, 2004; García-Pérez et al., 2013; Hugtenburg et al., 2013; Kennedy-Martin et al., 2017; Tang et al., 2017; WHO, 2003).

Koulayev et al. (2017) assume therapy as a continuous and regular intake of medications from a given drug group by the patient (Koulayev et al., 2017). The patient is held responsible for acquiring the medication from the pharmacy and for its consumption (Steiner and Prochazka, 1997). The therapy can be 'doctor-specific', if one considers only prescriptions from a given doctor, or it can be complemented from other doctors whom the patient might have seen in the meantime.[1]

Patients express higher levels of satisfaction when treated by physicians they know and trust. They also tend to visit the physician more often and are willing to pay substantially higher values to continue being treated by providers they trust (Johnson et al., 2016). This leads to higher levels of adherence, reducing adverse clinical outcomes (Johnson et al., 2016) and healthcare costs borne by the patient and the healthcare system (Wilke et al., 2013).

Reviews of adherence associated to long-term therapeutic regimens estimate that, on average, 20% to 80% of patients do not adhere to medical therapies (Aloudah et al., 2018; Blackburn et al., 2013; Fischer et al., 2010; Freccero et al., 2016; Gellad et al., 2009; Krueger et al., 2005). Lower levels of adherence are a complex problem, especially when considering chronic conditions. Our data report that 17.86% of the e-prescriptions are never dispensed, aligned with previous studies that have calculated non-adherence levels associated to diabetes to range from 7% to 64% (Bloomgarden et al., 2017; Kirkman et al., 2015; Pladevall et al., 2004; Polonsky and Henry, 2016; Shani et al., 2017; Wilke et al., 2013; WHO, 2003).[2] This represents a major obstacle to the metabolic control of diabetes and may lead to severe complications, disease progression, avoidable hospitalizations and increased mortality, in addition to higher economic burden for patients and the health service. It may also lead to loss of productivity and absenteeism (Atella et al., 2017; Bussière et al., 2020; DiMatteo, 2004; Guénette et al., 2015; Kennedy-Martin et al., 2017; Lublóy et al., 2015; Morillas et al., 2015; Odegard and Gray, 2008; Orom et al. 2018; Osterberg and Blaschke, 2005; Pagès-Puigdemont et al., 2016; Polonsky and Henry, 2016; Roebuck et al., 2011; Stavropoulou, 2012; Tang et al., 2017; Van Dulmen et al., 2007; Zullig et al., 2015).

[1] Patients can see more than one physician and each one of them may prescribe medications for different condition. Unless there is a primary care provider who coordinates these medication regimens, the number of different medicines and instructions may limit adherence while also increasing the risk of medication errors and harmful drug interactions (NPCIE, 2007).

[2] Poor adherence levels lead to worse blood glucose levels, higher rates of acute metabolic events, increased risk of hospitalization and mortality and higher healthcare costs (Wilke et al., 2013).

Nonadherence can come in any phase of the treatment. Patients – the principal decision-maker towards therapeutic adherence - may decide not to collect their medicines from the pharmacy and not initiate treatment (primary nonadherence) [3] (Pladevall et al., 2004), or they may not take their medication as prescribed, do not refill the prescription on time, or discontinue their medication altogether (secondary nonadherence) (Hugtenburg et al., 2013; Lam and Fresco, 2015; Lemstra et al., 2018; Pagès-Puigdemont et al., 2016; Wilke et al., 2013).

We focus our attention on primary adherence, evaluated by the percentage of pharmaceuticals that were filled within a stipulated period (prescription-level measurement).

The relationship between medication adherence and glycaemic control has been reported, i.e., increments on medication adherence tend to decrease the HbA1c level (Lin et al., 2017; Schectman et al., 2002). Patients who experience this improvement are also more likely to adhere to behavioural alterations, glucose self-monitoring, attendance with medical care, and other components of diabetes self-management. These factors are also likely contributing to improved outcomes. Thus, medication adherence can be both a cause and an effect for a patient who is going to do well (Lin et al., 2017).

Asche et al. (2011) mention that it is extremely challenging to quantify the relationship between adherence and outcomes such as glycemic control and disease progression. Vermeire et al. (2001) mentions the complexity of the therapeutic regime as one of the turn-offs on medication adherence. Kogut et al. (2004) find that nonadherence increases the likelihood of receiving higher dosages of an active ingredient in subsequent months but find no relationship with subsequent addition of another antidiabetic medication.

Grant et al. (2007) use medication intensification, defined as an increase in dose of initially prescribed oral hypoglycaemic medicine or the addition of a second glucose-lowering agent to the initial regimen, as the study outcome. Their study concludes that patients in the highest adherence quartile are significantly more likely to have their regimens intensified than patients in the lowest quartile. Similarly, patients with excellent adherence (>90%) were more likely to have their regimens intensified than patients with moderate (50 –90%) or poor (<50%) adherence.

Voorham et al. (2011) complement the perspective from Grant et al. (2007) by considering that perception of poor adherence has often been mentioned by physicians as

[3] Electronic prescriptions helped solve the difficulty of capturing primary adherence by allowing us to see if the prescription was filled (Lee et al., 2018; Lemstra et al., 2018).

a reason not to intensify treatment. Observational studies, however, have reported conflicting results on the association between medication adherence and treatment intensification. Both negative and positive associations have been observed between suboptimal adherence and treatment modifications, whereas no such associations were found in other studies.

More recently, Wheeler et al. (2014) conclude that increasing disease severity is associated with higher adherence rates. Egede et al. (2014), on the contrary, present their longitudinal retrospective study and show that poor glycemic control is tightly linked to medication nonadherence (MPR <80%).

4.2.3 Physician-Patient Interaction: A trustworthy agency relationship

Physicians play a central role in addressing the patients' needs by prescribing medication or screening adherence as well as by suggesting lifestyle changes (Orom et al., 2018).

The physician-patient interaction defines an agency relationship, in which healthcare professionals act as agents for patients (principal) and mostly decide and recommend on their behalf what health services/products they need (Folland and Goodman, 2016; Mooney and Ryan, 1993).

Motives behind this delegation of power are related with the fact that patient's awareness of their relatively uninformed nature about the most appropriate decisions to be made in health-terms. The best way to resolve this is to rely on an informed agent such as the physician (Folland and Goodman, 2016).

The agency relationship is usually long lasting, and trust is built over time through repeated interactions. Trust is usually forward looking and reflects a commitment to an ongoing relationship (Rowe and Calnan, 2003).

Through repeated interactions, patients learn about a physician's competence and trustworthy behaviour (Lind, 2019). This constitutes the fundamentals of interpersonal trust, which is often understood as the "optimistic acceptance of a vulnerable situation in which the truster believes the trustee will care for him and act on his best interests" (van der Schee et al., 2006).

This involves a set of beliefs or expectations about a physician's behaviour and determines how confidence is built over time (Dwyer et al., 2012; Lind et al., 2019; Peter and Bilton, 2018).

In practice, repeated interactions are also potentially beneficial because the physician becomes, over time, more familiar with the patient's disease and her perceptions about the distribution of health effects. They also gain more information about the patients' medical history, social circumstances, values, and preferences (Culyer and Newhouse, 2000); Saxell, 2014). The physician may thus better match a patient to a treatment choice (Mooney and Ryan, 1993; Saxell, 2014).

It has long been recognised that the doctor's and the patient's utility functions are, to a certain extent, independent (Mooney and Ryan, 1993), i.e., the agent has his own utility function, which he seeks to maximizes. This utility function may only partly coincide (Culyer and Newhouse, 2000; Ludwig et al., 2010; McGuire, 2000).

A perfect agent is assumed to make choices that a principal – the patient – would make if he had the same information, professional knowledge, and expertise (Blomqvist, 1991; Folland and Goodman, 2016; Gafni and Charles, 2009). These relationships are not perfect and there may be a gap between the information. The larger is this information asymmetry as well as the patient's vulnerability concerning their health, the more relevant the trust relationship between principal and agent become (Shortell et al., 1998).

The asymmetry of information in healthcare creates an incentive problem, resulting in more (or less) treatment being "demanded" that would have been the case if the patient had full information and knowledge (Mooney and Ryan, 1993).

Another issue that makes sense to stand out is the difference between information and knowledge, i.e. the quantity of information a patient receives and whether it is understood (i.e. the quality of information) (Scott and Vick, 1999). For this reason, it seems important to refer that a good communication between both parties can be useful to decrease the gap the information held and received.

There are clear variations in terms of the physician-patient interaction. They can range from "doctor-centered" to "patient-centered". They tend to be physician-specific, and patients may prefer one interaction style over the other (Krupat et al., 2000).

A good match between both parties is a product of the attitudes and orientations that the two participants bring to it (Krupat et al., 2000). This match has the capacity to improve communication, enhance patient involvement and make this agency-relationship confident and trustworthy. This way, patients become more involved in the therapeutic decision-making process as well as become more motivated to make healthy decisions which will increase adherence and long-lasting behaviours (Atella et al., 2017; Arab et al., 2014; Borgsteede et al., 2011; Orom et al., 2018; Schwartz et al., 2017).

The physician influence on health outcomes extends beyond the choice of clinical therapy. Higher levels of trust enhance communication and reinforce continuity of care. This yields better health outcomes due to an increase in patient's satisfaction as well as it promotes patient adherence to medical treatment (Dwyer et al., 2012; Gellad et al., 2009; Krueger et al., 2005; Lind, 2019).

Johnson et al. (2016) considers that patients express more satisfaction when they are treated by physicians they know and who are perceived to be empathetic. They may also be more likely to adhere to treatment regimens and less likely to sue in the event of adverse outcomes. The author goes deeper and considers that individuals are willing to pay substantially higher health insurance premiums to continue being treated by providers they trust.

This behaviour is assessed by studying this pairing scheme for a sufficiently long period to provide meaningful measures of patient adherence. Experimental data of this sort was usually unavailable, which introduced difficulties to the study. Recently available data of electronic prescriptions allowed to trace this interaction and permitted the study of the physician effect. As mentioned before, this is one of the advantages of our study.

Koulayev et al. (2013) introduced the study of physician-related factors, by showing that primary care physicians exert substantive influence on patients' health behaviour. Koulayev et al. (2017) analyse population-level registry data that track patient adherence over time and across different physician–patient pairings to provide the first empirical evidence on the relative importance of patient-level, physician-level, and match-level factors as determinants of patient medication compliance. Their research helps classify the impact of different inputs into the health investment function – compliance with clinical therapy being the most immediate and measurable manifestation of health investment. Another notable finding is that a sizeable component of the variation in patient compliance across doctor–patient pairs cannot be explained by fixed patient-specific or doctor-specific characteristics; instead, it appears that the quality of the doctor–patient match has a separate, and important, contribution. This suggests that the process by which patients are matched to doctors in a healthcare system is a significant determinant of the overall level of patient medication compliance.

Atella et al. (2017) also show that physician unobserved heterogeneity is an important determinant of health status, although patient heterogeneity appears to be significantly more important in explaining its variability. This evidence suggests that physicians play an important role in shaping patient health status, far beyond the standard determinants

of health analysed by clinical and health economic literature. These authors divide the factors that affects health outcomes into three broad categories: patient-related, physician-related, and team building-related. Patients can negatively contribute to health outcomes through lack of understanding of their disease, lack of involvement in the decision-making process, lack of adherence to therapy, and lack of medical literacy. On the other hand, physicians may fail to contribute to improve patient health outcomes, as they often do not recognize medication nonadherence in their patients, prescribe complex drug regimens without explaining their benefits and side effects, or do not take into account the potential financial burden for patients. Finally, the way patients and physicians interact may help overcome much of these difficulties.

Orom et al. (2018) complemented this perspective by showing that the quality of the physician-patient interaction is a significant factor in treatment adherence and therefore is likely to ultimately improve patient outcomes as well as healthcare efficiency. They consider that greater trust in physicians is associated with improved treatment adherence, lifestyle change, and ultimately better clinical outcomes. Also, a more patient-centred care, where patients are involved in decision making by the physician, is also associated with better adherence (Orom et al., 2018).

More recent works have arrived specially from Kwok (2019), Fadlon and Van Parys (2020) and Sabety (2020). They focus on regional variations and health utilization when patients switch primary care physicians.

The first author studies the effect of switching to different primary care physicians on utilization of health, especially in terms of spending among Medicare patients over age 65. The author shows that patients who switch from a primary care physician whose other patients have low utilization to one whose other patients have high utilization experience increases in long-run utilization, whereas patients who switch in the opposite direction experience decreases. With this, it is shown that primary care physician practice styles can affect healthcare use in the long run (Kwok, 2019).

The second authors provide evidence on how primary care physicians practice style intensity affects the care that patients receive. They consider that primary care physicians are institutionally positioned to play a central role in healthcare provision and in most cases work as patient's principal physician as well as may have more continuous interactions with their patients than other types of healthcare providers. They conclude that the practice styles of primary care physicians could have long- lasting and far-

reaching consequences on the quantity and quality of patient healthcare utilization and, hence, potentially on patient health (Fadlon and Van Parys, 2020).

The third author follows a similar approach and shows that relationships determine where patients demand care and that relationships involving primary care physicians are moderately important for patients' health (Sabety, 2020).

The study of the relationship involving the patient and the physician is relevant and has been a target of interest in the recent years due to its direct impact on patient's health. However, as mentioned by Sabety (2020), "researchers still lack strong evidence for whether and to what extent this relationship matters for patients, despite the number of recent and proposed reforms affecting this relationship".

Prescriptions are an observable output that come out of this interaction. They reflect the supply side of health provided by physicians and the demand for treatment required for a patient. They also reflect the patient decision to proceed or not with the recommended treatment provided by the physician. The access to this output through large datasets containing patient-provider linkages makes the study of the interaction between the physician and the patient and its impact in adherence possible as well as it allows us to contribute to the existing literature.

4.3 Data and Methodological Issues

4.3.1 Data

We use a large longitudinal matched physician-prescription-patient dataset for all Portuguese e-prescriptions collected from *Serviços Partilhados do Ministério da Saúde* (SPMS) between January 2015 and October 2019, from all regions in Portugal. [4] Our data comprise the pharmacological class A10 - Drugs Used in Diabetes: A10A (Insulins and Analogues) and A10B (Blood Glucose Lowering Drugs, excl. Insulins), complemented with information from the Therapeutic Group 8 of the Portuguese Therapeutic Medical Record (subclass 8.4. "*Insulinas, antidiabéticos e glucagon*").[5] The data are a representative 10% sample of the universe of e-prescriptions that contain at least one pharmaceutical used to treat Type-1 and Type-2 *Diabetes Mellitus*.

The dataset contains 27,937 physicians, 128,155 patients, 2,477,672 e-prescriptions and 42 different anti-diabetic pharmaceuticals, including oral hypoglycemic agents and insulins. Prescriptions were selected if: (1) the patients were 18 years or older, and (2) they had been prescribed with anti-diabetic pharmaceuticals within the selected time range.[6]

We only considered oral hypoglycaemic agents for the purpose of this study. Although we can control for insulin use and dispensing patterns, insulin dosage instructions depend on glycaemic levels that we do not observe (Roebuck et al., 2011). After this selection, we remain with an unbalanced panel that includes 27,125 physicians, 121,727 patients, 1,363,778 e-prescriptions events and 28 different oral anti-diabetic pharmaceuticals.

SPMS provided anonymized information at a prescription level (id number, prescription date, dispensing date, cost of drug for the NHS, price supported by the patient, number of pills, pharmaceutical form, number of packages, dosage, active ingredient and respective codes (CNPEM and national drug code), and posology). We also had access to patient information (age, gender, healthcare insurance, geographical location, health insurance), health provider information (medical specialty, workplace, type of care – hospital vs. primary care) and pharmacy information (geographical location). Each line of observation corresponds to a single prescription.

[4] E-prescribing data record all electronic prescriptions issued, regardless of whether they were filled or not.
[5] Further details can be found at: https://app10.infarmed.pt/prontuario/frameprimeiracapitulos.html.
[6] Data do not include other prescriptions for the observed patients that did not include at least one antidiabetic drug.

This dataset has important features. First, it covers a large number of patients and follows them through several interactions with more than one physician. Second, it provides important details on physicians' prescribing patterns. Third, it informs us about the patients' medication purchasing patterns. The fact that we observe frequent visits to the healthcare system informs on the mechanisms of the patient-physician interaction.

Still, there are some limitations. First, there is no information on patients' socioeconomic characteristics,[7] or on their demographics such as race/ethnicity, years of education, employment status, number of people in the household and marital status. Second, we have no information on sociodemographic aspects of the physician such as age, gender, place of medical education, level of education, and year of graduation from medical school.

4.3.2 Disease Severity Measure

In case of disease, individuals consult with a physician who prescribes a therapeutic regime and gives them advice about the appropriate treatment. In chronic diseases, the need to see a physician regularly to have access to prescriptions and feedback on the disease evolution is paramount.

Physicians rely on previously established clinical guidelines, and diabetes is no exception. The baseline approach considers non-pharmacological interventions (NPI) and they are considered in all stages of treatment. They include a healthy food regime, body weight control, promotion of physical activity, therapeutic education. The pharmacological approach, on the other hand, considers three-levels – mono, double, and triple therapy. Monotherapy regimes, characterized by relying on a single molecule (active ingredient), are the first line of treatment and are recommended for mild patients. Double-therapy regimes consist in combining two molecules (active ingredient). They are considered the second line of treatment and are recommended for moderate patients. Triple-therapy regimes consists in the combination of three molecules (active-ingredient). They are considered the third line of treatment and is the recommended therapy for more severe

[7] We infer the patients' economic status by one of two ways: (i) by considering that individuals with the higher level of reimbursement belong to a lower income group; or (ii) by using a proxy of household income of a specific district having into consideration public data merged into ours.

patients. The transition between these levels requires a criteria decision based on dimensions such as the revision period and conditions for admission.[8]

4.3.3 Adherence Measure

We select primary adherence as our measure of adherence. This rate of dispensed drugs per prescription is a patient-level measurement, that is computed as follows:

$$share\ dispensed\ drugs_{it} = \frac{\sum dispensed\ drugs_{it}}{\sum total\ prescribed\ drugs_{it}},$$

where i and t indexes the patient and the date of prescription, respectively.

This measure is a fraction that can assume values between 0 (no drug was dispensed) and 1 (all drugs were dispensed). It is an aggregated measure as it adds all drugs that were acquire per prescription even if the acquisition was done through multiple visits to the pharmacy.[9] An alternative measure for primary adherence was also considered to test for the robustness of our findings. In this case, the binary variable assumes the value zero if a prescription is not filled at all and one if at least one drug is dispensed by the pharmacy.

4.3.4 Methods

We consider Baetschmann et al. (2020) approach and run an Ordered Logit Model with fixed effects. According to this approach the observable ordered dependent variable y, which can take values $1, \dots, K$, is related to the observable characteristics x through a latent variable y^*. The latent variable y_{it}^* for individual i at time t depends linearly on x_{it} and two unobservable characteristics α_i and ε_{it} according to the following

$$y_{it}^* = x_{it}'\beta + \alpha_i + \varepsilon_{it} \qquad i = 1, \dots, N \quad t = 1, \dots, T \qquad (4.1)$$

In our case, the relationship becomes:

$$Disease\ Severity_{it} = \beta_0 + \beta_1 primary\ adherence_{it} + \beta_2 \boldsymbol{X}_{it} + \alpha_i + \varepsilon_i,$$

where $Disease\ Severity$ is measured by the three levels of therapeutic guidelines, i and t indexes the patient and date of prescription, X_{it} is a set of control variables for patient

[8] For further details consider Section 2: Subsection 2.3 – Patient Clinical Pathway – Therapeutic Guidelines for Diabetes.

[9] Patients can opt to fill the entire prescription when they go to the pharmacy, or they can adjust their purchasing pattern to their needs by going to the pharmacy as many times as the number of prescribed packages. With e-prescriptions, patients can get part of the prescribed medicines without the prescription becoming invalid, and with the additional benefit of being able to pick the remaining packages when and where they prefer.

(gender, age, health insurance, region, income level and comorbidities), healthcare system (principal physician measure, physician specialty, health sector – public/private, type of care – primary/hospital care, physician's region, principal physician and health sector interaction, number of other physicians seen by the patient and visits to other physicians), and treatment characteristics (renewable prescription, induce prescription, first-visit, first 6 months of treatment), and ε_i is a random error term assumed to be uncorrelated with the regressors.

The vector of covariates x_{it} doesn't include an intercept because α_i act as individual-specific intercepts. The time-invariant, individual-specific part of the unobservables (α_i) is called the fixed effect and can statistically depend on x_{it}. The following observation rule ties the latent variable y_{it}^* to the observed orders variable y_{it} through the threshold τ_{ik}:

$$y_{it} = k \quad \text{if} \quad \tau_{ik} < y_{it}^* < \tau_{ik+1} \qquad k = 1, \dots, K \tag{4.2}$$

Moreover, the fixed-effects ordered logit model assumes that the time-varying unobservable terms, ε_{it}, are independent and identically distributed with standard logistic cumulative density function.

$$F(\varepsilon_{it}|x_{it}, \alpha_i) = F(\varepsilon_{it}) = \frac{1}{1 + \exp(-\varepsilon_{it})} \equiv \Lambda(\varepsilon_{it}) \tag{4.3}$$

The probability of observing outcome k for individual i at time t is therefore:

$$\Pr(y_{it} = k|x_{it}, \alpha_i) = \Lambda(\tau_{ik+1} - x_{it}'\beta - \alpha_i) - \Lambda(\tau_{ik} - x_{it}'\beta - \alpha_i) \tag{4.4}$$

This probability depends on x_{it} and β, the parameter of primary interest. However, it also depends on α_i, τ_{ik} and τ_{ik+1}. As can be seem from equation (4.4), without further assumptions on the threshold, only $\tau_{ik} - \alpha_i \equiv \alpha_{ik}$ is identified because we can always define $\breve{\tau}_{ik} = \tau_{ik} + \eta$ and $\breve{\alpha}_i = \alpha_i + \eta$ for any $\eta \in \mathbb{R}^1$.

Our analysis is done at the patient-level, implying that unobserved heterogeneity and its possible correlation with the explanatory variables need to be tackled by the regression model. This means that the regression model should allow unobserved time-constant individual effects, which captures differences between individuals, to be related to individuals' characteristics.

4.4 Results

4.4.1 Descriptive Statistics

The selected sample encompasses a total of 1,363,778 prescriptions containing oral hypoglycaemic agents evenly distributed across all years. The total number of patients who have been prescribed with antidiabetic drugs between January 2015 and October 2019 amounts to 128,155.

Table 4.1 presents statistics regarding patient characteristics for the complete sample and divided by therapeutic level. Approximately 52.1% of the patients prescribed with oral antidiabetic medication are women. The mean age of the patients is 68.50 years, varying from 18 to 110 years old. Approximately 60% of our sample corresponds to patients aged between 60 and 80 years. Most prescriptions are exclusively covered by the national health service insurance (91.1%), and approximately 35% of individuals present lower levels of co-payment, possibly due to lower levels of income.

Women exhibit more mild cases of diabetes (monotherapy) (54.2%) than severe cases (triple therapy) (45.5%). They also seem to have more cases in which there is an improvement in the disease symptoms, i.e., transition to monotherapy occurs in 51.9% to 55% of women, in comparison with progression to dual (51.8 to 52.1%) or triple therapy (49.9 to 50.5%). Older individuals tend to have more controlled forms of the condition (68.18 years on level 1 vs. 64.92 on level 3), which may be related to the existence of caregivers who are responsible to fill the prescription on the patient's behalf and helping with the process of medication-taking. In fact, the transition to triple therapy regimes happens more in younger patients (64.5 to 67.7 years old) in comparison with monotherapy (68.2 to 72.6 years old).

Each patient has usually 2.1 health comorbidities in addition to diabetes. The probability of being associated to milder cases of diabetes seems to be inversely related with the number of comorbidities. Interestingly, patients requiring more complex therapy seem to have better economic conditions that those in less severe treatments (value that shows that 28.7 to 34.7% of individuals who are on level 3 or transitioning to this level are classified as lower income individuals in comparison with the 34.1 to 44.2% of individuals who are on level 1 or transitioning to this level).

Financing through the national health insurance happens in approximately 91% of cases, and that proportion is constant across therapy level.

Table 4.1 – Statistics regarding patient characteristics for the all sample and divided by therapeutic level

			Clinical Guideline = 1			Clinical Guideline = 2			Clinical Guideline = 3		
Variable	Description	All Sample	Entering in Level 1	Transition 2 to 1	Transition 3 to 1	Entering in Level 2	Transition 1 to 2	Transition 3 to 2	Entering in Level 3	Transition 2 to 3	Transition 1 to 3
Patient Gender	=1 for females; 0 otherwise	0.521	0.542	0.550	0.519	0.485	0.518	0.521	0.454	0.499	0.505
		(0.500)	(0.498)	(0.498)	(0.500)	(0.500)	(0.500)	(0.500)	(0.498)	(0.500)	(0.500)
Patient Age	Patient's Age	68.492	68.180	72.575	69.585	68.193	69.324	68.280	64.923	66.470	67.777
		(11.941)	(12.807)	(11.482	(10.909)	(11.623)	(11.626)	(10.764)	(10.832)	(10.597)	(10.636)
Level of Comorbidities	Number of other comorbidities (per patient)	2.115	2.191	1.920	1.536	2.111	2.147	1.822	2.136	2.253	2.266
		(1.294)	(1269)	(1.330)	(1.305)	(1.277)	(1.315)	(1.328)	(1.243)	(1.260)	(1.275)
Lower Income	=1 if lower income; 0 otherwise	0.353	0.341	0.442	0.391	0.343	0.368	0.361	0.287	0.321	0.347
		(0.478)	(0.474)	(0.497)	(0.488)	(0.475)	(0.482)	(0.480)	(0.452)	(0.467)	(0.476)
Insurance Type	=1 for NHS; 0 otherwise	0.911	0.910	0.914	0.916	0.905	0.913	0.912	0.910	0.911	0.914
		(0.285)	(0.286)	(0.281)	(0.277)	(0.293)	(0.282)	(0.283)	(0.286)	(0.285)	(0.281)
Number of Observations		1,363,778	499,073	129,480	30,806	195,994	179,353	93,535	47,942	132,201	55,394

Notes:
Mean values, Standard Deviation in parentheses

Table 4.2 presents statistics regarding physician and health system characteristics for the whole sample and by therapeutic level. Our sample contains 27,125 physicians divided between General Practitioners (83.4%), Endocrinologists (3%), Internal Medicine (6.5%) and other specialties (7.1%).

Endocrinologists and Internal Medicine physicians see a higher pool of more severe cases of diabetes (triple therapy). Endocrinologists have a share of prescriptions on triple therapy of 6.1 to 6.3% in comparison with 1.7 to 2.2% on monotherapy. Internal Medicine physicians have a share of prescriptions on triple therapy of 8.5 to 10.5% in comparison with 4.7 to 6.9% on monotherapy. GPs present a similar expression towards the therapeutic pathway (81.9 to 85.1% on level 1 or on transitions towards this therapeutic level, 82 to 85.6% on level 2 or on transitions towards this therapeutic level and 79.1 to 82.4% on level 3 or on transitions towards this therapeutic level).

The public sector issues more prescriptions and seem to attend the needs of more severe patients. In fact, 81.2% of all prescriptions and 22.9% of patients under triple therapy are followed in the public sector. Moreover, patients who have appointments in the public sector are more likely to transition to higher therapeutic levels (73.6 to 79% in monotherapy; 80 to 80.7% in dual therapy and 84.3 to 84.7% in triple therapy).

Approximately 70% of the prescriptions in our sample result from primary care visits and this percentage increases for more severe cases of diabetes.

The principal physician linked with the patient answers for a great part of therapeutic transitions, whether progressions to severe cases, or regressions to mild cases. They are represented in 67.9% of our sample and have more expression in transitions to severe cases (60.9 to 66.1% in dual therapy and 64.8 to 65.3% in triple therapy in comparison with 59.8 to 63.7% in monotherapy).

Patients visit a physician approximately 11.6 times in 5 years and they tend to visit more when in mono or dual therapy regimes (7.93 and 7.94 visits, respectively) in comparison with triple therapy (5.4 visits). We also observe that progression and regression in the disease is associated with higher number of visits.

Table 4.3 presents statistics regarding the prescription characteristics for the whole sample and by therapeutic level. There are 54.3% of renewable prescriptions and 43.1% of prescriptions contain at least one induced drug, i.e., drugs that must be purchased according to the physician's choice (patient is not able to choose). The more severe the condition is, the more likely is the patient associated to renewable (52.5% in monotherapy

vs. 55.8% in triple therapy) and induced prescriptions (18.3% in monotherapy vs. 74% in triple therapy).

Table 4.2 - Statistics regarding physician and health system characteristics for the all sample and divided by therapeutic level

			Clinical Guideline = 1			Clinical Guideline = 2			Clinical Guideline = 3		
Variable	Description	All Sample	Entering in Level 1	Transition 2 to 1	Transition 3 to 1	Entering in Level 2	Transition 1 to 2	Transition 3 to 2	Entering in Level 3	Transition 2 to 3	Transition 1 to 3
Physician Specialty	= 1 if General Practitioner	0.834	0.851	0.819	0.821	0.856	0.825	0.820	0.824	0.791	0.799
		(0.372)	(0.356)	(0.385)	(0.383)	(0.351)	(0.380)	(0.384)	(0.381)	(0.407)	(0.401)
	= 2 if Endocrinologist	0.030	0.021	0.017	0.022	0.019	0.030	0.033	0.061	0.063	0.063
		(0.170)	(0.145)	(0.129)	(0.147)	(0.137)	(0.170)	(0.179)	(0.239)	(0.243)	(0.242)
	= 3 if Internal Medicine	0.065	0.047	0.069	0.063	0.056	0.075	0.074	0.085	0.105	0.094
		(0.247)	(0.212)	(0.254)	(0.243)	(0.231)	(0.264)	(0.261)	(0.278)	(0.307)	(0.291)
	= 4 if Other	0.071	0.080	0.095	0.094	0.068	0.071	0.073	0.031	0.041	0.045
		(0.257)	(0.271)	(0.293)	(0.291)	(0.252)	(0.256)	(0.260)	(0.172)	(0.198)	(0.207)
Public Workplace	= 1 for physician working in the public healthcare sector	0.812	0.819	0.736	0.790	0.814	0.800	0.807	0.869	0.847	0.843
		(0.391)	(0.385)	(0.441)	(0.407)	(0.389)	(0.400)	(0.395)	(0.337)	(0.360)	(0.364)
	= 0 otherwise	0,188	0,181	0.264	0.210	0.186	0.200	0.193	0.131	0.153	0.157
		(0.391)	(0.385)	(0.441)	(0.407)	(0.389)	(0.400)	(0.395)	(0.337)	(0.359)	(0.364)
Primary Care	= 1 if Primary Care	0.699	0.725	0.626	0.663	0.713	0.686	0.676	0.726	0.686	0.688
		(0.459)	(0.447)	(0.484)	(0.473)	(0.453)	(0.464)	(0.468)	(0.446)	(0.464)	(0.463)
	= 0 otherwise	0.301	0.275	0.374	0.337	0.287	0.314	0.324	0.274	0.314	0.312
		(0.459)	(0.447)	(0.484)	(0.472)	(0.453)	(0.464)	(0.468)	(0.446)	(0.464)	(0.463)
Principal Physician – Active Treatment Provider	= 1 if principal physician (for a specific patient)	0.679	0.715	0.637	0.598	0.700	0.661	0.609	0.698	0.648	0.653
		(0.467)	(0.452)	(0.481)	(0.490)	(0.458)	(0.473)	(0.488)	(0.459)	(0.478)	(0.476)
	= 0 otherwise	0.321	0.285	0.363	0.402	0.300	0.339	0.391	0.302	0.352	0.347
		(0.467)	(0.451)	(0.481)	(0.490)	(0.458)	(0.473)	(0.488)	(0.459)	(0.478)	(0.476)
Number of visits	Number of visits made by patients to physicians	11.596	7.937	16.799	16.647	7.949	15.073	16.978	5.444	16.345	16.149
		(10.065)	(7.355)	(12,.306)	(11.644)	(7.292)	(10.416)	(11.277)	(5.254)	(10.269)	(10.341)
Number of Observations		1,363,778	499,073	129,480	30,806	195,994	179,353	93,535	47,942	132,201	55,394

Notes:
Mean values, Standard Deviation in parentheses

Table 4.3 - Statistics regarding prescription characteristics for the all sample and divided by therapeutic level

			Clinical Guideline = 1			Clinical Guideline = 2			Clinical Guideline = 3		
Variable	Description	All Sample	Entering in Level 1	Transition 2 to 1	Transition 3 to 1	Entering in Level 2	Transition 1 to 2	Transition 3 to 2	Entering in Level 3	Transition 2 to 3	Transition 1 to 3
Renewable Prescription	=1 if Renewable Prescription	0.543	0.525	0.445	0.413	0.515	0.583	0.520	0.558	0.679	0.677
		(0.498)	(0.499)	(0.497)	(0.492)	(0.500)	(0.493)	(0.500)	(0.497)	(0.467)	(0.467)
	= 0 otherwise	0.457	0.475	0.555	0.587	0.485	0.417	0.480	0.442	0.321	0.323
		(0.498)	(0.499)	(0.497)	(0.492)	(0.499)	(0.493)	(0.499)	(0.497)	(0.467)	(0.467)
Induced Prescription	=1 if prescription contains drugs that are specifically selected by the physician	0.431	0.183	0.258	0.219	0.639	0.557	0.640	0.740	0.729	0.699
		(0.495)	(0.387)	(0.437)	(0.414)	(0.480)	(0.497)	(0.480)	(0.439)	(0.445)	(0.459)
	= 0 otherwise	0.569	0.817	0.742	0.781	0.361	0.443	0.360	0.260	0.271	0.301
		(0.495)	(0.387)	(0.437)	(0.414)	(0.480)	(0.497)	(0.480)	(0.439)	(0.445)	(0.459)
Number of Observations		1,363,778	499,073	129,480	30,806	195,994	179,353	93,535	47,942	132,201	55,394

Notes:
Mean values, Standard Deviation in parentheses

4.4.2 Regressions

Table 4.4 presents the estimates of the Ordered Logit Model and the Fixed-Effects Ordered Logit Model, respectively. Due to the large number of control variables, namely patient characteristics (age, gender, insurance type, region, income level), physician and health system features (physician specialty, principal physician, type of care, region, interactions with other physicians) and treatment characteristics (renewable prescription, induced prescription, time of prescription – first / 6 months), we only show the estimated coefficients and marginal effects of the main variables of interest – primary adherence, patient's comorbidities, the healthcare setting (public vs. private) and the number of visits made by patients to physicians.

Columns 1 and 2 of Table 4.4 present the estimates of a cross-sectional ordered logit with primary adherence as a continuous and binary variable, respectively. Columns 3 and 4 present the estimates yielded by a fixed effects ordered logit using primary adherence as a continuous variable and as a dichotomous variable, respectively.

Estimates are presented in terms of coefficients, which describe the size of the effect the explanatory variable is having on the dependent variable, and in marginal effects (dy/dx), which give the change in percentage points (pp) in the dependent variable given by a one-unit change in the explanatory variable, ceteris paribus.

To fit the model parameters, only individuals (panel units) who have variation in their dependent variables are informative. This condition is met by 52,195 individuals, which results in 845,206 observations. On average, people in the estimation sample are therefore observed about 16 times.

The ordered dependent variable presents 3 categories, so 2 different dichotomizations are possible. However, because not all dichotomizations lead to copies with variation in the binary dependent variable, we end up with 1,250,422 copies that contribute to the estimation procedure. Because the copies are not independent of each other, the utilized model calculates cluster-adjusted standard errors at the individual level (52,195 individuals). The Wald test indicates that all included variables are jointly statistically significant.

The estimated coefficients for primary adherence exhibit a negative impact on disease progression, especially after controlling for time-invariant characteristics and the other variables in the model. This effect is particularly relevant in preventing patients from

needing triple therapy. These results suggest that primary adherence may be an important determinant of the success in managing the disease.

Marginal effects at the average are also considered for the scope of the analysis. They are computed using the relative frequencies of the corresponding categories in the estimation sample. Higher levels of primary adherence (continuous approach) increase the probability of controlling Diabetes using monotherapy (level 1) by 7.4 to 10.4 percentage points. This increasing pattern on the medication purchase decreases the probability of transition to dual therapy (level 2) by 0.9 to 2.5 percentage points. The effect of adherence is higher when patients are required to switch to the triple therapy (level 3), i.e, the higher the adherence pattern the lower it is the probability of reaching higher levels of medication complexity by 4.9 to 9.5 percentage points.

Considering the binary variable approach, the results follow the same pattern as the continuous variable however the effect is smaller.

This means that adherence increases the probability of controlling diabetes using monotherapy (level 1) by 2.9 to 4.5 percentage points. Continuing to fill the prescription decreases the probability of transition to dual therapy (level 2) by 0.3 to 1.5 percentage points. The effect of adherence is higher when patients are required to switch to triple therapy (level 3), i.e, the higher the adherence pattern the lower it is the probability of reaching higher levels of medication complexity by 2.7 to 3 percentage points.

The presence of comorbidities increases the likelihood of a patient needing more intensive therapy due to a potential negative interaction among diseases. That is particularly the case when patients have four or more associated comorbidities.

Marginal effects show the following: patients with other comorbidities present a decreasing probability of staying with monotherapy of 1.9 to 12.6, 2.8 to 22.2, 3.2 to 29.9 and 2.9 to 37.6 percentage points (continuous approach) or by 2.1 to 12.9, 3 to 22.7, 3.7 to 30.5 and 3.5 to 38.4 percentage points (binary approach) whether you have one, two, three or four comorbidities.

At the same time, this increases the probability of putting the patients in triple therapy (level 3) by 1.2 to 11.4, 1.8 to 20.2, 2.1 to 27.2 and 1.9 to 34.1 percentage points (continuous approach) or by 1.3 to 11.7, 1.9 to 20.6, 2.4 to 27.7 and 2.3 to 34.8 percentage points (binary approach) whether you have one, two, three or four comorbidities.

Comorbidities introduce more drugs to the therapeutic schemes which may lead to forgetfulness and therapeutic misunderstanding. This decreases the therapeutic approach, thus reducing adherence levels as well leading to worse health outcomes.

The public health setting follows the same path as primary adherence. The public sector presents an improvement of the disease control while avoiding its progression in comparison with the private health setting. In fact, patients located at the public sector present higher probability of about 1.8 to 2.3 percentage points (continuous approach) or by 1.5 to 2 percentage points (binary approach) of staying in monotherapy regimens (level 1). Staying in the public health setting decreases the probability of transitioning to dual therapy (level 2) by 0.6 to 0.2 percentage points (continuous approach) or by 0.5 to 0.2 percentage points (binary approach). They also present a decrease in the probability of progressing to triple therapy (level 3) of 1.5 to 2.2 percentage points (continuous approach) or 1 to 1.8 percentage points (binary approach).

The number of visits made by patients to physicians also play an important role on adherence and better health outcomes. The higher the number of visits, the higher the probability of transitioning to the next therapeutic level. An increase of one visit increases the probability of being associated to more complex therapeutic schemes. More visits (interactions) are associated to more connection with the physician, who becomes more aware of the patient's condition and more capable of introducing changes on the therapeutic pathway. A higher probability of transition to higher therapeutic levels only indicates that this relationship is strong enough for the physician to increase the number of drugs to try to stabilize the condition.

Table 4.4 - Estimates of the Ordered Logit Model and Fixed-Effects Ordered Logit Model

	Ordered Logit - Continuous Variable		Ordered Logit - Binary Variable		Fixed-Effects Ordered Logit - Continuous Variable		Fixed-Effects Ordered Logit - Binary Variable	
	Coefficient	Marginal Effects	Coefficient	Marginal Effects	Coefficient	Marginal Effects	Coefficient	Marginal Effects
Primary Adherence	-0.417***		-0.252***		-0.485***		-0.139***	
	(0.005)		(0.005)		(0.010)		(0.010)	
Therapeutic Guideline = 1		0.074***		0.045***		0.104***		0.029***
		(0.001)		(0.001)		(0.002)		(0.002)
Therapeutic Guideline = 2		-0.025***		-0.015***		-0.009***		-0.003***
		(0.0003)		(0.0003)		(0.0002)		(0.0002)
Therapeutic Guideline = 3		-0.049***		-0.030***		-0.095***		-0.027***
		(0.001)		(0.001)		(0.002)		(0.002)
Comorbidities - 1	0.106***		0.116***		0.587***		0.601***	
	(0.006)		(0.006)		(0.012)		(0.012)	
Therapeutic Guideline = 1		-0.019***		-0.021***		-0.126***		-0.129***
		(0.001)		(0.001)		(0.003)		(0.003)
Therapeutic Guideline = 2		0.007***		0.007***		0.012***		0.012***
		(0.0004)		(0.0004)		(0.0002)		(0.0002)
Therapeutic Guideline = 3		0.012***		0.013***		0.114***		0.117***
		(0.001)		(0.001)		(0.002)		(0.002)
Comorbidities - 2	0.155***		0.170***		1.035***		1.058***	
	(0.006)		(0.006)		(0.013)		(0.013)	
Therapeutic Guideline = 1		-0.028***		-0.030***		-0.222***		-0.227***
		(0.001)		(0.001)		(0.003)		(0.003)
Therapeutic Guideline = 2		0.009***		0.011***		0.020***		0.021***
		(0.0004)		(0.0004)		(0.0003)		(0.0003)
Therapeutic Guideline = 3		0.018***		0.019***		0.202***		0.206***
		(0.001)		(0.001)		(0.003)		(0.003)

Comorbidities - 3	0.183***		0.204***		1.395***		1.424***	
	(0.007)		(0.007)		(0.014)		(0.014)	
Therapeutic Guideline = 1		-0.032***		-0.037***		-0.299***		-0.305***
		(0.001)		(0.001)		(0.003)		(0.003)
Therapeutic Guideline = 2		0.012***		0.013***		0.028***		0.028***
		(0.0004)		(0.0004)		(0.0003)		(0.0003)
Therapeutic Guideline = 3		0.021***		0.024***		0.272***		0.277***
		(0.001)		(0.001)		(0.003)		(0.003)
Comorbidities - 4	0.166***		0.194***		1.752***		1.789***	
	(0.007)		(0.007)		(0.016)		(0.016)	
Therapeutic Guideline = 1		-0.029***		-0.035***		.0.376***		-0.384***
		(0.001)		(0.001)		(0.003)		(0.003)
Therapeutic Guideline = 2		0.011***		0.013***		0.035***		0.035***
		(0.0004)		(0.0004)		(0.0003)		(0.0003)
Therapeutic Guideline = 3		0.019***		0.023***		0.341***		0.348***
		(0.001)		(0.001)		(0.003)		(0.003)
Public	-0.102***		-0.0851***		-0.109***		-0.094***	
	(0.009)		(0.009)		(0.031)		(0.030)	
Therapeutic Guideline = 1		0.018***		0.015***		0.023***		0.020***
		(0.002)		(0.002)		(0.007)		(0.007)
Therapeutic Guideline = 2		0.006***		0.005***		-0.002***		-0.002***
		(0.001)		(0.001)		(0.001)		(0.001)
Therapeutic Guideline = 3		-0.012***		-0.010***		-0.021***		-0.018***
		(0.001)		(0.001)		(0.006)		(0.006)
Number of Visits	0.016***		0.0143***		0.009***		0.007***	
	(0.0002)		(0.0002)		(0.001)		(0.001)	
Therapeutic Guideline = 1		-0.003***		0.003***		-0.002***		-0.001***
		(0.000)		(0.000)		(0.000)		(0.000)
Therapeutic Guideline = 2		0.001***		0.001***		0.0002***		0.0001***

		(0.000)		(0.000)		(0.000)		(0.000)
Therapeutic Guideline = 3		0.002***		0.002***		0.002***		0.001***
		(0.000)		(0.000)		(0.000)		(0.000)
Number of Observations	1,363,778	1,363,778	1,363,778	1,363,778	1,250,422	1,250,422	1,250,422	1,250,422

Notes:
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
Regression includes controls variables for: (i) patient sociodemographic characteristics (age, gender, patient location (region), health insurance); (ii) health sector characteristics (type of care, specialty, patient-physician interactions (visits)) and (iii) treatment characteristics (time and type of prescription).

4.5 Robustness Checks

The validity of our results can be confirmed by introducing sample restrictions and observing if and how the results change. We've decided to include the options mentioned next.

I. Changes on the Adherence Measure

   a. Exclusion of prescriptions with full non-adherence, i.e., primary adherence equals zero.

By excluding complete non-adherence, we exclude cases where the patient decided that was not the right treatment at all.

Results provided by this estimation are present in Table 4.5 and show that primary adherence presents a negative effect on disease progression, especially after controlling for time-invariant characteristics and the other variables in the model. The same occurs when the patient is in the public health setting.

Higher levels of primary adherence increase the probability of controlling diabetes in the lower therapeutic level (level 1) by 10.1 to 19.9 percentage points. This increasing pattern on the medication purchase decreases the probability of transition to dual therapy (level 2) by 0.8 to 3.5 percentage points. The effect of adherence is higher when patients are required to switch to a triple therapy scheme (level 3), i.e, the higher the adherence pattern the lower it is the probability of reaching higher levels of medication complexity by 7.1 to 19.2 percentage points.

The public health setting follows the same path as primary adherence. The public sector presents an improvement of the disease control while avoiding its progression in comparison with the private health setting. In fact, patients located at the public sector present higher probability of about 1.9 to 2.8 percentage points of staying in monotherapy (level 1). Staying in the public health setting decreases the probability of transitioning to dual therapy (level 2) by 0.1 to 0.6 percentage points and to triple therapy (level 3) by 1.3 to 2.7 percentage points.

Regarding comorbidities, the effect is increasing and reaches its highest expression when patients have four or more associated comorbidities.

Regarding other conditions that diabetic patients may have, we estimate that patients with other comorbidities present a decreasing probability of staying with monotherapy of 1.8 to 12.6, 2.6 to 22, 3.1 to 29.8 and 2.7 to 37.6 percentage points whether you have one,

two, three or four comorbidities. At the same time, this increases the probability of putting the patients in triple therapy (level 3) by 1.2 to 12.1, 1.7 to 21.2, 2 to 28.7 and 1.8 to 36.2 percentage points whether you have one, two, three or four comorbidities.

The number of visits made by patients to physicians also play an important role on adherence and better health outcomes. The higher the number of visits, the higher the probability of transitioning to the next therapeutic level.

These results are aligned with the output provided for the full sample (Subsection 3.4.2 – Table 4.4: Regressions).

Table 4.5 - Determinants of disease progression considering a sample of adherent individuals

	Ordered Logit - Continuous Variable		Fixed-Effects Ordered Logit - Continuous Variable	
	Coefficient	Marginal Effects	Coefficient	Marginal Effects
Primary Adherence	-0.581***		-0.953***	
	(0.008)		(0.016)	
Therapeutic Guideline = 1		0.105***		0.199***
		(0.001)		(0.003)
Therapeutic Guideline = 2		-0.035***		-0.008***
		(0.001)		(0.0001)
Therapeutic Guideline = 3		-0.071***		-0.192***
		(0.001)		(0.003)
Comorbidities - 1	0.0979***		0.600***	
	(0.007)		(0.013)	
Therapeutic Guideline = 1		-0.018***		-0.126***
		(0.001)		(0.003)
Therapeutic Guideline = 2		0.006***		0.005***
		(0.001)		(0.0001)
Therapeutic Guideline = 3		0.012***		0.121***
		(0.001)		(0.003)
Comorbidities - 2	0.142***		1.052***	
	(0.007)		(0.014)	
Therapeutic Guideline = 1		-0.026***		-0.220***
		(0.001)		(0.003)
Therapeutic Guideline = 2		0.009***		0.008***
		(0.001)		(0.0001)
Therapeutic Guideline = 3		0.017***		0.212***
		(0.001)		(0.003)
Comorbidities - 3	0.167***		1.423***	
	(0.007)		(0.016)	
Therapeutic Guideline = 1		-0.031***		-0.298***
		(0.001)		(0.003)
Therapeutic Guideline = 2		0.011***		0.011***
		(0.001)		(0.0001)
Therapeutic Guideline = 3		0.020***		0.287***
		(0.001)		(0.003)
Comorbidities - 4	0.149***		1.797***	
	(0.007)		(0.018)	
Therapeutic Guideline = 1		-0.027***		-0.376***
		(0.001)		(0.004)
Therapeutic Guideline = 2		0.009***		0.014***
		(0.001)		(0.0001)
Therapeutic Guideline = 3		0.018***		0.362***
		(0.001)		(0.004)
Public	-0.103***		-0.133***	
	(0.011)		(0.035)	

Therapeutic Guideline = 1		0.019***		0.028***
		(0.002)		(0.007)
Therapeutic Guideline = 2		-0.006***		-0.001***
		(0.001)		(0.0003)
Therapeutic Guideline = 3		-0.013***		-0.027***
		(0.001)		(0.007)
Number of Visits	0.0214***		0.0132***	
	(0.0002)		(0.001)	
Therapeutic Guideline = 1		-0.004***		0.003***
		(0.000)		(0.0002)
Therapeutic Guideline = 2		0.001***		0.0001***
		(0.0000)		(0.0000)
Therapeutic Guideline = 3		0.003***		0.003***
		(0.000)		(0.0002)
Number of Observations	1,120,199	1,120,199	979,077	979,077

Notes:
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
Regression includes controls variables for: (i) patient sociodemographic characteristics (age, gender, patient location (region), health insurance); (ii) health sector characteristics (type of care, specialty, patient-physician interactions (visits)), and (iii) treatment characteristics (time and type of prescription).

II. Changes on Healthcare System Measures

a. Consider exclusively a Public Sample.

By isolating the presence of the patient to each one of the healthcare setting we aim to study its impact on adherence. This is considered as a cross-test to assess the existence of disease progression related with the healthcare sector where the interaction between the physician and the patient occurs.

Results provided by the estimation considering an exclusive sample representing the public health setting are present in Table 4.6.

Primary adherence (continuous and binary approach) presents a negative effect on disease progression, especially after controlling for time-invariant characteristics and the other variables in the model.

Higher levels of primary adherence increase the probability of controlling Diabetes using monotherapy (level 1) by 7.3 to 10.9 percentage points (continuous approach) or by 3.1 to 4.2 percentage points (binary approach).

This increasing pattern on the medication purchase decreases the probability of transition to dual therapy (level 2) by 0.3 to 2.2 percentage points (continuous approach) or by 0.3

to 1.3 percentage points (binary approach). The effect of adherence is higher when patients are required to switch to a triple therapy scheme (level 3), i.e, the higher the adherence pattern the lower it is the probability of reaching higher levels of medication complexity by 5.1 to 10.7 percentage points (continuous approach) or by 2.9 to 10.7 percentage points (binary approach).

The presence of comorbidities presents an increasing effect and reaches its highest expression when patients have four or more associated comorbidities.

Regarding other conditions that diabetic patients may have, we estimate that patients with other comorbidities, present a decreasing probability of staying with monotherapy of 2.5 to 13.7, 3.5 to 24, 3.8 to 32.1 and 3.1 to 39.4 percentage points (continuous approach) or by 2.8 to 14.1, 3.8 to 24.6, 4.3 to 32.8 and 3.7 to 40.4 percentage points (binary approach) whether you have one, two, three or four comorbidities.

At the same time, this increases the probability of putting the patients in triple therapy (level 3) by 1.7 to 13.3, 2.3 to 23.3, 2.6 to 31.2 and 2.1 to 38.3 percentage points (continuous approach) or by 1.8 to 13.7, 2.6 to 23.9, 2.9 to 31.9 and 2.5 to 39.2 percentage points (binary approach) whether you have one, two, three or four comorbidities.

The number of visits made by patients to physicians also play an important role on adherence and better health outcomes. The higher the number of visits the higher the probability of transitioning to the next therapeutic level.

These results are aligned with the output provided for the full sample (Subsection 3.4.2 – Table 4.4: Regressions).

Table 4.6 - Determinants of disease progression considering a sample for public health setting

	Ordered Logit - Continuous Variable		Ordered Logit - Binary Variable		Fixed-Effects Ordered Logit - Continuous Variable		Fixed-Effects Ordered Logit - Binary Variable	
	Coefficient	Marginal Effects	Coefficient	Marginal Effects	Coefficient	Marginal Effects	Coefficient	Marginal Effects
Primary Adherence	-0.422***		-0.244***		-0.528***		-0.150***	
	(0.006)		(0.006)		(0.011)		(0.012)	
Therapeutic Guideline = 1		0.073***		0.042***		0.109***		0.031***
		(0.001)		(0.001)		(0.023)		(0.003)
Therapeutic Guideline = 2		-0.022***		-0.013***		-0.003***		0.001***
		(0.0003)		(0.0003)		(0.0001)		(0.000)
Therapeutic Guideline = 3		-0.051***		-0.029***		-0.107***		0.030***
		(0.001)		(0.001)		(0.002)		(0.002)
Comorbidities - 1	0.146***		0.159***		0.660***		0.678***	
	(0.008)		(0.007)		(0.014)		(0.014)	
Therapeutic Guideline = 1		-0.025***		-0.028***		0.137***		0.141***
		(0.001)		(0.001)		(0.003)		(0.003)
Therapeutic Guideline = 2		0.008***		0.009***		0.004***		0.004***
		(0.0004)		(0.0004)		(0.0001)		(0.0000)
Therapeutic Guideline = 3		0.017***		0.018***		0.133***		0.137***
		(0.001)		(0.001)		(0.003)		(0.003)
Comorbidities - 2	0.200***		0.220***		1.154***		1.183***	
	(0.007)		(0.007)		(0.015)		(0.015)	
Therapeutic Guideline = 1		-0.035***		-0.038***		0.240***		0.246***
		(0.001)		(0.001)		(0.003)		(0.003)
Therapeutic Guideline = 2		0.011***		0.012***		0.007***		0.007***
		(0.0004)		(0.0004)		(0.0001)		(0.0001)
Therapeutic Guideline = 3		0.023***		0.026***		0.233***		0.239***
		(0.001)		(0.001)		(0.003)		(0.003)

Comorbidities - 3	0.222***		0.248***		1.543***		1.579***	
	(0.008)		(0.008)		(0.016)		(0.016)	
Therapeutic Guideline = 1		-0.038***		-0.043***		0.321***		0.328***
		(0.001)		(0.001)		(0.003)		(0.003)
Therapeutic Guideline = 2		0.012***		0.014***		0.009***		0.009***
		(0.0004)		(0.0004)		(0.00001)		(0.0001)
Therapeutic Guideline = 3		0.026***		0.029***		0.312***		0.319***
		(0.001)		(0.001)		(0.003)		(0.003)
Comorbidities - 4	0.180***		0.213***		1.897***		1.942***	
	(0.008)		(0.008)		(0.018)		(0.018)	
Therapeutic Guideline = 1		-0.031***		-0.037***		0.394***		0.404***
		(0.001)		(0.0013)		(0.004)		(0.004)
Therapeutic Guideline = 2		0.010***		0.012***		0.011***		0.012***
		(0.0004)		(0.001)		(0.0001)		(0.0001)
Therapeutic Guideline = 3		0.021***		0.025***		0.383***		0.392***
		(0.001)		(0.001)		(0.004)		(0.004)
Number of Visits	0.0205***		0.0190***		0.0115***		0.00873***	
	(0.0002)		(0.0002)		(0.001)		(0.001)	
Therapeutic Guideline = 1		-0.004***		-0.003***		0.002***		0.002***
		(0.000)		(0.000)		(0.000)		(0.000)
Therapeutic Guideline = 2		0.001***		0.001***		0.0001***		0.00005***
		(0.000)		(0.000)		(0.000)		(0.000)
Therapeutic Guideline = 3		0.002***		0.002***		0.002***		0.002***
		(0.000)		(0.000)		(0.000)		(0.000)
Number of Observations	1,107,279	1,107,279	1,107,279	1,107,279	983,483	983,483	983,483	983,483

Notes:
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
Regression includes controls variables for: (i) patient sociodemographic characteristics (age, gender, patient location (region), health insurance); (ii) health sector characteristics (type of care, specialty, patient-physician interactions (visits)) and (iii) treatment characteristics (time and type of prescription).

I. Lagged Adherence

Medication adherence and glycaemic control are related (Lin et al., 2017; Schectman et al., 2002). Patients who experience improvement in their health status may also be more likely to adhere to behavioural alterations, glucose self-monitoring, attendance with medical care, and other components of diabetes self-management. These factors are also likely to contribute to improved outcomes. Thus, medication adherence can be both a cause and an effect for a patient who is going to do well (Lin et al., 2017), which may introduce endogeneity issues.

To mitigate this problem, we observe how the results change when primary adherence is lagged one period. The results are presented in Table 4.7.

Higher levels of primary adherence increase the probability of controlling diabetes in the lower therapeutic level (level 1) by 0.5 percentage points. This increasing pattern on the medication purchase decreases the probability of transition to dual therapy (level 2) by 0.2 percentage points. The effect of adherence is higher when patients are required to switch to a triple therapy scheme (level 3), i.e, the higher the adherence pattern the lower it is the probability of reaching higher levels of medication complexity by 0. Longitudinally we have opposite results (positive effect on disease progression). However, the effect is practically null due to its lower effect.

The public sector presents an improvement of the disease control while avoiding its progression in comparison with the private health setting. In fact, patients located at the public sector present higher probability of about 1.5 to 1.9 percentage points of staying in monotherapy (level 1). Staying in the public health setting decreases the probability of transitioning to dual therapy (level 2) by 0.2 to 0.5 percentage points and to triple therapy (level 3) by 1 to 1.8 percentage points.

Regarding comorbidities, the effect is increasing and reaches its highest expression when patients have four or more associated comorbidities.

Regarding other conditions that diabetic patients may have, we estimate that patients with other comorbidities present a decreasing probability of staying with monotherapy of 2.4 to 13, 3.6 to 22.9, 4.2 to 30.7 and 4.1 to 38.6 percentage points whether you have one, two, three or four comorbidities.

At the same time, this increases the probability of putting the patients in triple therapy (level 3) by 1.5 to 11.9, 2.3 to 20.9, 2.7 to 28.2, 2.7 to 35.4 percentage points whether you have one, two, three or four comorbidities.

The number of visits made by patients to physicians also play an important role on adherence and better health outcomes. Although the effect is small, it still shows that the higher the probability of transitioning to the next therapeutic level.

These results are aligned with the output provided for the full sample (Subsection 3.4.2 – Table 4.4: Regressions).

Table 4.7 - Determinants of disease progression considering lagged adherence

	Ordered Logit - Continuos Variable		Fixed-Effects Ordered Logit - Continuos Variable	
	Coefficient	Marginal Effects	Coefficient	Marginal Effects
Primary Adherence	-0.0298***		0.0173**	
	(0.00475)		(0.00783)	
Therapeutic Guideline = 1		0.005***		-0.004**
		(0.001)		(0.002)
Therapeutic Guideline = 2		-0.002***		0.0003**
		(0.0003)		(0.000)
Therapeutic Guideline = 3		-0.004***		0.003**
		(0.001)		(0.002)
Comorbidities - 1	0.132***		0.607***	
	(0.00663)		(0.0123)	
Therapeutic Guideline = 1		-0.024***		-0.130***
		(0.001)		(0.003)
Therapeutic Guideline = 2		0.009***		0.011***
		(0.0004)		(0.0002)
Therapeutic Guideline = 3		0.015***		0.119***
		(0.001)		(0.002)
Comorbidities - 2	0.194***		1.069***	
	(0.00656)		(0.0133)	
Therapeutic Guideline = 1		-0.036***		-0.229***
		(0.001)		(0.003)
Therapeutic Guideline = 2		0.013***		0.019***
		(0.0004)		(0.0002)
Therapeutic Guideline = 3		0.023***		0.209***
		(0.001)		(0.003)
Comorbidities - 3	0.230***		1.438***	
	(0.00689)		(0.0147)	
Therapeutic Guideline = 1		-0.042***		-0.307***
		(0.001)		(0.003)
Therapeutic Guideline = 2		0.015***		0.025***
		(0.000)		(0.0002)
Therapeutic Guideline = 3		0.027***		0.282***
		(0.001)		(0.003)
Comorbidities - 4	0.226***		1.806***	
	(0.00700)		(0.0165)	
Therapeutic Guideline = 1		-0.041***		-0.386***
		(0.001)		(0.004)
Therapeutic Guideline = 2		0-015***		0.032***
		(0.0004)		(0.0002)
Therapeutic Guideline = 3		0.027***		0.354***
		(0.001)		(0.003)
Public	-0.0834***		-0.0932***	
	(0.0102)		(0.0313)	

Therapeutic Guideline = 1		0.015***		0.019***
		(0.002)		(0.007)
Therapeutic Guideline = 2		-0.005***		-0.002***
		(0.001)		(0.001)
Therapeutic Guideline = 3		-0.010***		-0.018***
		(0.001)		(0.006)
Number of Visits	0.0126***		0.00562***	
	(0.000195)		(0.000671)	
Therapeutic Guideline = 1		-0.002***		-0.001***
		(0.000)		(0.0001)
Therapeutic Guideline = 2		0.001***		0.0001***
		(0.000)		(0.000)
Therapeutic Guideline = 3		0.002***		0.001***
		(0.000)		(0.0001)
Number of Observations	1,242,051	1,242,051	1,160,078	1,160,078

Notes:
Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
Regression includes controls variables for: (i) patient sociodemographic characteristics (age, gender, patient location (region), health insurance); (ii) health sector characteristics (type of care, specialty, patient-physician interactions (visits)) and (iii) treatment characteristics (time and type of prescription).

4.6 Discussion

Therapeutic non-adherence is a common concern worldwide since it limits the effectiveness of treatment for many conditions, reducing mortality as well as the economic burden for the health system (Fischer et al., 2011; McGovern et al., 2016). This study contributes to the understanding of the impact of primary adherence, in the context of the Portuguese NHS. In particular, the study analyses the role of the primary adherence on disease progression while controlling for patient, healthcare sector and treatment features of adherence.

There is a considerable proportion of people with Type-2 diabetes (T2DM) that do not take their medication as prescribed, with only 67–85% of oral medication doses prescribed taken (McGovern et al., 2016). Some authors present a more concerning perspective, by considering that only 50 to 70% of individuals take their medications regularly (Khan and Socha-Dietrich, 2018). Our adherence patterns present an average share of dispensed drugs per prescription of 68,8%. A share of 0% adherence is seen on 17,86% of the total amount of prescriptions considered.

Patients wouldn't have access to proper treatment and advice if the interface between them and the physician wouldn't exist. It is a required interaction, in which health professionals act as agents for patients (principal) and mostly decide on their behalf what health services/products they need. The physician influence on health outcomes extends beyond the choice of clinical therapy since they also promote patient adherent behaviour (Gellad et al., 2009; Krueger et al., 2005).

As studied on Section 3, this behaviour was assessed by studying the physician-patient pairing scheme for a sufficiently long period and we have found evidence that this relationship provides a positive and meaningful effect of patient adherence. Higher levels of adherence are responsible for reducing the waste towards resources as well as it decreases disease complications while decreasing disease progression and avoidable hospitalizations. This introduces positive effects on decreasing the burden for patients and the health service (Atella et al., 2017; Al-Ubaydli et al., 2017; Bussière et al., 2020; DiMatteo, 2004; Kennedy-Martin et al., 2017; Lublóy et al., 2015; Morillas et al., 2015; Orom et al., 2018; Osterberg and Blaschke, 2005; Roebuck et al., 2011; Stavropoulou, 2012; Tang et al., 2017; Van Dulmen et al., 2007; Zullig et al., 2015).

Our study considers recently available data of electronic prescriptions and primary adherence to understand its influence on disease progression and severity. This contributes to the research suggestion provided by Al-Ubaydli et al. (2017).

The literature has directed their efforts to understand the drivers of therapeutic adherence. This way, measures applied to the identified drivers can be used to increase adherence levels. This analysis adds to the literature by making the inverse study, i.e, what is the contribution of primary adherence on patients' health outcomes.

According to Asche et al. (2011), they consider that it seems intuitive to think that improved adherence influences positive health outcomes in diabetes, however they also refer that it is extremely challenging to quantify the relationship between adherence and its outcomes such as glycaemic control and disease progression. So far, primary adherence was a difficult matter to access due to data availability. Electronic prescriptions made it possible and as far we are aware, this is the primary study to estimate the impact of the primary adherence on disease progression while accounting for patient, healthcare system and treatment characteristics in a large Portuguese population.

We implemented a fixed-effects ordered logit model approach that considered the three ordered levels of clinical guidelines as the dependent variable and uses a set of control variables for patient, healthcare system and treatment characteristics as explanatory variables. Our main variable of interest is the primary adherence level, i.e., the filled fraction of prescribed drugs.

Our main result suggests a positive correlation between the existence of a suitable adherence level and a decrease in patient transition to higher levels of therapeutic approach (disease progression). An increase on disease severity is usually related with the use of more pharmaceuticals, which leads to a more complex therapeutic scheme. This requires more coordination and understanding of the therapeutic regime that is being implemented, which can lead to higher levels of non-adherence if patients get confused or forget to take their medication.

Vermeire et al. (2001) mention the complexity of the therapeutic regime as one of the turn-offs on medication adherence. This perspective is proved by Egede et al. (2014), who find in their longitudinal retrospective study that poor glycaemic control is tightly linked to medication nonadherence (MPR <80%).

Also, if in mild cases of the disease, where the therapeutic regime is simple and straightforward, the patient does not comply with the implemented routine he will be more likely to move to more complicated stages of the disease and more complex stages of treatment approach.

To reach an equilibrium, it is required that the patient maximizes the levels of adherence so he can control the disease progression and remain at lower levels of therapeutic guidelines (Atella et al., 2017; Al-Ubaydli et al., 2017; Bussière et al., 2020; Kennedy-Martin et al., 2017; Lublóy et al., 2015; Orom et al., 2018; Tang et al., 2017).

The relationship between medication adherence and glycaemic control has already been reported, i.e., increments on medication adherence, tend to decrease the HbA1c level (Lin et al., 2017).

This perspective is presented in our results. According to the applied econometric approach, we show that higher levels of adherence increase the probability of disease control avoiding the need to introduce more complex therapeutic regimes.

Still, Voorham et al. (2011) consider that the perception of poor adherence has often been mentioned by physicians as a reason not to intensify treatment. Observational studies, however, have reported conflicting results on the association between medication adherence and treatment intensification. Both negative and positive associations have been observed between suboptimal adherence and treatment modifications, whereas no such associations were found in other studies.

For this reason, it is especially important to find a way of maximizing patient's health and reduce all the negative impact of a non-controlled condition on the individual and on the health system. Efforts should be made to provide an incentive to adherence putting the patient as a central focus of attention. These incentives should be done (i) by promoting a proper match among the patient and the physician (Orom et al., 2018) or (ii) by incentivize pharmacies to actively participate on this matter.

Polinski et al. (2014) and Lee et al. (2018) in a previous study, presents that "*poor patient-physician communication caused patients' distrust in the healthcare provider*" which will increase nonadherence. An increase of nonadherence will lead to worse health outcomes.

The number of visits to physicians suggests that patients present more complex therapeutic regimes when they present an increasing number of visits. The more visits and interaction with the healthcare provider, the more information the physician and the

patient share which makes it a valuable contribution to treatment decision (Cutler et al., 2019). This shows the existence of a long-run agency-relationship between the patient and the physician that could bring positive aspects for both but also to the health system, i.e, the interaction makes the physician more aware of the needs of the patient which may lead to lifestyle changes, and ultimately better clinical outcomes, namely the reduction of unnecessary hospitalizations which translates into significant excess costs (Orom et al., 2018).

Other interesting result is related with the fact that the public health setting presents an improvement of the disease control while avoiding its progression in comparison with the private health setting. The National Health Service provides universal coverage and a broad range of benefits. Approximately half of the population is exempt and on the past few years, reforms were focused in improving access to care and tackling shortages in the health workforce. [10] Although there are still some access barriers for some population, namely reported unmet needs for medical care due to costs, distance and waiting times, the fact is that the NHS presents some thresholds that are required to be achieved in order to provide good performance indicators. [11]

Decrease the mortality and hospitalizations due to Diabetes as well as improve therapeutic adherence in one of their goals and this is reflected on our results.

The presence of other health conditions makes the individuals to be considered as poly-medicated. The higher the number of other health conditions, the higher the likelihood to be associated with more complex therapeutic regimes. This will automatically increase the number of drugs that the patient must deal with, and it can introduce difficulties towards adherence due to misunderstanding, complexity, and forgiveness.

The study of the different factors involved on adherence and disease progression is a matter of great concern that requires further study to provide evidence to decision-makers. As previously mentioned, the introduction of measures that improve adherence and disease control are a matter of great interest since they not only increase the patients utility and health status, but also help the NHS to decrease unnecessary procedures and costs.

[10] Available at https://ec.europa.eu/health/sites/health/files/state/docs/2019_chp_pt_english.pdf (accessed on January 25, 2020)

[11] Available at https://www.sns.gov.pt/wp-content/uploads/2017/07/DGS_PP_MetasSaude2020.pdf (accessed on June 24, 2021)

4.7 Concluding Remarks

The aim of this study is to analyse and provide additional evidence on the effect of adherence on improved outcomes, especially regarding disease progression associated to Diabetes. The setting where the patient is being followed regarding its condition (public vs. private health provider) also matters and we were also able to teste where is this effect more evident.

Adherence rate is defined as patients who do fill the prescribed medication according to the Portuguese prescription rules (primary non-adherence) and we expressed it as the rate of filled medication among the prescribed within a prescription episode. Approximately 82.1% of prescriptions contain at least one drug that was dispensed and the average adherence rate for the selected period is 68.9%.

We build on the framework of the three levels of therapeutic guidelines followed by physicians and use a Fixed Effects Ordered Logit Model as our principal econometric approach, while considering a large longitudinal matched physician-prescription-patient dataset for all Portuguese e-prescriptions containing information on prescription and dispensing, for the period between January 2015 and October 2019 for all regions in Portugal.

We provide key contributions to the current literature on the outcomes of primary adherence in a large Portuguese population. Our study provides evidence that higher levels of adherence increase the probability of disease control avoiding the need to introduce more complex therapeutic regimes.

Also, this process can be influenced by the health setting where the patient is associated to with the public sector providing better health outcomes.

This is especially important to find a way of maximizing patient's health and reduce all the negative impact of a non-controlled condition on the individual and on the health system. Efforts should be made to provide an incentive to adherence putting the patient as a central focus of attention. These incentives should be done (i) by promoting a proper match among the patient and the physician (Orom et al., 2018) or (ii) by incentivize pharmacies to actively participate on this matter.

These strategies should also be focusing their attention on the public health setting in order to continue to improve disease control as well as reduce indirect costs to the health service, such as worst health outcomes and unnecessary hospitalizations.

5 Differences in dual-practice prescription of recent hypoglycaemic agents: a private vs. public provider approach.

Abstract

Health care professionals are key actors in the dissemination of innovation in health care. They may work in different sectors, thus responding differently to the same incentives which makes the causality between job location and physician behaviour difficult to study.

By observing the prescription behaviour of physicians who work in both public and private sectors, we check for the existence of differences in the adoption and diffusion processes of innovation by physicians working in a single establishment (public *vs.* private sector) and those working in both public and private entities.

We consider a two-folded strategy: a Cox proportional hazard model and a Negative Binomial Model using a panel of patients' prescriptions and dispensing events with the universe of all prescriptions and dispensing in Portugal from January 2015 to October 2019 (N=2,477,672). The individual prescription data is matched with individual, physician, prescription drug, pharmacy and geographical characteristics enabling controlling for a broad range of cofounders.

Our finding suggest that adoption is promoted by the public sector when in exclusivity regimes, while the private sector is responsible for a large proportion in job-duality schemes. Diffusion is promoted by the private sector whether in exclusivity or in job-duality regimes.

Keywords: Job-Duality, Public-Private practice, Electronic prescription, Prescription Drugs, Diffusion

JEL Codes: I11, I13, I15, O33

5.1 Introduction

"*Ideas and products and messages and behaviours spread just like viruses do.*"
— Malcolm Gladwell, The Tipping Point (Cain and Mittman, 2002)

Health care professionals are key actors in the dissemination of innovation in health care. Their main goal may be to maximize the patients' health status, but their decisions are constrained by (i) incentives designed by the pharmaceutical industry and its marketing communication channels, (ii) clinical practice guidelines and budget restrictions imposed by institutions or public authorities, and (iii) their own self-interest.

These constraints might affect the physicians' supply, the volume of health care production, and the quality of the provided services (Biglaiser and Ma, 2007; Cheng et al., 2018; Eggleston and Bir, 2006; Socha, 2010; Socha and Bech, 2011). Because the incentive structure and the nature of these conflicting interests differ, the physicians' behaviour may not be the same when they work exclusively in the private, in the public, or accumulate functions in both sectors (Eggleston and Bir, 2006; Socha, 2010; Socha and Bech, 2011).

The causality between job location and physician behaviour may be difficult to study, namely if the doctors who work in the different sectors respond differently to the same incentives. If that is the case, differences in physician outcomes confound differences coming from each sector's incentives and the physicians' specific utility function.

This challenge can be surpassed by observing over time the prescription behaviour of physicians who work in both public and private sectors, those that work in one of them, and those that shift sectors. This way, and also by eliminating time invariable physician characteristics supported on the panel nature of the sample, we isolate within-doctor variation in prescription outcomes associated with differences in incentives between sectors.

We focus on one specific behaviour to answer the following question: are there differences in the adoption and diffusion processes of innovation by physicians working in a single establishment (public *vs.* private sector) and those working in both public and private entities?

To answer this question, we use a large longitudinal matched physician-prescription-patient dataset of e-prescriptions collected by *Serviços Partilhados do Ministério da Saúde* (SPMS) between January 2015 and October 2019, encompassing all regions in Portugal. The Portuguese healthcare system allows physicians to practice in a single establishment or in both public and private entities simultaneously.[1] In our sample, we observe the behaviour of 16,162 doctors that work exclusively in the public sector, 6,684 that work exclusively in the private sector, and 6,091 that work in both. Moreover, for the physicians that work in both, we can classify which of the sectors is their main job based on the number of prescriptions issued in each location.

Our sample encompasses 2,477,672 e-prescriptions that contained at least one pharmaceutical used to treat Type-1 and Type-2 Diabetes Mellitus. *Diabetes* is a common chronic condition, with a worldwide prevalence, and availability of new therapeutic alternatives with high relative cost. Its successful control requires proper diagnosis and adequate therapeutic regimens. If one of these requirements fails, it can lead to severe complications, increased mortality, and higher economic burden for patients and the health system (Bussière et al., 2020; Kennedy-Martin et al., 2017; Lublóy et al., 2014; Morillas et al., 2014; Zullig et al., 2015).

Access to electronic prescription data, which are an output of the physician-patient relationship and a direct way to measure health supply, especially for chronic conditions (Abulhaj et al., 2013; Alowi and Kani, 2018; Gönül et al., 2001; Socha, 2010), is a useful tool to understand how patients access pharmaceuticals, constituting an appropriate setting to study the effect of job-duality on prescription patterns.

Our empirical strategy is two-folded. First, we use a Cox proportional hazard model to analyse the time it takes for each doctor to prescribe a new therapy for the first time. Second, we use a Negative Binomial Model to test for the determinants of diffusion using the total number of prescriptions containing the innovative drugs that is issued by each physician over time. This model deals with (i) the probability of a physician prescribing recent hypoglycemic agents' tomorrow being higher for physicians who prescribe them today, and (ii) the fact that physicians may present different prescription rates, with some prescribing more than others.

[1] Further information is available in Section 2 – Institutional Framework.

Our results suggest that adoption, for the entire sample, is specially promoted by the private sector when in exclusivity regimens. Job-duality schemes usually require more time to prescribe, in comparison with public exclusive regimes.

When isolating exclusivity schemes, we have that the private sector takes less time to prescribe, thus increasing the pace of adoption. By considering a sample of job-duality, we see thar the public sector is responsible to induce adoption.

Diffusion is promoted by all the other work regimes – private exclusive, public job-duality, private job-duality – in comparison with public exclusivity.

When isolating exclusivity or job-duality regimes, we have a positive effect of private sector over the public sector, i.e., physicians located in this sector are usually associated to more prescriptions containing the drugs of interest.

These are interesting findings as several systems, including the Portuguese, consider legislate towards making exclusivity contracts mandatory.

This study contributes to the literature in two ways. First, most research has been focusing on physicians working in a single setting, with findings have not been conclusive. Second, to the best of our knowledge, this is the first study to estimate the impact of the physician work location on pharmaceutical prescription while accounting for patient, healthcare system, and treatment characteristics. Third, it helps understand the mechanisms associated to prescription patterns in a job-duality scheme.

Our study has some limitations. First, we do not have information on the effect of the pharmaceutical industry in the physician learning and prescribing processes as well as on the money spent on detailing. Consequently, we approach the doctor's learning process as being exclusively determined by experimentation and interaction with patients. Second, our data lack information on important doctor-level covariates such as age, gender or training that could help us to better characterize physician prescription behaviour. Third, we do not observe the patient involvement in the process of choosing the therapy.

The study is organized as follows. The next section reviews the literature on dual practice and innovation diffusion. Section 5.3 presents the data and the methodological approach. Section 5.4 presents the main results and section 5.5 addresses some robustness tests. The results are then discussed in section 5.6, and, finally, section 5.7 concludes.

5.2 Theoretical Background

5.2.1 Moonlighting: Dual-Practice Approach

Physicians play a crucial role in helping patients meet their objectives, namely by making accurate diagnosis, promoting adequate therapeutics, and suggesting lifestyle changes (Orom et al., 2018). The physician-patient interaction embodies an agency relationship, in which health professionals act as agents for patients (principal) and mostly decide and recommend on their behalf what health services/products the patients need and that affects their health outcomes (Folland and Goodman, 2016; Mooney and Ryan, 1993).[2] The main reason behind this delegation of power is that patients are aware of their scarce knowledge on how to address their healthcare needs (Shapiro, 2018), having to rely on an informed agent such as the physician (Folland and Goodman, 2016).

A perfect agent is assumed to make choices that a principal – the patient – would make if he had the same information, professional knowledge, and expertise as the doctor (Blomqvist, 1991; Folland and Goodman, 2016; Gafni and Charles, 2009). But these relationships are not perfect as there may be a gap between the information held by those delivering healthcare and those on the receiving end of it (Folland and Goodman, 2016; Scott and Vick, 1999). This information asymmetry creates an incentive problem, resulting in more (or less) treatment being "demanded" that would have been the case if the patient had full information and knowledge (Mooney and Ryan, 1993).

The doctor's and patient's utility functions are, to a certain extent, independent (Mooney and Ryan, 1993)., i.e., the agent has his own utility function, which he maximizes, and this utility function only partly coincides with the utility function of the principal (Culyer and Newhouse, 2000; Ludwig et al., 2010; McGuire, 2000). Physicians are usually motivated by financial self-interest, concern for their patients, and concern for the social good (Alexander, 2013; Culyer and Newhouse, 2000; McGuire, 2000; Mooney and Ryan, 1993).

In this framework, it is crucial to understand the nature of the incentives that the physician faces that may separate her decision from the one that a fully informed patient would make in his own self-interest. One such decision may be the introduction and diffusion

[2] In this context, the actual issuing of a prescription is thus indicative of a physician's recognition that a specific product is the best alternative to address the patient's condition. It is also the primary metric to measure prescribing behaviour (Groves et al., 2010).

of innovation and the nature of incentives may be determined by the setting in which the provision of care is ensured.

Although the main goal of healthcare professionals should be to maximize the patient's health status, different motivations raised by the different health sectors may introduce variation in medical practice. In most systems, the primary job is mainly public, where hourly wages are fixed, while private hourly income tends to be determined by the supply and demand of private health care (García-Prado and González, 2011; González, 2004; Kimmel and Smith-Conway, 2001; Socha and Bech, 2011)[3]. Physicians can show different levels of satisfaction resulting from their public and private work as motivations between both sectors may vary.[4]

This dichotomy of incentives between public and private sectors may affect physicians' labour supply, volume and quality of production, and risk-taking behaviour. The situation may become even more complex when physicians work simultaneously in both the public and the private sector.

Biglaiser and Ma (2007) use healthcare as the prime example of mixed private-public provision, as physicians often work in both sectors. The terms "*moonlighting*", "*job-duality*", or "*dual-practitioners*" are used interchangeably to describe this dual public-private job participation (Biglaiser and Ma, 2007; Brekke and Sogard, 2007; Socha, 2010; Socha and Bech, 2011).[5] Job-duality is common in several health care systems. In Austria, approximately 100% of senior health specialists work in both sectors, while in the United Kingdom this percentage is reduced to 60%. In Ireland, more than 90% of physicians employed in public hospitals also have privileges to practice in the private sector. Outside Europe, there is available data for Australia and New Zealand, where 79% and 43% of

[3] These assumptions may consider that public-sector physicians engaged in dual-practice are driven by self-interest and financial reasons, compromising their vow towards the patient with the pursuit of profit-maximization. This perspective must not be generalized since (i) many physicians remain in the public sector despite the lower wages, especially because public hospitals are more likely to be associated with universities and research centers; and (ii) among those who are engaged in dual practice, many spend comparatively little time in their private practice (García-Prado and González, 2011; Socha, 2010). Still, due to better remuneration, some dual-practitioners may concentrate their attention and work effort on the private practice at the expense of the public one (Socha, 2010).

[4] Other factors have been identified such as lack of career development opportunities in the public sector (early stages of their medical careers might decide to undertake some work in the private sector to acquire new skills in preparation and anticipation of a move into full-time private practice in the future), poor infrastructure in public facilities, and greater autonomy in the private sector (Cheng et al., 2018).

[5] We were not able to identify any study that compares the choice of procedures by physicians working under different compensation systems and the relationship with health outcomes (public, private or both).

public sector doctors, respectively, hold some job in the private sector (El Koussa et al., 2016; González and Macho-Stadler, 2013).

Dual-practitioners establish close links between the public and the private sector on both the demand and the supply side (Brekke and Sogard, 2007). This practice is usually regulated by the Government and, when authorized, there's always a belief that the public sector might be hurt. Besides differences in incentives between the public and private sectors, there is also a potential difference in physicians' characteristics that work in each sector. For example, not every physician chooses to moonlight, i.e., some remain in the public sector and offer quality services despite the lack of proper incentives (Biglaiser and Ma, 2007).

In the presence of job-duality, physicians are expected to provide faster and higher-quality services in the private sector and consumers who are willing to pay for these superior services opt out of the public system (Biglaiser and Ma, 2007). Dual-practitioners are also assumed to favour long public waiting times to boost the demand for the private services or to cream-skim profitable patients from the public waiting lists to the private practice[6] (Socha and Bech, 2011).

On the demand side, we assume that public and private care are (horizontally) differentiated products, reflecting different service combinations, specialisations, treatment methods, amongst others. The fact that the public service is tendentially free, while private health care is charged a price, implies that most patients have a preference for the public sector.

Allowing physicians to offer (substitutable) private services outside the NHS system may have several potential effects on the provision of public health care. Since the price of private care is a decreasing function of public and private sectors capacities, the physicians have an incentive to restrict their labour supply in both sectors. This is a standard market power incentive due to imperfect competition in the private sector. The strength of this incentive depends on the number of physicians in the market and the degree of substitutability between public and private health care (Brekke and Sogard, 2007).

[6] Physicians can allocate their labour supply according to the benefit they obtain in each sector (Brekke and Sogard, 2007).

Physicians engaged in dual practice are subject to models of labour supply in which workers face upper constraints on main job hours[7] which may limit primary job's earnings capacity (Dickey et al., 2011; García-Prado and González, 2011; Kimmel and Smith-Conway, 2001). Some individuals would prefer to work more hours at their highest paying job rather than holding multiple jobs (Eggleston and Bir, 2006), but are not being offered the opportunity to do so.

The labour economics literature on moonlighting assumes that, when in job-duality, physicians: (i) aim to maximize their income, and (ii) have the possibility of having some nonpecuniary benefit not available on the first job (García-Prado and González, 2011; González, 2004; Kimmel and Smith-Conway, 2001; Socha and Bech, 2011). Either way, the standard theoretical framework assumes that individual's labour supply decisions on both the primary and secondary jobs are based on utility-maximizing behaviour (Dickey et al., 2011).

When located in the public health care sector, physicians assume that although services are free of charge for patients, they are subject to rationing, which can make patients seek private health care and pay for it out-of-pocket. When located in private practice, they assume that they were attracted by better remuneration and other benefits such as professional autonomy, status and recognition, and control over whom they work with, the timing and quantity of the treatments supplied, and the number of patients that they deal with (Biglaiser and Ma, 2007; Brekke and Sogard, 2007; Cheng et al., 2018; Dickey et al., 2011; Socha, 2010; Socha and Bech, 2011). [8]

Biglaiser and Ma (2007) and Lublóy (2014) show that physicians working exclusively in the private sector prescribe more than those who work in the public sector. Lin et al. (2011) concludes that the type of medical centre, public or private, affects prescription behaviour due to different degrees of budget control, but they ignore the possibility that the number of current workplaces may have an impact as well. Zhang et al. (2019), on the other hand, find that physician prescribing characteristics are strong predictors of

[7] The hours of labour supplied to the two jobs are not perfect substitutes. Individuals may choose to work a second job for reasons not connected to primary job hours or earnings, such as the opportunity to gain credentials and experience, for instance (Dickey et al., 2011).

[8] Physicians working simultaneously in both practices can trigger the problem of "cream-skimming", since private providers have incentives to select patients with less severe conditions, attracting patients with higher ability to pay. Public hospitals remain with the more complex patients (Biglaiser and Ma, 2007; Cheng et al., 2018).

adoption patterns, but factors such as the affiliations related with public hospitals do not affect the rate of adoption of new drugs. García Lirola et al. (2000) found that doctors with more than one workplace adopted new drugs earlier than those that do not. As presented by Ellis et al. (2007), other forms of incentives can range from payments depending on the provider's own characteristics (payments vary according to provider characteristics, such as specialty, training, or experience) to payments based exclusively on patient's characteristics (capitation system). An intermediary scheme is the one based on the services provided (payments do not depend on who provides the services or who receives them). Regarding incentives to prescription, Nguyen (2011) examines the prescribing patterns of private providers and shows that private providers were able to induce demand by prescribing more drugs than public providers for a similar illness and patient profile.

5.2.2 First learning, then prescribing: How does adoption and diffusion works?

Newly developed pharmaceuticals include "*highly innovative first-in-class medicines with new molecular entity with added therapeutic benefit*[9] *and new ATC (Anatomical Therapeutic Chemical Classification System) code,* or *me-too or follow-on drugs, which enter the market in an already existing drug class and are chemically very similar to already approved drugs"* (Karampli et al., 2014; Lublóy, 2014; Simoens, 2008).

Diffusing of new drugs amongst prescribers is a required step for patients to access their benefits (Coscelli and Shum, 2004; Garjón et al., 2012). As new pharmaceuticals enter the market and are authorized by the regulatory authorities to be used for a specific clinical indication, physicians decide whether to use the new molecule or remain with the pre-existing ones, according to their risk-aversion degrees and information about the new product (Ackerberg, 2003; Ching et al., 2013; Chintagunta et al. 2009).

Learning about new medical products is crucial for physicians. It can involve: (i) informative advertising, or (ii) feedback (Ackerberg, 2003; Ching et al., 2013; Culyer and

[9] It might also include new esters, new salts, or other non-covalent derivatives, new indications for existing products, new dosage forms, new formulations, or new combinations (Karampli et al., 2014; Lublóy, 2014; Simoens, 2008).

Newhouse, 2000). The first is often called "indirect bayesian learning effect" and it's mostly seen in the introductory phase of a drug's life cycle. It helps to identify the "true" efficacy of the drug and reduce the uncertainty around it (Bourke and Roper, 2014; Ching, 2010; Chintagunta et al., 2012; Culyer and Newhouse, 2000; Gönül et al., 2001; Narayanan et al., 2005). In this process, the main intervenient is the pharmaceutical industry and its marketing communication channels,[10] who spend almost twice as much on promotion[11] as on R&D (Yang et al., 2014).

The second effect is the experimentation process through which physicians increase their knowledge (Ferreyra and Kosenok, 2011). It acts as a substitute or a complement to detailing signals (Ching and Ishihara, 2010; Ching et al., 2013; Chintagunta et al., 2012; Narayanan et al., 2005; Ward, 2013). Physicians gather evidence that influences their preferences through goodwill accumulation. This evidence results from the actual prescription of the new drug to patients (shifts in consumer utility), or the interaction with other physicians (peer effect/contagion effect) (Narayanan et al., 2005; Vakratsas and Kolsarici, 2008).[12]

Pharmaceutical diffusion is a slow and time-consuming process. The main factors that determine and influence the speed of diffusion of drugs include: (i) marketing activities directed to potential adopters, such as advertising, personal selling, meetings and events (Garjón et al., 2012; Liu and Gupta, 2012; Lublóy, 2014); (ii) social contagion (also known as interpersonal network effect, word-of-mouth effect, or peer influence) which refers to the fact that an individual's adoption behaviour is affected by exposure to others' knowledge, attitude, or behaviour regarding the product (Liu and Gupta, 2012; Lublóy, 2014; Lublóy et al., 2014; Lublóy et al., 2016, Lublóy et al., 2018); (iii) intrinsic propensity of individual physicians to adopt, which may be partly related to observable characteristics such as physician specialty, category prescription volume, and

[10] The industry usually has access to more information about the quality of the products than the prescribers. It shares information using sales representatives, direct mailouts, advertisements in journals and prescribing software, as well as drug launch meetings. Sales representatives present and promote new drugs to physicians, who will introduce them to patients (Ching, 2010; Ching and Ishihara, 2010; Manchanda et al., 2005; Prosser and Walley, 2003),

[11] There is a clear and positive effect of targeted detailing, journal advertising, and meetings and events sponsored by drug manufacturers on physicians' innovation adoption (Liu and Gupta, 2012).

[12] Prescribers start with a set of prior beliefs based on the information set that is available up to the previous period. They update this with the information acquired in the current period to form a set of posterior beliefs. Physicians then use this set of posterior beliefs to make decisions in the current period. This set of posterior beliefs forms the set of prior beliefs for the next period (Coscelly and Shum, 2005; Ferreyra and Kosenok, 2011; Narayanan et al., 2005).

sociodemographic factors of the neighborhoods where the physician practices (Anderson et al., 2018; Garjón et al., 2012; Liu and Gupta, 2012; Lublóy, 2014); and (iv) the influence on the physician of the patient's request for the drug (Abulhaj et al., 2013; Liu and Gupta, 2012; Lublóy, 2014).

The adoption of medical technology differs across organizations and individuals, since they can either promote or prevent its diffusion.[13] Predicting and understanding physicians' prescribing behaviour is a complex, multifactorial exercise. However, patients, physicians, policymakers, and pharmaceutical companies would all benefit from a more comprehensive understanding of the influencing factors and their interaction (Lublóy, 2014).

As considered by Selder (2005) and Bruni et al. (2009), the prescribing behaviour, as well as product diffusion, are affected by economic incentives alongside with organisational and institutional features of the system under which the physician operates, the insurance environment in which the product is reimbursed, public policy regulation, competitive or cooperative interactions among providers, and demographic composition. [14]

Physicians under stronger incentives may be able to write more prescriptions or make an extra effort to make the patient fill the prescription. On the other hand, if physicians shift their prescribing towards other medications, this may stem from altruism or from pressure applied by the patient (Dickstein, 2016).

Job duality may influence the physician prescribing pattern, but the literature on the topic presents ambiguous findings so far. Biglaiser and Ma (2007) show that physicians working exclusively in the private sector tend to prescribe more recent drugs than those who work in public workplaces. Lublóy (2014) adds that private practices are more likely to adopt earlier new drugs than public practices and that doctors in not-for-profit institutions were more likely to prescribe new drugs than doctors in for-profit institutions. García-Lirola et al. (2000) found that doctors located in more than one workplace adopted new drugs earlier than those located in just one workplace; however, the authors did not specify differences across workplace (public *vs.* private). Lin et al. (2011) finds that the type of medical centre, public or private, affects prescription behaviour due to different

[13] The WHO defines health technology as the application of organized knowledge and skills in the form of devices, medicines, vaccines, procedures, and systems developed to solve a health problem and improve quality of lives (Cain and Mittman, 2002; Sanson-fisher, 2004, WHO, 2021).

[14] This is all part of the economic theory of incentives that assumes that an agent gets utility from the wage he receives and disutility from the effort he exerts on behalf of the principal (Bruni et al., 2009).

degrees of budget control. Their results oppose Biglaiser and Ma (2007) and Lublóy (2014), who show that private practices are less likely to adopt new drugs earlier than public practices and that the number of current workplaces is irrelevant.

Zhang et al. (2019) show that physician demographic and professional characteristics, such as medical training, risk preference and personality, physician practice style, as well as social interactions and practice characteristics, influence prescription behaviour and are strong predictors of adoption patterns. On the other hand, they find that affiliation with public hospitals does not appear to affect the rate of adoption of new drugs.

Though physicians working in private practices tend to show more predisposition to prescribe recent drugs, it is important to understand the diffusion pattern under job-duality status (public and private) (Biglaiser and Ma, 2007; Lublóy, 2014).

5.3 Data and Methodological Issues

5.3.1 Data

We use a large longitudinal matched physician-prescription-patient dataset of e-prescriptions collected by *Serviços Partilhados do Ministério da Saúde* (SPMS) between January 2015 and October 2019, from all regions in Portugal.[15]

The prescriptions were selected if they contained at least one drug in pharmacological class A10 - Drugs Used in Diabetes: A10A (Insulins and Analogues) and A10B (Blood Glucose Lowering Drugs, excl. Insulins) according to the Anatomical Therapeutic Chemical (ATC) Classification System, complemented with information from the Therapeutic Group 8 of the Portuguese Therapeutic Medical Record (subclass 8.4. "*Insulinas, antidiabéticos e glucagon*"). [16]

The data represent 10% of the universe of e-prescriptions associated with pharmaceuticals used to control *Diabetes*, which encompasses more than 20 million observations that contain a pharmaceutical used to treat Type-1 and Type-2 *Diabetes Mellitus*.

The complete dataset covers 27,937 physicians, 128,155 patients, 2,477,672 e-prescriptions and 42 different anti-diabetic pharmaceuticals, including oral hypoglycemic agents and insulins. Prescriptions were randomly selected and were included if the patient: (1) was 18 years or older, and (2) had been prescribed an anti-diabetic pharmaceutical within the selected time range. This reduced the sample to 1,517,320 e-prescriptions.[17] Each observation corresponds to a single line of prescription and includes details about the prescription (id number, prescription date, dispensing date, cost of drug for the NHS, price supported by the patient, number of pills, pharmaceutical form, number of packages, dosage, active ingredient and respective codes (CNPEM and national drug code) and posology), the patient (age, gender, health care insurance, geographical location, health insurance), the provider (medical specialty, workplace, type of care – hospital vs. primary care), and the pharmacy (geographical location).

The dataset has some limitations. First, we have no information regarding patients' socioeconomic and demographics characteristics such as race/ethnicity, years of

[15] The data contain all issued electronic prescriptions, regardless of whether they were eventually filled or not.

[16] Further details can be accessed at https://app10.infarmed.pt/prontuario/frameprimeiracapitulos.html.

[17] The data include all the situations in which the patient was prescribed an antidiabetic drug, but it may also include prescription of drugs for other pathologies. We use that information to determine the number of comorbidities.

education, employment status, number of people in the household and marital status.[18] Second, we have no information on the physicians' sociodemographic features such as age, gender, place of medical education, level of education and year of graduation from medical school. Third, we are not able to see the physicians' connections with their peers, since we do not know the exact institution they work in. Finally, we are not able to consider differences across regions caused by asymmetries in population density, area, and distribution of care.

5.3.2 Recent Hypoglycaemic Agents: Why use?

There are twelve groups of drugs associated with antidiabetic drugs (ATC10)[19].

Figure 5.1 shows a schematic representation of the market introduction of antidiabetic pharmaceuticals. The allocation of the different drugs according to the patient's condition is described in the clinical therapeutic guidelines' representation, available on Section 2, subsection 2.3: Patient Clinical Pathway – Therapeutic Guidelines for Diabetes (Table 2.5 – Therapeutic Guidelines for Diabetes)

We analyse the introduction and diffusion of new drugs belonging to the ATC10B subgroup. This group has a small or null percentage of generic drugs, which makes it more costly to the patient and to the government. Moreover, the Defined Daily Dosage (DDD) tends to be lower, which makes therapeutic regimens easier to follow. We've selected formulations whose first prescription fits within a time range in which a generic formulation wasn't available. The included formulations are: Alogliptin, Canagliflozin, Dulaglutide, Empagliflozin, Metformin + Alogliptin, Metformin + Canagliflozin, Metformin + Dapagliflozin, Metformin + Linagliptin, Pioglitazone + Alogliptin and Empagliflozin + Metformin.

[18] We can infer some information regarding the patients' socioeconomic characteristics by using one of two alternatives: (i) by considering that individuals with the higher level of reimbursement belong to a lower income group or (ii) by using the district's average income. We've implemented option (i).

[19] Detailed characterization of this group is available on Section 2, subsection 2.3 – Table 2.4..

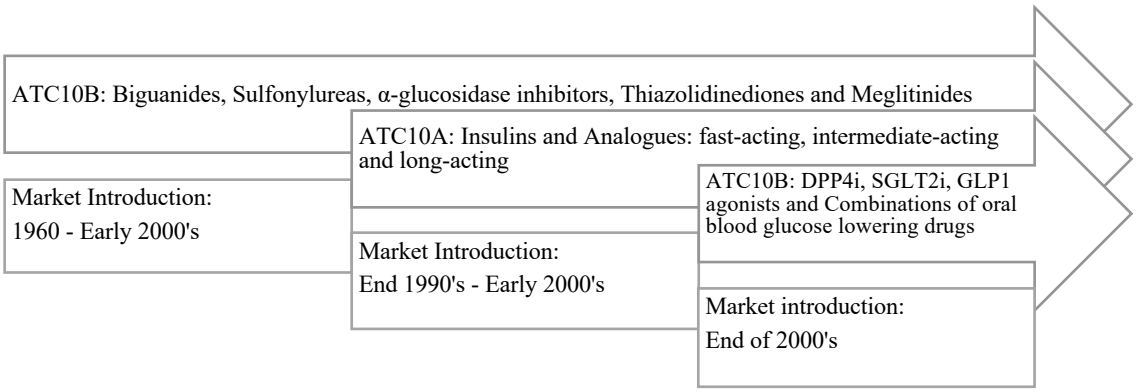


Figure 5.1 - Market introduction of pharmaceuticals belonging to ATC level 10 (Source: Own elaboration)

Prescribing ATC10B's involves considerable medical complexity (Lublóy et al., 2014). Biguanides, the first line of treatment, are the most highly valued medication due to their ability to control the glycaemic level. Newer classes of antidiabetic drugs, including Dipeptidyl peptidase-4 inhibitors (DPP4-i), Glucagon-like peptide-1 agonists (GLP1-a), and Sodium-glucose co-transporter-2 inhibitors (SGLT2-i), as well as their combinations, have higher costs to the patient, but they offer advantages over previously available therapies, such as reduced risk of hypoglycaemia, lower effect on body weight, positive results on other comorbidities (hypertension, hyperlipidaemia), and cardiovascular benefits (Gaviria-Mendoza et al., 2018; Karampli et al., 2020).

5.3.3 Job-Duality Measure

The interaction between public and private health care provision within NHS system allows physicians to practice in more than one workplace, private or public.

Primary job location is usually defined in two ways: (i) where the individual spends more working-hours, or (ii) where the individual receives the highest earnings (Kimmel and Smith-Conway, 2001; Socha and Bech, 2011). In our study, and due to the lack of available information on working hours and wages, we define primary job as the workplace where physicians have more prescriptions issued. We adopted the following

logic to identify the physician workplace: i) if a physician prescribes exclusively from one sector, whether public or private, he is exclusively working on that sector; ii) if the physician prescribes in both the public and private sectors, then we consider that the physician is in job-duality. In the job-duality case, we set as primary job the workplace where the physician has more issued prescriptions of the two. Four groups were then defined: (i) public, exclusive; (ii) private, exclusive; (iii) public in job-duality and (iv) private in job-duality.

5.3.4 Adoption: Time to First Prescription Measure

Adoption is measured by the time it takes a physician to first prescribe the active ingredient after market introduction.[20] For some physicians that moment does not occur until the end of the observation period, which is taken into consideration in the implemented econometric approaches.

5.3.5 Diffusion: Number of Prescriptions Measure

The number of prescriptions written by the physician allows us to test for the diffusion of the innovation. We adopt a broader perspective of the process by considering the prescription of any of the innovative drugs. Prescriptions are classified into two categories: (i) those that contain recent hypoglycaemic agents, or (ii) those that do not.
The total number of prescriptions containing recent hypoglycaemic agents per period t is measured at the physician level j.

$$Total\ Number\ of\ Prescriptions_{jt} = \sum prescriptions\ containing\ innovative\ drugs_{jt}$$

For each period we consider the cumulative sum of prescriptions containing recent hypoglycaemic agents. As referred above, there is a significant number of physicians who don't prescribe any of the innovative agents, making the distribution of this variable left skewed.

[20]Anderson et al. (2018) consider that this measure does not capture heterogeneity in the uptake of a drug once it is first prescribed. For example, time to first prescription may misclassify a physician as a rapid adopter if he/she writes a single prescription for a drug even if she/he is refilling a prescription initiated by another physician. Although this can be a limitation, it is the best available measure of adoption.

5.3.6 Methods

We aim to estimate the impact of physician workplace and exclusivity regime in the adoption and diffusion of recent hypoglycaemic agents. Survival analysis is a useful tool to achieve that goal. We implement a Cox proportional hazard model to analyze survival data without imposing a specific parametric form for the baseline hazard function. This model, which assumes that the covariates multiplicatively shift the baseline hazard function, is popular due to its elegance and computational feasibility (Cleves et al., 2016; Son, 2020).

We limit our sample to the five most representative recent drugs (Dulaglutide, Empagliflozin, Metformin + Alogliptin, Metformin + Dapagliflozin, Metformin + Linagliptin).[21]

The Cox model is expressed by a *hazard function* denoted by $h(t)$, that can be interpreted as the risk of prescribing at time t. It can be estimated as follows:

$$h(t) = h_0(t).\exp\left(\beta_1 PhysicianStatus_1 + \delta \boldsymbol{X}\right) \quad (4.1)$$

where t is the survival time, $h(t)$ is the hazard function determined by a set of covariates, h_0 is the baseline hazard which corresponds to the value of the hazard if all the covariates equal to zero, the coefficients β_p measure the effect of covariates, and $\boldsymbol{X}$ is a set of control variables for patient, healthcare system, and treatment characteristics.

The selected model also deals with the fact that our data are an unbalanced panel as we have information on prescriptions for 27,937 physicians over a five-year period, but there are physicians that enter later or leave our sample.

To test for adoption determinants, we use the quantity of prescriptions containing recent hypoglycaemic drugs. Our dependent variable is a count variable, i.e., a positive integer whose distribution is skewed to the left, making the Negative Binomial Model the most appropriate choice (Cameron and Trivedi, 1998). We have repeated observations for the same physician, as data shows a panel structure allowing the computation of prescription supply for a period of more than five years. This allows us to control for physician characteristics that are not observable but are assumed constant over time.

[21] We select these five agents considering that: (i) they provide a good sample size in terms of "failures", i.e., we guarantee a sample of over 2000 physicians that prescribe the selected drugs for the first time, and (ii) the period of observation for the selected drugs is large enough (minimum of 24 months and maximum of 54 months) to provide robust results.

We could also consider adopting a Poisson model, but our data suffer from two departures from the Poisson assumption. First, our data deals with "occurrence dependence", i.e., the chances of a physician prescribing recent hypoglycaemic agents' tomorrow are higher for physicians who prescribe them today (Winkelmann, 1995; Winkelmann, 2015). [22] Second, it also has into consideration "unobserved heterogeneity", i.e, physicians have different prescription rates, with some prescribing more than others, due to different unobserved factors. Both occurrence dependence and unobserved heterogeneity invalidate the assumptions underlying the Poisson model (Winkelmann, 2015).[23]Unobserved heterogeneity leads to "overdispersion": in the conditional model for y as a function of x, the variance increases over-proportionally with the mean (Winkelmann, 2015)., i.e, the variance exceeds the mean.

The Negative Binomial Model (NBM) deals with both unobserved heterogeneity and occurrence dependence. Since our data are overdispersed[24] and NBM allows the variance to differ from the mean, this model yields better predictions of the outcome probabilities. We would also like to account for unobserved heterogeneity of physicians by means of a fixed effect model. Portela et al. (2009) explain how to deal with unobserved heterogeneity while using a Negative Binomial Model. Wooldridge (1999) refers that a fixed effects Negative Binomial Model assumes overdispersion for each cross-sectional unit, which can be difficult to test. Portela et al. (2009) complement this perspective with Allison and Waterman (2002) that explain that the fixed effects in the context of a NBM do not have the same meaning that we are used to in other contexts, as they only apply to the overdispersion parameter rather than to the covariates. This model specification solves the overdispersion problem, still does not guarantee that the physician-specific effects are conditional out of the likelihood. To avoid this problem, Portela et al. (2009) suggest that we estimate our model based on the pooled sample, an unconditional NBM with dummy variables to account for the health sector/exclusivity contract fixed effects. This seems a pertinent solution to deal with unobserved heterogeneity in a count data

[22] Such models are said to display "*True Contagion*" (Winkelmann, 1995).

[23] Poisson regression assumes that each observed count y_i follows a Poisson distribution with parameter λ_i. It also has the property that mean, and variance are equal (equidispersion property): $E(y) = \lambda$ and $V(y) = \lambda$. The consequences of overdispersion are like those of heteroscedasticity in the linear regression model. When applying a Poisson regression to overdispersed data the estimates for the standard deviation of the coefficients will be biased towards zero, yielding inflated z statistics.

[24] Further information available at Appendix 5.1 and Appendix 5.2.

model while considering the difference between the variance and the mean of the distribution.[25]

The effect of the physician workplace, as well as their association to job-duality or exclusivity regimens is then studied using the following count model:

$$TNIP_{jt} = \beta_0 + \beta_1 PhysicianStatus_{jt} + \delta \boldsymbol{X_{jt}} + \varepsilon_{jt} \quad (4.2)$$

where the $TNIP_{jt}$ is the total number of prescriptions containing innovative pharmaceuticals for physician j at a time t, $PhysicianStatus_{jt}$ is a set of binary variables for each one of the four categories mentioned before, X_{jt} is a set of control variables for patient, healthcare system, treatment characteristics, and ε_{it} is a random error term assumed to be uncorrelated with the regressors.

[25] For further details on complementary methodological approaches, see Section 5.5 – Robustness Check.

5.4 Results

5.4.1 Descriptive Statistics

Prescription of pharmaceuticals should follow clinical therapeutic guidelines. These try to guide and standardize the physicians' choices considering the patients' needs. Still, the physicians' prescribing decisions can also be influenced by: (i) patient, (ii) institutional incentives, and (iii) nature of treatment.

Table 5.1 provides information on statistics regarding the nature of provider and table 5.2 provides information on patient and treatment characteristics.

The total number of physicians prescribing antidiabetic drugs between January 2015 and October 2019 amounts to 27,937. They are divided between exclusivity and job-duality regimens. In our sample, 15,162 physicians practice exclusively in the public (54.3%), 6,684 in the private setting (23.9%), while dual practitioners amount to 6,091 physicians (21.8%).

The selected sample of physicians contains 81.6% of General Practitioners, followed by Internal Medicine physicians (7.4%) and Endocrinologists (3.8%). The presence of General Practitioners is dominant in the public setting (90.1% in exclusivity and 82.3% in public job-duality), while specialists such as endocrinologists (9% in exclusivity vs. 10.9% in job-duality), internal medicine physicians (11.3% in exclusivity vs. 14% in job-duality) and others have higher expression in the private sector (26.4% in exclusivity vs. 15.1% in job-duality).

Prescriptions have their origin from primary care facilities (68%) with higher expression in the public sector (85.8% in exclusivity and 80.1% in public job-duality).

The physician-patient interaction presents differences across health sectors as well. Each physician consults nearly 38 patients, with a total of 107 consultations during the selected period. They also interact with a specific patient approximately 11 times in the 5-year range.[26] The number of repeated interactions between the physician and the patient is more expressive when physicians are associated with job-duality regimens, especially in the private setting (12.67 interactions in exclusivity vs. 14.17 interactions in private job-duality), which means that physicians working in the private sector exhibit higher volume of health care production (116.34 consults in exclusivity vs. 151.37 in private job-

[26] The number of consultations corresponds to the appointments where antidiabetic drugs are prescribed.

duality). Physicians also see more patients in the private setting both in exclusivity (38.99 visits) and in job-duality (50.49 visits).

The total number of patients who have been prescribed with antidiabetic drugs between January 2015 and October 2019 adds to 128,155. On average, 52.3% of patients prescribed with antidiabetic medication are women and the mean age of patients is 67.9 years, varying from 17 to 110 years old.

A major part of the prescriptions is exclusively covered by the national health service insurance (91.2%) and approximately 34% of individuals present lower levels of co-payment due to lower levels of income.

Physicians working in the private sector consult a higher proportion of women and interact with older patients. The levels of prescriptions associated with NHS-insurance are higher on the public sector as is the number of patients associated with lower income.

The selected period includes a total of 1,517,320 prescriptions containing hypoglycaemic agents evenly distributed across all years.

Prescriptions comprise the therapeutic approach and can contain up to 6 pharmaceuticals with each prescription containing an average of 1.37 drugs. Each patient has, on average, 2 additional health comorbidities besides diabetes and this is nearly constant across health sector and work contract.

Openness to innovation differs across physicians. Each one prescribes approximately 0,6 recent drugs and they present a more conservative trend when associated to the private sector (0.26 drugs in exclusivity and 0.32 in private job-duality) in comparison with the public setting (0.73 drugs in exclusivity and 0.91 in public job-duality).

Table 5.1 - Statistics regarding the nature of provider in different settings

	General Practitioner	Endocrinologist	Internal Medicine Physician	Other Specialty	Primary Care	Patients seen by the physician	Repeated Interactions	Number of Consultations	Openness to Innovation
ALL SAMPLE									
N = 1,517,320	0.816	0,038	0,074	0,072	0,680	37,231	10,649	107.934	0.602
	(0.388)	(0.192)	(0.262)	(0.259)	(0.467)	(31.410)	(10.078)	(114.602)	(1.041)
EXCLUSIVITY									
Public Health Sector									
N = 834,529	0.901	0,009	0,058	0,032	0,858	31,954	10.039	93.753	0.737
	(0.299)	(0.093)	(0.235)	(0.176)	(0.349)	(17.194)	(8.171)	(80.963)	(1.103)
Private Health Sector									
N = 159,823	0.532	0,090	0,113	0,264	0,007	38,997	12.671	116.342	0.266
	(0.499)	(0.286)	(0.317)	(0.441)	(0.084)	(56.536)	(13,.38)	(178.561)	(0.696)
JOB-DUALITY									
Public Health Sector									
N = 389,933	0.823	0,056	0,068	0,053	0,801	43,299	9.925	120.016	0.912
	(0.381)	(0.230)	(0.252)	(0.223)	(0.399)	(28.883)	(8.480)	(113.071)	(1.266)
Private Health Sector									
N = 133,035	0599	0,109	0,140	0,151	0,013	50,430	14.174	151.375	0.324
	(0.490)	(0.312)	(0.347)	(0.358)	(0.113)	(51.497)	(16.660)	(170.986)	(0.743)

Notes:
Mean values, Standard Deviation in parentheses

Table 5.2 - Statistics regarding the patient and treatment characteristics in different settings

	Gender (Female=1)	Age	Insurance Type	Lower Income	Disease Severity	Comorbidities
ALL SAMPLE						
N = 1,517,320	0.523	67.985	0.912	0.338	1.370	2.039
	(0.499)	(12.655)	(0.283)	(0.473)	(0.647)	(1.324)
EXCLUSIVITY						
Public Health Sector						
N = 834,529	0.516	67.900	0.924	0.358	1.376	2.078
	(0.500)	(11.963)	(0.265)	(0.479)	(0.647)	(1.313)
Private Health Sector						
N = 159,823	0.527	68.384	0.837	0.223	1.323	1.908
	(0.499)	(14.266)	(0.369)	(0.416)	(0.625)	(1.348)
JOB-DUALITY						
Public Health Sector						
N = 389,933	0.521	67.139	0.935	0.357	1.400	2.050
	(0.500)	(12.671)	(0.247)	(0.479)	(0.669)	(1.323)
Private Health Sector						
N = 133,035	0.563	70.520	0.864	0.298	1.293	1.914
	(0.496)	(14.313)	(0.343)	(0.458)	(0.597)	(1.351)

Notes:
Mean values, Standard Deviation in parentheses

Table 5.3 provides information about the time (in days) required to adopt a new drug. We observe that, on average, it takes four years to prescribe a new drug for the first time. This is not atypical as, after being authorized into the market, reimbursement decisions and detailing procedures must be made. The literature shows that half of physicians take 4 years to adopt a new drug (Huskamp et al., 2013), and this period can range between 30 to 61 months (Son, 2020).

Physicians located in different health sectors present a similar pattern of average days required to adopt, still they tend to be faster at the private sector.

Physicians in the private sector prescribe recent hypoglycaemic agents at a faster pace than those in the public sector, independently of the exclusivity regimen associated to the physician.

Table 5.3 - Time (in days) required to adopt a new drug (time = date of first prescription – date of market introduction (Garjón et al., 2012))

				EXCLUSIVITY		JOB-DUALITY		DIFFERENCE		
ACTIVE-INGREDIENT	**ALL SAMPLE**	**EXCLUSIV. (A)**	**JOB-DUAL. (B)**	**PUBLIC (C)**	**PRIVATE (D)**	**PUBLIC (E)**	**PRIVATE (F)**	**A-B**	**C-D**	**E- F**
Alogliptin										
N	737	481	256	442	39	204	52			
Mean	1603.421	1604.339	1601.695	1605.482	1591.385	1602.534	1598.404	-	-	-
Std. Dev.	400.507	394.434	412.454	393.156	413.723	412.926	414.592			
Min.	783	783	801	858	783	823	801			
Max.	2239	2237	2239	2237	2237	2238	2239			
Canagliflozin										
N	955	541	414	460	81	303	111			
Mean	1947.726	1950.124	1944.592	1950.093	1950.296	1940.812	1954.91	-	-	-
Std. Dev.	148.923	148.511	149.581	148.836	147.574	148.949	151.489			
Min.	1629	1641	1629	1641	1655	1629	1636			
Max.	2176	2176	2176	2176	2176	2176	2174			
Dulaglutide										
N	2,015	1,218	797	977	241	522	275			
Mean	1502.757	1523.089	1471.685	1529.104	1498.705	1475.701	1464.062	***	**	-
Std. Dev.	206.561	197.878	215.617	195.544	205.692	215.255	216.489			
Min.	1046	1046	1047	1054	1046	1047	1051			
Max.	1805	1805	1805	1805	1804	1805	1805			
Empagliflozin										
N	5,494	3,503	1,991	2,999	504	1,452	539			
Mean	1584.293	1596.582	1562.672	1600.951	1570.589	1551.584	1592.54	***	**	***
Std. Dev.	258.196	253.124	265.572	250.919	264.637	267.424	258.403			
Min.	1015	1016	1015	1027	1016	1015	1028			
Max.	1988	1988	1988	1988	1987	1988	1988			

Empagliflozin + Metformin										
N	220	128	92	111	17	70	22			
Mean	1595.786	1594.945	1596.957	1594.541	1597.588	1596.214	1599.318	-	-	-
Std. Dev.	13.988	14.625	13.037	14.692	14.322	13.1479	12.684			
Min.	1561	1561	1569	1561	1576	1569	1578			
Max.	1618	1618	1618	1618	1618	1618	1618			
Metformin + Alogliptin										
N	2,596	1,662	934	1,486	176	757	177			
Mean	1593.012	1611.106	1560.815	1614.688	1580.858	1557.042	1576.949	***	-	-
Std. Dev.	397.871	397.179	397.277	398.195	388.283	400.206	385.187			
Min.	794	794	797	794	807	797	819			
Max.	2233	2233	2233	2233	2231	2233	2232			
Metformin + Canagliflozin										
N	76	40	36	34	6	33	3			
Mean	1991.947	1991.800	1992.111	1993.735	1980.833	1993.939	1972	-	*	**
Std. Dev.	14.912	15.344	14.632	13.889	19.833	13.679	9.539			
Min.	1961	1961	1966	1968	1961	1968	1966			
Max.	2017	2017	2016	2017	2008	2016	1983			
Metformin + Dapagliflozin										
N	5,523	3,554	1,969	3,088	466	1,426	543			
Mean	1554.550	1572.432	1522.274	1577.393	1539.556	1511.953	1549.378	***	**	*
Std. Dev.	385.423	381.613	390.232	376.828	410.839	387.651	396.012			
Min.	725	725	735	725	747	735	736			
Max.	2114	2114	2114	2114	2114	2114	2114			
Metformin + Linagliptin										
N	2,692	1,719	973	1,498	221	740	233			
Mean	1868.910	1873.988	1859.939	1881.467	1823.29	1859.482	1861.391	-	*	-
Std. Dev.	474.312	476.238	470.999	473.563	492.098	476.846	452.923			
Min.	985	991	985	991	991	985	993			

Max.	2659	2659	2659	2659	2656	2659	2651			
Pioglitazone + Alogliptin										
N	121	71	50	53	18	37	13			
Mean	1567.719	1577.028	1554.500	1575.208	1582.389	1537.703	1602.308	-	-	-
Std. Dev.	416.545	396.687	447.008	399.908	398.406	460.411	420.282			
Min.	748	866	748	868	866	748	977			
Max.	2226	2226	2197	2226	2170	2197	2179			

Notes: *** p<0.01, ** p<0.05, * p<0.1

Graphical representations of the adoption of recent hypoglycaemic agents between exclusive and job-duality (public and private setting) is also shown in Figures 5.2 to 5.9 The number of prescriptions containing recent hypoglycaemic agents is an alternative indicator of diffusion. A sample of 10,687 physicians (38.25%) has at least one prescription containing recent hypoglycaemic agents, between January 2015 and October 2019.

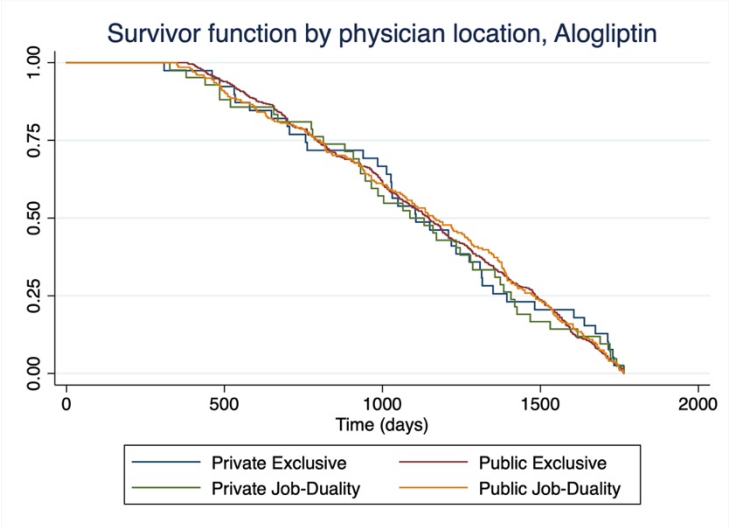


Figure 5.2 – Survivor function for Alogliptin

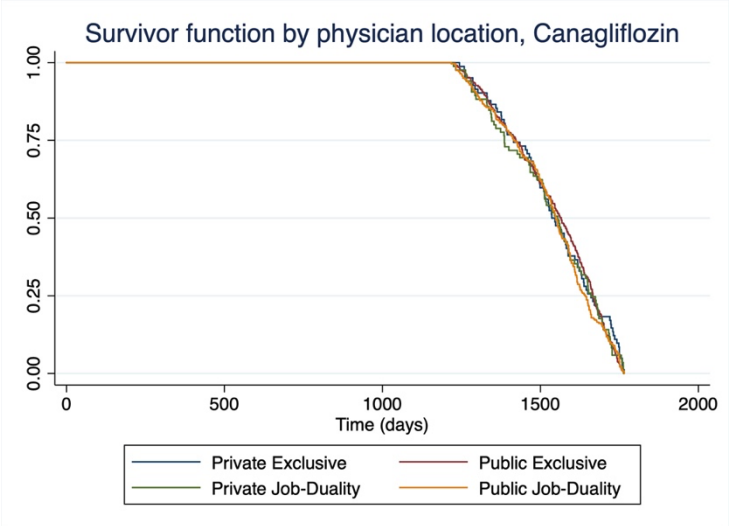


Figure 5.3 - Survivor Function for Canagliflozin

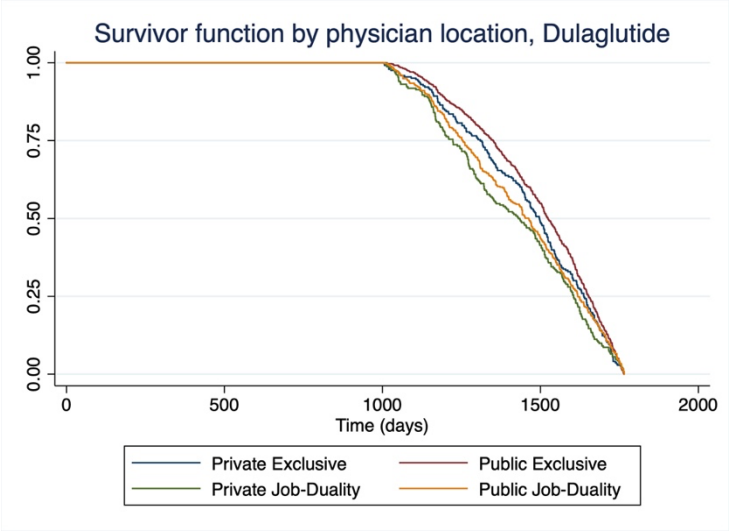


Figure 5.4 - Survivor Function for Dulaglutide

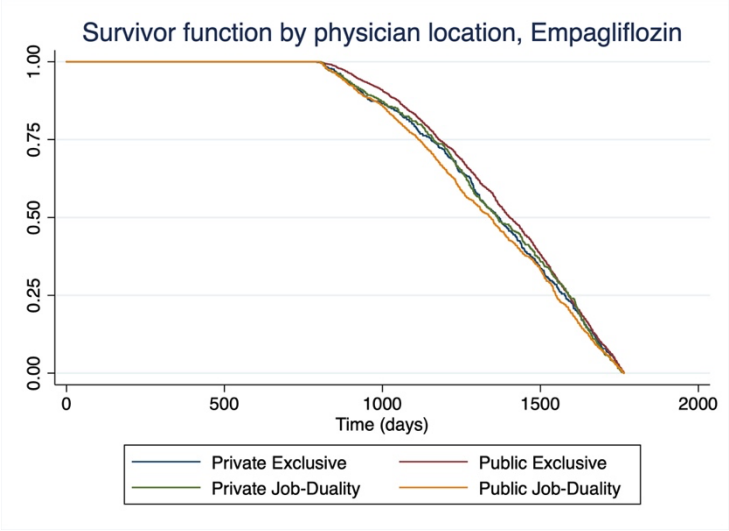


Figure 5.5 - Survivor Function for Empagliflozin

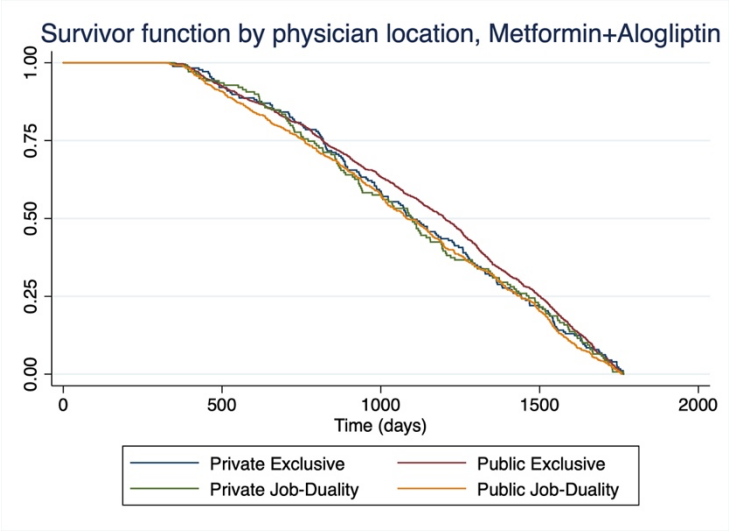


Figure 5.6 - Survivor Function for Metformin+Alogliptin

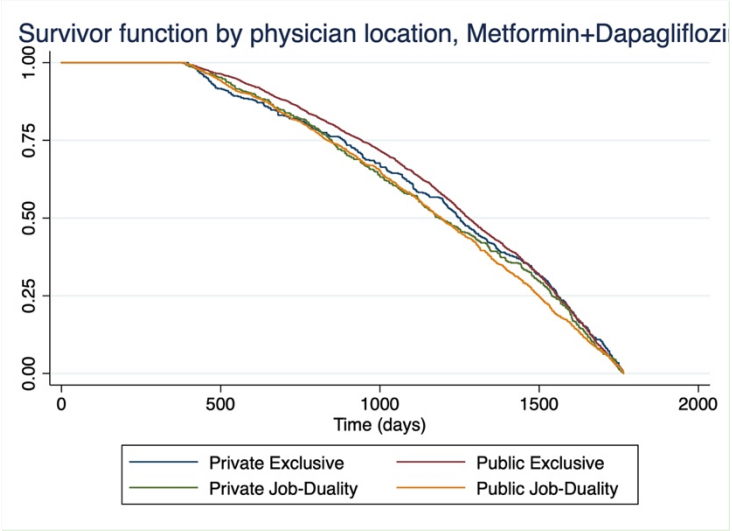


Figure 5.7 - Survivor Function for Metformin + Dapagliflozin

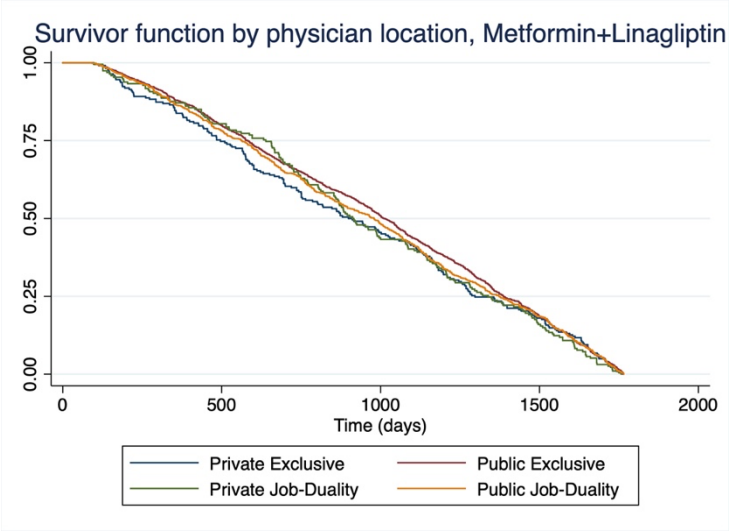


Figure 5.8 - Survivor Function for Metformin + Linagliptin

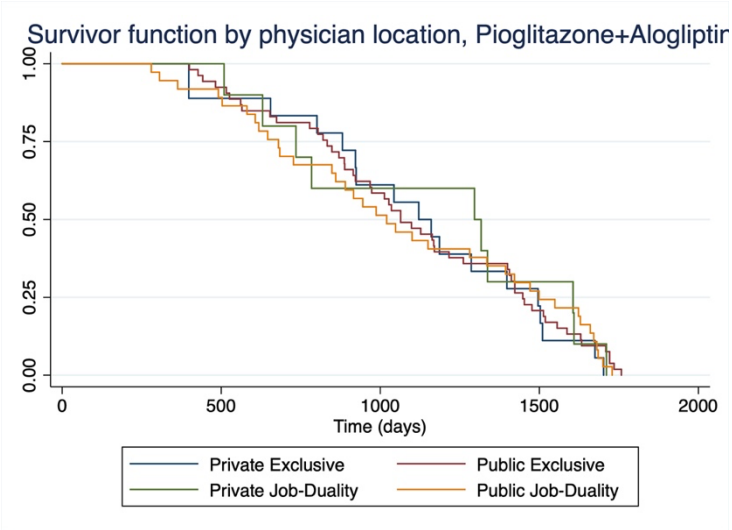


Figure 5.9 - Survivor Function for Pioglitazone + Alogliptin

5.4.2 Survival Analysis Model

Results from the Cox Proportional Hazard Model are presented by Hazard-Ratios (HR), also called relative risks, which indicate the change on the dependent variable relatively to the base group, *ceteris paribus*.

The hazard rate is the probability that if the event in question has not already occurred, it will occur in the next time interval, divided by the length of that interval. The time interval is made very short, so that in effect the hazard rate represents an instantaneous rate.

The interpretation should be considered in the following way: a hazard ratio equal to 1 means a lack of association; a hazard ratio greater than 1 suggests an increased risk (reduces the expected time to adoption), and a hazard ratio below 1 suggests a smaller risk (increases the expected time to adoption).

This model allows us to study the factors influencing the time required to adopt a new drug for the first time. We considered the five most representative drugs in our sample: Dulaglutide, Empagliflozin, Metformin + Alogliptin, Metformin + Dapagliflozin, Metformin + Linagliptin.

Physicians who choose to serve exclusively the public healthcare sector are the most frequent group and are considered our reference group.

Our baseline approach considers the full sample. Working exclusively in the private sector reduces the expected time required to adopt (higher pace of adoption) a specific drug by 11.7 to 41.6%, in comparison with physicians practicing exclusively in the public sector.

To present a proper comparison between groups we've divided the sample into: (a) public, (b) private, (c) exclusivity and (d) job-duality.

Results on (a) show that practicing in public job-duality increases the expected time required to adopt a new drug (lower pace of adoption) by 0.5 to 9%, in comparison with physicians practicing exclusively in the public sector; (b) shows that practicing in private job-duality also increases the expected time to adoption from 40 to 63.3%, in comparison with physicians practicing exclusively in the private sector; (c) shows that that the same physician in job-duality, requires is expected to require more time to adopt a new drug (14.9 to 49%) in the private sector, in comparison with its practice in the public sector; (d) shows that physicians working exclusively in the private sector are expected to require less time to adopt a specific drug by 0.9 to 35.3% in comparison with physicians working exclusively in the public sector. The results remain constant and robust across the five drugs.

The outcomes towards medical specialty show us that specialists such as Endrocrinologists (*physician_end*) and Internal Medicine physicians (*physician_im*) require less time to adopt new drugs, in comparison with General Practitioners, which is used as our reference group. This is usually related with pharmaceutical sales representatives' visits, i.e, the pharmaceutical industry starts by introducing and making

efforts to present their drugs to the physicians responsible for using them with their patients. Endocrinologists and Internal Medicine physician are able to present more interactions with diabetic patients and for this reason they are more likely to adopt these drugs.

Endrocrinologists and Internal Medicine physicians increase the pace of adoption of a specific drug by 19.8 to 83.1% and 18.5 to 43.8%, respectively. The results are consistent among other drugs, except for Metformin + Alogliptin in which these specialties are expected to take more time to adopt (approximately 48.2% and 17.5%, respectively).

Adoption levels are also dependent on physician's learning experience. Our data allow us to consider physician's gain of information based on experience from prescribing new drugs to patients.

We consider two alternatives to measure this process: (i) physician's number of given consults to any patient (*nconsults*), and (ii) the number of interactions between a specific pair (*interactionspair*). Both measures are considered as interval variables, with each interval being considered by considering its percentiles.

The first option considers the number of consults given to any patient. This reflects a multitude of stimuli from different interactions and does not necessarily imply a consistent and long-term relationship between a specific physician-patient pair. An increase on the number of interactions also increases the opportunity of feedback, which is translated into a decrease on the expected time required to prescribe (all hazard ratios are above 1 and are mainly statistically significant).

This perspective is complemented with the number of patients seen by the physician (*other_patients*) which also shows that higher the number of different patients seen, the higher the pace of adoption (all hazard ratios are above 1 and are mainly statistically significant), in comparison with physicians that see only one patient.

The second option introduces the concept of a long-term and trustworthy relationship developed between the patient and the physician. The more these two parties interact, the less the asymmetry of information associated to this interaction, however, the level of information shared between both parties regarding new drugs is limited to patients that have the drug on their therapeutic regime, which may not happen for all patients. For this reason, it may happen that it takes more time to prescribe a new drug, and this is showed in our regression results. As an example, we have that the more interactions (over 30 in

the sample period) increases the time required to prescribe a new drug by 58.5 to 86.6% in comparison with only one interaction.

We also considered the patient's principal physician (Active-Treatment Provider – ATP [27]). This provider responsible for the active treatment as well as their maintenance. They are usually General Practitioners and work on primary care sector.

Results are only statistically significant for the drug Dulaglutide, which show that these physicians decrease the pace of adoption by 37.5 % in comparison with only one interaction.

For the sake of simplicity, we will have considered the results provided by the full sample, however, when splitting the options into (a) public, (b) private, (c) exclusivity and (d) job-duality, the results remain consistent.

Tables 5.4 to 5.8 present the Survival Analysis (Cox Proportional Hazard Model) used to explain adoption of recent hypoglycaemic agents.

[27] The physician is considered the principal physician for a patient due to its guidance and follow-up on the active treatment. This approach uses the long-term relationship by considering the physician who is responsible for the active treatment (according to implemented therapeutic guidelines), i.e, the physician responsible for the higher number of therapeutic choices and changes.

Table 5.4 - Estimates from the Survival Analysis (Cox Proportional Hazard Model) for Dulaglutide

	Sample: All	Sample: Only Public	Sample: Only Private	Sample: Only Job-Duality	Sample: Only Exclusivity
	Hazard Ratio	Hazard Ratio	Hazard Ratio	Hazard Ratio	Hazard Ratio
public, exclusive	(ref)	(ref)	-	-	(ref)
private, exclusive	1.289**	-	(ref)	-	1.241*
	(0.134)				(0.142)
public, jobduality	0.956	0.951	-	(ref)	-
	(0.066)	(0.068)			
private, jobduality	0.693***	-	0.598***	0.802*	-
	(0.072)		(0.080)	(0.095)	
physician_gp	(ref)	(ref)	(ref)	(ref)	(ref)
physician_end	1.831***	1.684***	1.358	1.969***	1.649***
	(0.226)	(0.326)	(0.302)	(0.358)	(0.297)
physician_im	1.438***	1.165	1.406**	1.995***	1.141
	(0.152)	(0.198)	(0.227)	(0.335)	(0.159)
physician_other	0.917	0.595***	1.187	1.082	0.849
	(0.103)	(0.110)	(0.175)	(0.223)	(0.119)
principal physician – ATP	0.625***	0.543***	0.709**	0.708**	0.558***
	(0.057)	(0.066)	(0.102)	(0.097)	(0.069)
other_patients (1)	(ref)	(ref)	(ref)	(ref)	(ref)
other_patients (1-10)	1.618***	1.369	2.221***	0.246***	1.872***
	(0.297)	(0.357)	(0.577)	(0.125)	(0.360)
other_patients (10-20)	2.866***	2.465***	3.745***	0.346**	3.739***
	(0.583)	(0.675)	(1.219)	(0.178)	(0.831)
other_patients (20-30)	4.108***	3.353***	5.942***	0.614	5.158***
	(0.909)	(0.974)	(2.215)	(0.335)	(1.255)
other_patients (30-40)	5.091***	3.912***	8.422***	0.930	5.728***
	(1.179)	(1.174)	(3.394)	(0.512)	(1.505)
other_patients (40-50)	4.221***	3.020***	8.500***	0.873	4.095***
	(1.041)	(0.951)	(3.746)	(0.495)	(1.193)
other_patients (50-60)	5.577***	4.157***	9.516***	1.021	6.273***
	(1.435)	(1.340)	(4.509)	(0.582)	(1.956)
other_patients (>60)	5.186***	3.619***	11.54***	1.045	4.838***
	(1.330)	(1.176)	(5.353)	(0.603)	(1.562)
nconsults (1)	(ref)	(ref)	(ref)	(ref)	(ref)
nconsults (5-10)	1.222	1.345	0.945	1.781	1.084
	(0.219)	(0.301)	(0.287)	(0.989)	(0.208)
nconsults (10-30)	1.302*	1.573**	0.816	1.388	1.235
	(0.206)	(0.308)	(0.227)	(0.720)	(0.208)

nconsults (30-50)	1.350*	1.640**	0.903	1.662	1.232
	(0.235)	(0.349)	(0.280)	(0.881)	(0.238)
nconsults (50-70)	1.171	1.469*	0.751	1.324	1.098
	(0.223)	(0.337)	(0.260)	(0.724)	(0.234)
nconsults (70-100)	1.262	1.765**	0.581	1.262	1.291
	(0.249)	(0.417)	(0.218)	(0.694)	(0.289)
nconsults (100-150)	1.313	1.726**	0.738	1.245	1.375
	(0.263)	(0.415)	(0.277)	(0.686)	(0.316)
nconsults (150-200)	1.407	2.063***	0.537	1.535	1.318
	(0.299)	(0.513)	(0.223)	(0.862)	(0.330)
nconsults (250-300)	1.557*	2.483***	0.541	1.571	1.766*
	(0.395)	(0.737)	(0.252)	(0.924)	(0.581)
nconsults (>300)	1.404	2.051**	0.585	1.718	1.004
	(0.345)	(0.606)	(0.263)	(0.989)	(0.358)
interactionspair (1)	(ref)	(ref)	(ref)	(ref)	(ref)
interactionspair (1-5)	0.998	0.934	1.193	1.200*	0.878
	(0.065)	(0.069)	(0.150)	(0.130)	(0.071)
interactionspair (5-10)	0.890	1.319	0.703	1.186	0.742
	(0.231)	(0.414)	(0.255)	(0.576)	(0.217)
interactionspair (10-15)	1.038	0.816	1.485	2.727***	0.732
	(0.236)	(0.274)	(0.466)	(0.994)	(0.205)
interactionspair (15-20)	0.854	1.025	0.575	0.801	0.817
	(0.227)	(0.325)	(0.297)	(0.540)	(0.242)
interactionspair (20-25)	1.504*	1.293	2.208*	3.708***	1.021
	(0.369)	(0.394)	(0.940)	(1.435)	(0.316)
interactionspair (25-30)	1.146	1.161	1.031	0.828	1.225
	(0.347)	(0.425)	(0.578)	(0.606)	(0.413)
interactionspair (>30)	1.131	0.957	1.558	1.068	1.137
	(0.253)	(0.296)	(0.509)	(0.360)	(0.342)
Number of Observations	632,456	471,215	161,241	210,392	422,064

Notes:

(i) Failure: First time the drug of interest is prescribed;

(ii) Number of subjects: 34.030 (There are 27.937 physicians, however 6093 work non-exclusively which makes us consider their presence twice);

(iii) Std. Err. adjusted for 27.937 clusters in Id. physician.

(iv) Robust Standard errors in parentheses;

(v) *, **, and *** denote significance at 10%, 5%, and 1% respectively

(vi) Regression includes controls variables for: patient characteristics, healthcare setting and treatment features.

Table 5.5 - Estimates from the Survival Analysis (Cox Proportional Hazard Model) for Empagliflozin

	Sample: All	Sample: Only Public	Sample: Only Private	Sample: Only Job-Duality	Sample: Only Exclusivity
	Hazard Ratio	Hazard Ratio	Hazard Ratio	Hazard Ratio	Hazard Ratio
public, exclusive	(ref)	(ref)	-	-	(ref)
private, exclusive	1.200***	-	(ref)	-	1.137*
	(0.077)				(0.080)
public, jobduality	0.928**	0.954	-	(ref)	-
	(0.034)	(0.036)			
private, jobduality	0.622***	-	0.491***	0.784***	-
	(0.041)		(0.042)	(0.059)	
physician_gp	(ref)	(ref)	(ref)	(ref)	(ref)
physician_end	1.198**	0.952	1.447**	1.444***	0.904
	(0.110)	(0.129)	(0.214)	(0.187)	(0.132)
physician_im	1.331***	1.196*	1.288**	1.642***	1.118
	(0.0905)	(0.127)	(0.147)	(0.182)	(0.099)
physician_other	1.240***	1.019	1.541***	1.813***	0.965
	(0.085)	(0.112)	(0.151)	(0.211)	(0.082)
principal physician – ATP	0.939	0.945	0.938	0.911	0.962
	(0.054)	(0.065)	(0.099)	(0.083)	(0.070)
other_patients (1)	(ref)	(ref)	(ref)	(ref)	(ref)
other_patients (1-10)	2.170***	2.035***	2.301***	0.439	2.242***
	(0.258)	(0.309)	(0.440)	(0.226)	(0.269)
other_patients (10-20)	4.851***	4.304***	5.498***	1.088	4.915***
	(0.626)	(0.683)	(1.241)	(0.571)	(0.657)
other_patients (20-30)	7.112***	6.307***	8.525***	1.810	6.963***
	(0.983)	(1.048)	(2.177)	(0.966)	(1.015)
other_patients (30-40)	7.772***	6.818***	9.680***	2.110	7.393***
	(1.121)	(1.169)	(2.723)	(1.137)	(1.145)
other_patients (40-50)	8.927***	7.826***	11.43***	2.502*	8.255***
	(1.328)	(1.378)	(3.346)	(1.357)	(1.330)
other_patients (50-60)	7.468***	6.750***	7.826***	2.164	6.643***
	(1.163)	(1.231)	(2.667)	(1.181)	(1.170)
other_patients (>60)	9.402***	7.836***	13.35***	2.798*	7.652***
	(1.457)	(1.435)	(4.100)	(1.523)	(1.375)
nconsults (1)	(ref)	(ref)	(ref)	(ref)	(ref)
nconsults (5-10)	1.332***	1.646***	0.471***	1.119	1.377***
	(0.127)	(0.171)	(0.123)	(0.332)	(0.141)
nconsults (10-30)	1.189**	1.324***	0.845	1.004	1.240**
	(0.0993)	(0.124)	(0.164)	(0.250)	(0.113)

nconsults (30-50)	1.155	1.236**	0.960	1.021	1.169
	(0.108)	(0.131)	(0.202)	(0.260)	(0.124)
nconsults (50-70)	1.188*	1.363***	0.767	1.024	1.220*
	(0.122)	(0.155)	(0.183)	(0.269)	(0.145)
nconsults (70-100)	1.025	1.122	0.774	0.768	1.143
	(0.111)	(0.136)	(0.190)	(0.208)	(0.142)
nconsults (100-150)	1.106	1.247*	0.771	0.804	1.274*
	(0.121)	(0.154)	(0.194)	(0.219)	(0.162)
nconsults (150-200)	1.231*	1.292*	1.131	0.958	1.360**
	(0.144)	(0.171)	(0.293)	(0.267)	(0.191)
nconsults (250-300)	0.968	1.050	0.782	0.635	1.338
	(0.159)	(0.201)	(0.256)	(0.205)	(0.286)
nconsults (>300)	1.338**	1.390*	1.017	1.090	1.340
	(0.196)	(0.247)	(0.302)	(0.323)	(0.284)
interactionspair (1)	(ref)	(ref)	(ref)	(ref)	(ref)
interactionspair (1-5)	0.893***	0.881***	0.921	0.959	0.849***
	(0.034)	(0.038)	(0.080)	(0.062)	(0.041)
interactionspair (5-10)	0.717**	0.775	0.738	1.293	0.522***
	(0.104)	(0.151)	(0.165)	(0.305)	(0.095)
interactionspair (10-15)	0.670***	0.670**	0.673*	1.095	0.561***
	(0.090)	(0.112)	(0.159)	(0.296)	(0.088)
interactionspair (15-20)	0.551***	0.552***	0.537**	0.973	0.446***
	(0.084)	(0.098)	(0.156)	(0.332)	(0.078)
interactionspair (20-25)	0.493***	0.452***	0.638	0.675	0.411***
	(0.091)	(0.094)	(0.235)	(0.277)	(0.085)
interactionspair (25-30)	0.464***	0.421***	0.552	0.509	0.411***
	(0.101)	(0.107)	(0.212)	(0.243)	(0.101)
interactionspair (>30)	0.413***	0.314***	0.556**	0.461***	0.363***
	(0.069)	(0.072)	(0.134)	(0.116)	(0.079)
Number of Observations	632,358	471,147	161,211	210,201	422,157

Notes:

(i) Failure: First time the drug of interest is prescribed;
(ii) Number of subjects: 34.030 (There are 27.937 physicians, however 6093 work non-exclusively which makes us consider their presence twice);
(iii) Std. Err. adjusted for 27.937 clusters in Id. physician;
(iv) Robust Standard errors in parentheses;
(v) *, **, and *** denote significance at 10%, 5%, and 1% respectively
(vi) Regression includes controls variables for: patient characteristics, healthcare setting and treatment features.

Table 5.6 - Estimates from the Survival Analysis (Cox Proportional Hazard Model) for Metformin + Alogliptin

	Sample: All	Sample: Only Public	Sample: Only Private	Sample: Only Job-Duality	Sample: Only Exclusivity
	Hazard Ratio	Hazard Ratio	Hazard Ratio	Hazard Ratio	Hazard Ratio
public, exclusive	(ref)	(ref)	-	-	(ref)
private, exclusive	1.416***	-	(ref)	-	1.353**
	(0.163)				(0.170)
public, jobduality	0.986	0.995	-	(ref)	-
	(0.053)	(0.053)			
private, jobduality	0.475***	-	0.367***	0.510***	-
	(0.057)		(0.057)	(0.078)	
physician_gp	(ref)	(ref)	(ref)	(ref)	(ref)
physician_end	0.518***	0.440***	0.591	0.626*	0.210***
	(0.111)	(0.122)	(0.222)	(0.159)	(0.122)
physician_im	0.825*	0.763*	0.713	0.830	0.831
	(0.096)	(0.116)	(0.167)	(0.156)	(0.125)
physician_other	0.753**	0.559***	1.061	0.652**	0.831
	(0.0848)	(0.087)	(0.182)	(0.125)	(0.120)
principal physician – ATP	0.990	1.023	0.892	0.979	0.996
	(0.079)	(0.093)	(0.156)	(0.125)	(0.102)
other_patients (1)	(ref)	(ref)	(ref)	(ref)	(ref)
other_patients (1-10)	2.232***	1.844**	2.900***	1.223e+07***	2.355***
	(0.473)	(0.493)	(1.018)	(2.852e+06)	(0.505)
other_patients (10-20)	4.395***	3.516***	6.036***	2.067e+07***	5.057***
	(0.982)	(0.958)	(2.453)	(3.992e+06)	(1.183)
other_patients (20-30)	6.518***	5.269***	7.622***	3.208e+07***	7.359***
	(1.504)	(1.472)	(3.396)	(5.156e+06)	(1.795)
other_patients (30-40)	8.260***	6.407***	13.15***	4.160e+07***	9.173***
	(1.934)	(1.806)	(6.101)	(6.463e+06)	(2.282)
other_patients (40-50)	10.13***	7.905***	16.03***	4.939e+07***	11.70***
	(2.417)	(2.259)	(7.888)	(7.886e+06)	(2.981)
other_patients (50-60)	7.189***	5.662***	9.797***	4.279e+07	6.943***
	(1.785)	(1.665)	(5.557)	(0,000)	(1.936)
other_patients (>60)	10.45***	8.393***	13.26***	5.844e+07***	10.21***
	(2.540)	(2.432)	(6.965)	(9.055e+06)	(2.712)
nconsults (1)	(ref)	(ref)	(ref)	(ref)	(ref)

nconsults (5-10)	2.168***	2.335***	1.653	1.823	2.188***
	(0.329)	(0.383)	(0.667)	(0.725)	(0.362)
nconsults (10-30)	2.212***	2.306***	2.007*	1.778	2.277***
	(0.298)	(0.340)	(0.737)	(0.623)	(0.341)
nconsults (30-50)	2.640***	2.905***	1.751	2.390**	2.619***
	(0.389)	(0.468)	(0.719)	(0.857)	(0.444)
nconsults (50-70)	3.195***	3.481***	2.145*	3.119***	3.020***
	(0.502)	(0.597)	(0.937)	(1.145)	(0.556)
nconsults (70-100)	3.241***	3.366***	2.959**	3.083***	3.080***
	(0.518)	(0.594)	(1.278)	(1.138)	(0.581)
nconsults (100-150)	3.125***	3.236***	2.886**	2.409**	3.405***
	(0.516)	(0.587)	(1.317)	(0.906)	(0.659)
nconsults (150-200)	3.491***	3.797***	2.569*	3.015***	3.541***
	(0.619)	(0.739)	(1.269)	(1.159)	(0.758)
nconsults (250-300)	3.360***	3.852***	1.893	2.735**	3.860***
	(0.768)	(0.971)	(1.097)	(1.172)	(1.160)
nconsults (>300)	3.518***	3.894***	2.608*	3.184***	3.286***
	(0.811)	(1.003)	(1.434)	(1.341)	(1.126)
interactionspair (1)	(ref)	(ref)	(ref)	(ref)	(ref)
interactionspair (1-5)	0.703***	0.653***	1.046	0.796**	0.652***
	(0.038)	(0.038)	(0.148)	(0.072)	(0.045)
interactionspair (5-10)	0.646*	0.770	0.697	0.602	0.652
	(0.157)	(0.253)	(0.251)	(0.355)	(0.175)
interactionspair (10-15)	0.300***	0.281***	0.400*	0.273*	0.294***
	(0.076)	(0.084)	(0.193)	(0.191)	(0.082)
interactionspair (15-20)	0.197***	0.212***	0.097**	0.463	0.157***
	(0.054)	(0.061)	(0.101)	(0.234)	(0.051)
interactionspair (20-25)	0.244***	0.226***	0.307	0.428*	0.194***
	(0.065)	(0.065)	(0.231)	(0.200)	(0.064)
interactionspair (25-30)	0.253***	0.213***	0.462	0.419*	0.196***
	(0.074)	(0.072)	(0.287)	(0.195)	(0.073)
interactionspair (>30)	0.134***	0.081***	0.385**	0.220***	0.081***
	(0.036)	(0.029)	(0.159)	(0.079)	(0.035)
Number of Observations	632,506	471,170	161,336	210,251	422,255

Notes:

(i) Failure: First time the drug of interest is prescribed;
(ii) Number of subjects: 34.030 (There are 27.937 physicians, however 6093 work non-exclusively which makes us consider their presence twice);
(iii) Std. Err. adjusted for 27.937 clusters in Id. physician;
(iv) Robust Standard errors in parentheses;
(v) *, **, and *** denote significance at 10%, 5%, and 1% respectively
(vi) Regression includes controls variables for: patient characteristics, healthcare setting and treatment features.

Table 5.7 - Estimates from the Survival Analysis (Cox Proportional Hazard Model) for Metformin + Dapagliflozin

	Sample: All	Sample: Only Public	Sample: Only Private	Sample: Only Job-Duality	Sample: Only Exclusivity
	Hazard Ratio	Hazard Ratio	Hazard Ratio	Hazard Ratio	Hazard Ratio
public, exclusive	(ref)	(ref)	-	-	(ref)
private, exclusive	1.353***	-	(ref)	-	1.276***
	(0.089)				(0.094)
public, jobduality	0.895***	0.904***	-	(ref)	-
	(0.033)	(0.033)			
private, jobduality	0.669***	-	0.534***	0.851*	-
	(0.047)		(0.047)	(0.071)	
physician_gp	(ref)	(ref)	(ref)	(ref)	(ref)
physician_end	1.085	1.062	0.795	1.205	0.900
	(0.100)	(0.134)	(0.128)	(0.154)	(0.130)
physician_im	1.025	0.996	0.815	1.234*	0.878
	(0.072)	(0.102)	(0.102)	(0.139)	(0.078)
physician_other	0.824***	0.640***	1.004	1.101	0.693***
	(0.058)	(0.069)	(0.097)	(0.130)	(0.059)
principal physician – ATP	1.059	1.066	1.071	0.930	1.142**
	(0.056)	(0.067)	(0.106)	(0.086)	(0.075)
other_patients (1)	(ref)	(ref)	(ref)	(ref)	(ref)
other_patients (1-10)	1.772***	1.855***	1.572***	0.999	1.743***
	(0.203)	(0.305)	(0.254)	(0.989)	(0.202)
other_patients (10-20)	3.773***	3.792***	3.554***	2.051	3.821***
	(0.463)	(0.642)	(0.676)	(2.009)	(0.491)
other_patients (20-30)	4.928***	5.230***	3.515***	2.791	5.063***
	(0.638)	(0.913)	(0.781)	(2.745)	(0.692)
other_patients (30-40)	5.759***	5.810***	5.502***	3.904	5.292***
	(0.767)	(1.031)	(1.354)	(3.845)	(0.757)
other_patients (40-50)	5.824***	5.913***	5.349***	3.588	5.797***
	(0.808)	(1.078)	(1.432)	(3.544)	(0.870)
other_patients (50-60)	6.265***	5.979***	8.307***	4.365	5.454***
	(0.902)	(1.117)	(2.445)	(4.316)	(0.879)
other_patients (>60)	7.120***	6.686***	9.297***	4.533	6.664***
	(1.014)	(1.247)	(2.463)	(4.488)	(1.055)
nconsults (1)	(ref)	(ref)	(ref)	(ref)	(ref)
nconsults (5-10)	1.682***	1.761***	1.626**	1.403	1.728***
	(0.160)	(0.187)	(0.368)	(0.369)	(0.178)
nconsults (10-30)	1.562***	1.596***	1.701***	1.414	1.568***
	(0.130)	(0.148)	(0.348)	(0.307)	(0.146)

nconsults (30-50)	1.855***	1.839***	2.277***	1.689**	1.847***
	(0.171)	(0.191)	(0.505)	(0.376)	(0.195)
nconsults (50-70)	1.995***	2.083***	2.100***	1.654**	2.107***
	(0.199)	(0.235)	(0.509)	(0.380)	(0.246)
nconsults (70-100)	1.965***	1.994***	2.290***	1.561*	2.123***
	(0.204)	(0.234)	(0.566)	(0.369)	(0.256)
nconsults (100-150)	1.752***	1.846***	1.797**	1.479	1.826***
	(0.187)	(0.221)	(0.474)	(0.352)	(0.230)
nconsults (150-200)	1.633***	1.678***	1.833**	1.398	1.680***
	(0.193)	(0.222)	(0.521)	(0.348)	(0.241)
nconsults (250-300)	1.228	1.292	1.254	1.077	1.236
	(0.212)	(0.261)	(0.441)	(0.317)	(0.302)
nconsults (>300)	1.452**	1.560**	1.226	1.282	1.386
	(0.228)	(0.291)	(0.411)	(0.353)	(0.322)
interactionspair (1)	(ref)	(ref)	(ref)	(ref)	(ref)
interactionspair (1-5)	0.807***	0.784***	0.884	0.942	0.736***
	(0.031)	(0.033)	(0.074)	(0.059)	(0.035)
interactionspair (5-10)	0.585***	0.770	0.501***	0.693	0.524***
	(0.096)	(0.166)	(0.119)	(0.236)	(0.096)
interactionspair (10-15)	0.406***	0.384***	0.452***	0.893	0.311***
	(0.060)	(0.070)	(0.115)	(0.269)	(0.053)
interactionspair (15-20)	0.373***	0.380***	0.319***	0.608	0.306***
	(0.057)	(0.065)	(0.103)	(0.237)	(0.052)
interactionspair (20-25)	0.394***	0.388***	0.311**	0.544	0.328***
	(0.068)	(0.073)	(0.142)	(0.207)	(0.064)
interactionspair (25-30)	0.398***	0.306***	0.692	0.520	0.340***
	(0.077)	(0.072)	(0.240)	(0.207)	(0.076)
interactionspair (>30)	0.415***	0.328***	0.575**	0.571**	0.331***
	(0.063)	(0.063)	(0.131)	(0.133)	(0.066)
Number of Observations	632,634	471,332	161,302	210,401	422,233

Notes:

(i) Failure: First time the drug of interest is prescribed;
(ii) Number of subjects: 34.030 (There are 27.937 physicians, however 6093 work non-exclusively which makes us consider their presence twice);
(iii) Std. Err. adjusted for 27.937 clusters in Id. physician;
(iv) Robust Standard errors in parentheses;
(v) *, **, and *** denote significance at 10%, 5%, and 1% respectively
(vi) Regression includes controls variables for: patient characteristics, healthcare setting and treatment features.

Table 5.8 – Estimates from the Survival Analysis (Cox Proportional Hazard Model) for Metformin + Linagliptin

	Sample: All	Sample: Only Public	Sample: Only Private	Sample: Only Job-Duality	Sample: Only Exclusivity
	Hazard Ratio	Hazard Ratio	Hazard Ratio	Hazard Ratio	Hazard Ratio
public, exclusive	(ref)	(ref)	-	-	(ref)
private, exclusive	1.117	-	(ref)	-	1.009
	(0.107)				(0.106)
public, jobduality	0.900**	0.919	-	(ref)	-
	(0.047)	(0.048)			
private, jobduality	0.406***	-	0.374***	0.534***	-
	(0.042)		(0.049)	(0.065)	
physician_gp	(ref)	(ref)	(ref)	(ref)	(ref)
physician_end	1.417**	1.226	1.461*	1.532**	1.290
	(0.203)	(0.234)	(0.300)	(0.310)	(0.276)
physician_im	1.185*	1.191	1.089	1.534***	0.969
	(0.115)	(0.155)	(0.185)	(0.232)	(0.122)
physician_other	0.840*	0.763*	1.050	1.069	0.733**
	(0.087)	(0.108)	(0.157)	(0.187)	(0.094)
principal physician – ATP	0.868*	0.852	0.926	0.982	0.801**
	(0.074)	(0.0842)	(0.156)	(0.132)	(0.088)
other_patients (1)	(ref)	(ref)	(ref)	(ref)	(ref)
other_patients (1-10)	2.841***	2.783***	3.151***	0.699	2.970***
	(0.559)	(0.698)	(1.006)	(0.711)	(0.598)
other_patients (10-20)	5.292***	5.091***	5.502***	1.302	5.521***
	(1.082)	(1.302)	(1.942)	(1.334)	(1.179)
other_patients (20-30)	9.275***	8.788***	9.952***	2.739	8.943***
	(1.929)	(2.276)	(3.769)	(2.801)	(1.947)
other_patients (30-40)	10.01***	8.825***	16.33***	3.385	8.789***
	(2.122)	(2.322)	(6.335)	(3.470)	(1.976)
other_patients (40-50)	11.61***	10.69***	14.20***	3.754	10.52***
	(2.515)	(2.860)	(6.040)	(3.857)	(2.436)
other_patients (50-60)	15.07***	13.50***	22.34***	4.544	14.34***
	(3.294)	(3.632)	(9.951)	(4.674)	(3.354)
other_patients (>60)	12.87***	10.25***	29.47***	4.465	10.93***
	(2.850)	(2.809)	(12.06)	(4.589)	(2.676)
nconsults (1)	(ref)	(ref)	(ref)	(ref)	(ref)
nconsults (5-10)	2.602***	2.897***	1.539	2.130**	2.722***
	(0.326)	(0.388)	(0.504)	(0.647)	(0.378)
nconsults (10-30)	2.775***	3.040***	1.941**	2.526***	2.795***
	(0.316)	(0.375)	(0.574)	(0.686)	(0.363)

nconsults (30-50)	3.051***	3.344***	2.232**	1.863**	3.814***
	(0.393)	(0.467)	(0.739)	(0.540)	(0.563)
nconsults (50-70)	3.372***	3.770***	2.268**	2.241***	4.096***
	(0.468)	(0.569)	(0.797)	(0.668)	(0.671)
nconsults (70-100)	3.550***	3.874***	2.548**	2.390***	4.240***
	(0.513)	(0.611)	(0.930)	(0.726)	(0.735)
nconsults (100-150)	2.770***	3.282***	1.415	1.904**	3.283***
	(0.425)	(0.544)	(0.564)	(0.598)	(0.612)
nconsults (150-200)	3.593***	4.382***	1.628	1.986**	5.049***
	(0.601)	(0.791)	(0.692)	(0.659)	(1.024)
nconsults (250-300)	3.303***	3.428***	2.122	2.153**	3.913***
	(0.781)	(0.944)	(1.050)	(0.825)	(1.364)
nconsults (>300)	3.250***	3.606***	1.494	2.184**	3.449***
	(0.759)	(1.004)	(0.744)	(0.826)	(1.260)
interactionspair (1)	(ref)	(ref)	(ref)	(ref)	(ref)
interactionspair (1-5)	0.736***	0.676***	1.092	0.701***	0.751***
	(0.038)	(0.038)	(0.141)	(0.061)	(0.049)
interactionspair (5-10)	0.452***	0.458**	0.573	0.606	0.408***
	(0.115)	(0.157)	(0.221)	(0.284)	(0.124)
interactionspair (10-15)	0.448***	0.392***	0.685	0.686	0.403***
	(0.097)	(0.105)	(0.265)	(0.286)	(0.102)
interactionspair (15-20)	0.319***	0.267***	0.578	0.152*	0.329***
	(0.079)	(0.079)	(0.268)	(0.156)	(0.088)
interactionspair (20-25)	0.268***	0.189***	0.844	0.186*	0.280***
	(0.082)	(0.066)	(0.418)	(0.190)	(0.089)
interactionspair (25-30)	0.157***	0.0915***	0.492	0	0.205***
	(0.067)	(0.054)	(0.312)	(0)	(0.089)
interactionspair (>30)	0.166***	0.0933***	0.371**	0.267***	0.0911***
	(0.047)	(0.039)	(0.151)	(0.098)	(0.043)
Number of Observations	632,402	471,125	161,277	210,170	422,232

Notes:

(i) Failure: First time the drug of interest is prescribed;
(ii) Number of subjects: 34.030 (There are 27.937 physicians, however 6093 work non-exclusively which makes us consider their presence twice);
(iii) Std. Err. adjusted for 27.937 clusters in Id. physician;
(iv) Robust Standard errors in parentheses;
(v) *, **, and *** denote significance at 10%, 5%, and 1% respectively
(vi) Regression includes controls variables for: patient characteristics, healthcare setting and treatment features.

5.4.3 Count Model

Results from the Negative Binomial Model are presented in Table 5.9. We present both the incidence rate ratios (IRR), which reports the incident rate of the variable in comparison with the reference group, as well as marginal effects (dy/dx), which give the change in percentage points (pp) in the dependent variable given by a one-unit change in the explanatory variable, *ceteris paribus*.

Our discussion is based on the incidence rate ratio interpretation which has a multiplicative effect in the y scale. This model allows us to study the factors influencing the pharmaceutical diffusion by considering the quantity of prescriptions containing the selected drugs. All ten hypoglycaemic agents were considered.

Between January 2015 and October 2019, a total of 1.517.320 e-prescriptions from 27.937 physicians were assigned to 128.155 patients. The willingness to diffuse recent hypoglycaemic agents can vary for many reasons. Our baseline approach considers the full sample. Physicians working exclusively in the public health setting present lower levels of diffusion in comparison with other work options.

A physician working exclusively in private sector has an incidence rate of 1,546 times the incidence of a physician working exclusively in the public sector, while if the physician works mainly in private sector but job-duality, the incidence rate decreases to 1,302 times. Physicians working mainly in the public sector but with job-duality present an incidence rate of 1.062 times the incidence rate of the reference group, though not statistically significant.

In order to present a proper comparison between groups we implement a similar strategy considered in the survival analysis. We divided our data into four samples: (a) public, (b) private, (c) exclusivity and (d) job-duality.

Outcomes on (a) show that practicing in public job-duality have an incidence rate of 1.108 times the incidence rate of physicians practicing exclusively in the public sector; (b) shows that practicing in private job-duality produces an incidence rate of 1.002 times the incidence rate of physicians practicing exclusively in the private sector; (c) presents the same physician in job-duality and shows that when the physician practices in the private the incidence rate is 1.397 times the incidence rate of when the physician works in the public sector; (d) shows that physicians working exclusively in the private sector present

an incidence rate of 1.296 times the incidence rate of physicians working exclusively in the public sector.

General Practitioners (GPs) are in higher number since they are usually the first physician seen by the patient. They are usually fast adopters however other specialties such as Endocrinologists and Internal Medicine physicians are seen as more as are active diffusers. Regarding the last characterization, they present an incidence rate of 1.996 and 1.137 the incidence rate of GPs, respectively. Other specialists present in our sample have the opposite influence with an incidence rate of 0.650 the incidence rate of GPs.

The patient's principal physician (Active-Treatment Provider – ATP) requires less time to adopt these drugs as well as present an active behaviour towards diffusing them, i.e, they present an incidence rate of 1.242 times the incidence rate of non-principal physicians.

The physician learning process requires feedback from patients. The more patients the physician interacts with, the higher the likelihood to diffuse recent hypoglycemic agents. The same happens if the physician increases the number of interactions with the same patient (consults between the pair).

The control variables used in each one of the previous models present consistent and constant results as well as are according to our expectations.

We also test for overdispersion with the NBM using the likelihood ratio test (parameter alpha) at the bottom of the regression analysis. When the overdispersion parameter is zero the Negative Binomial distribution is equivalent to a Poisson distribution. In cases where alpha is significantly different from zero, which is our case, it reinforces that the Poisson distribution is not the most appropriate. The overall results for the adoption and diffusion of new drugs are presented in the following table.

Table 5.9 - Exclusivity vs. Job Duality

	Adoption	Diffusion
Exclusivity	Private [a)] (+)	Private [c)] (+)
Job-Duality	Public [b)] (+)	Private [b)] (+)

Notes:

a) In comparison with Public Exclusive
b) In comparison with the same physician in the public sector
c) In comparison with Public Exclusive

Table 5.10 – Estimates from the Count Model (Negative Binomial Model)

	Sample: All		Sample: Only Public		Sample: Only Private		Sample: Only Job-Duality		Sample: Only Exclusivity	
	Coefficient	IRR	Coefficient	IRR	Coefficient	IRR	Coefficient	IRR	Coefficient	IRR
public, exclusive	(ref)	(ref)	(ref)	(ref)	-	-	-	-	(ref)	(ref)
private, exclusive	0.436***	1.546***	-	-	(ref)	(ref)	-	-	0.329***	1.390***
	(0.160)	(0.247)							(0.108)	(0.151)
public, jobduality	0.059	1.062	0.157***	1.170***	-	-	(ref)	(ref)	-	-
	(0.046)	(0.049)	(0.042)	(0.0493)						
private, jobduality	0.264***	1.302***	-	-	-0.180	0.835	0.183**	1.200**	-	-
	(0.080)	(0.105)			(0.119)	(0.099)	(0.079)	(0.096)		
physician_gp	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)
physician_end	0.691**	1.996**	0.217	1.242	0.476	1.610	0.367*	1.444*	1.210**	3.352**
	(0.298)	(0.596)	(0.144)	(0.179)	(0.336)	(0.541)	(0.188)	(0.272)	(0.543)	(1.820)
physician_im	0.129	1.137	0.095	1.100	-0.117	0.889	0.194	1.214	0.071	1.074
	(0.118)	(0.134)	(0.127)	(0.140)	(0.129)	(0.114)	(0.131)	(0.159)	(0.165)	(0.177)
physician_other	-0.432***	0.650***	-0.611***	0.543***	-0.318**	0.728**	-0.363**	0.696**	-0.443***	0.642***
	(0.108)	(0.070)	(0.151)	(0.082)	(0.125)	(0.091)	(0.149)	(0.104)	(0.146)	(0.094)
principal physician – ATP	0.217***	1.242***	0.213***	1.238***	0.0861	1.090	0.191***	1.211***	0.222***	1.249***
	(0.026)	(0.032)	(0.019)	(0.025)	(0.055)	(0.060)	(0.030)	(0.036)	(0.029)	(0.036)
other_patients (1)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)
other_patients (1-10)	0.640*	1.897*	0.200	1.221	0.934***	2.544***	-1.799***	0.165***	1.049***	2.854***
	(0.327)	(0.621)	(0.471)	(0.575)	(0.266)	(0.677)	(0.612)	(0.101)	(0.224)	(0.640)
other_patients (10-20)	1.829***	6.229***	1.476***	4.375***	1.729***	5.633***	-0.620	0.538	2.205***	9.066***
	(0.332)	(2.067)	(0.474)	(2.073)	(0.269)	(1.517)	(0.617)	(0.332)	(0.224)	(2.035)
other_patients (20-30)	2.577***	13.16***	2.143***	8.526***	2.618***	13.71***	0.306	1.357	2.897***	18.12***

	(0.336)	(4.426)	(0.476)	(4.056)	(0.290)	(3.971)	(0.627)	(0.851)	(0.227)	(4.117)
other_patients (30-40)	2.941***	18.94***	2.449***	11.58***	3.324***	27.77***	0.703	2.019	3.235***	25.41***
	(0.336)	(6.361)	(0.475)	(5.504)	(0.282)	(7.836)	(0.620)	(1.251)	(0.227)	(5.765)
other_patients (40-50)	3.214***	24.89***	2.689***	14.72***	3.729***	41.65***	1.031*	2.804*	3.445***	31.35***
	(0.339)	(8.433)	(0.477)	(7.015)	(0.306)	(12.75)	(0.625)	(1.753)	(0.231)	(7.232)
other_patients (50-60)	3.379***	29.33***	2.817***	16.73***	4.121***	61.62***	1.180*	3.253*	3.585***	36.06***
	(0.345)	(10.13)	(0.478)	(7.992)	(0.376)	(23.19)	(0.631)	(2.054)	(0.238)	(8.582)
other_patients (>60)	3.933***	51.08***	3.187***	24.22***	4.801***	121.6***	1.600**	4.951**	4.335***	76.31***
	(0.347)	(17.73)	(0.478)	(11.57)	(0.329)	(40.01)	(0.623)	(3.084)	(0.263)	(20.08)
interactionspair (1)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)
interactionspair (1-5)	0.083***	1.086***	0.059***	1.062***	0.205***	1.227***	0.054***	1.055***	0.099***	1.105***
	(0.014)	(0.015)	(0.014)	(0.015)	(0.028)	(0.034)	(0.018)	(0.019)	(0.019)	(0.021)
interactionspair (5-10)	0.239***	1.269***	0.366***	1.442***	0.235*	1.265*	0.332**	1.394**	0.216**	1.241**
	(0.089)	(0.112)	(0.116)	(0.167)	(0.128)	(0.162)	(0.167)	(0.232)	(0.096)	(0.119)
interactionspair (10-15)	0.274***	1.315***	0.224*	1.252*	0.485***	1.625***	0.453**	1.574**	0.249**	1.282**
	(0.104)	(0.137)	(0.133)	(0.166)	(0.138)	(0.224)	(0.185)	(0.291)	(0.115)	(0.147)
interactionspair (15-20)	0.490***	1.632***	0.550***	1.733***	0.364***	1.439***	0.337*	1.400*	0.501***	1.651***
	(0.095)	(0.154)	(0.105)	(0.183)	(0.138)	(0.199)	(0.179)	(0.251)	(0.099)	(0.163)
interactionspair (20-25)	0.404***	1.498***	0.438***	1.549***	0.481***	1.618***	0.434**	1.544**	0.404***	1.497***
	(0.086)	(0.129)	(0.095)	(0.147)	(0.160)	(0.259)	(0.189)	(0.292)	(0.093)	(0.139)
interactionspair (25-30)	0.484***	1.622***	0.594***	1.811***	0.282	1.326	0.357**	1.429**	0.527***	1.694***
	(0.091)	(0.148)	(0.094)	(0.169)	(0.196)	(0.260)	(0.172)	(0.245)	(0.102)	(0.173)
interactionspair (>30)	0.361***	1.435***	0.408***	1.504***	0.437***	1.548***	0.336***	1.399***	0.318***	1.374***
	(0.065)	(0.094)	(0.079)	(0.119)	(0.103)	(0.160)	(0.097)	(0.136)	(0.080)	(0.110)
constant	-1.488***	0.226***	-0.958*	0.384*	-1.387***	0.250***	0.735	2.085	-1.672***	0.188***
	(0.390)	(0.088)	(0.500)	(0.192)	(0.339)	(0.085)	(0.641)	(1.337)	(0.318)	(0.059)
lnalpha	0.865***	2.374***	0.709***	2.031***	1.179***	3.250***	0.716***	2.047***	0.936***	2.550***
	(0.032)	(0.076)	(0.025)	(0.050)	(0.059)	(0.195)	(0.042)	(0.086)	(0.035)	(0.089)

Number of Observations	727,231	727,231	544,234	544,234	182,997	182,997	246,778	246,778	480,453	480,453

Notes:
Robust Standard errors in parentheses;
*, **, and *** denote significance at 10%, 5%, and 1% respectively
Regression includes controls variables for: patient characteristics, healthcare setting, treatment features and year time dummies.

5.5 Robustness Checks

To test for the consistency of the results, we decided to consider two alternative approaches. The first, considered on the appendix, uses other econometric models - OLS and Logistic regression model [28] - to test the same hypothesis. The second, introduces sample restrictions on Count Models, such as the options mentioned next.

I. Changes in Job-Duality Measure

   a. Consider exclusively physicians in job-duality as well as physicians in exclusivity contracts.

This will allow us to understand the influence of each one of the healthcare sectors involved: public *vs.* private. Results from the Survival Model and Count Model are presented on Table XXX (Section 4 – Results; Subsection 5.4.2 and 5.4.3) [29].

II. Changes on Healthcare System Measures

   a. Consider exclusively Public and Private Samples.

By isolating the presence of a Job-Duality associated with each one of the healthcare sectors we aim to study its impact on prescription. Results from the Survival Model and Count Model are presented on Table XXX (Section 4 – Results; Subsection 5.4.2 and 5.4.3) [30].

   b. Divide the analysis between General Practitioners and Specialists.

GPs play an important role on diffusion. When we eliminate specialists, the results remain constant, however when we eliminate GP, physicians on public job-duality present a negative impact on diffusion in comparison with physicians on public exclusivity.

[28] It considers a binary dependent variable, that assumes the value 1 if the prescription contains innovative hypoglycemic agents and 0 otherwise. We consider zero as negative outcome (failure) and treats all other values as positive outcomes (successes). This is a more limited approach since it considers a dichotomous behaviour (prescribes vs. not prescribe) which eliminates prescription progression.

[29] Appendix 5.3 and appendix 5.4 presents the results using OLS and Logistic Model approach, respectively. These models provide us results that follow the same direction as the Survival and Count Model.

[30] Appendix 5.3 and appendix 5.4 presents the results using OLS and Logistic Model approach, respectively. These models provide us results that follow the same direction as the Survival and Count Model.

Results regarding the principal physician and physician interaction with patients remain positive and are consistent with previous outcomes.

Table 5.11 provides us the Estimates from the Count Model (Negative Binomial Model) for a sample of General Practitioners vs. Specialists [31].

Table 5.11 - Estimates from the Count Model (Negative Binomial Model) for a sample of General Practitioners vs. Specialists

	Sample: Only General Practitioners		Sample: Only Specialists	
	Coefficient	IRR	Coefficient	IRR
public, exclusive	(ref)	(ref)	(ref)	(ref)
private, exclusive	0.059	1.061	0.619***	1.856***
	(0.160)	(0.170)	(0.185)	(0.344)
public, jobduality	0.111**	1.117**	-0.0346	0.966
	(0.0489)	(0.054)	(0.103)	(0.099)
private, jobduality	0.0881	1.092	0.217*	1.242*
	(0.119)	(0.130)	(0.115)	(0.143)
principal physician – ATP	0.149**	1.161**	0.221***	1.247***
	(0.061)	(0.071)	(0.022)	(0.028)
other_patients (1)	(ref)	(ref)	(ref)	(ref)
other_patients (1-10)	1.585***	4.877***	0.609*	1.839*
	(0.475)	(2.318)	(0.315)	(0.580)
other_patients (10-20)	2.702***	14.91***	1.687***	5.404***
	(0.471)	(7.022)	(0.326)	(1.762)
other_patients (20-30)	3.400***	29.95***	2.377***	10.77***
	(0.473)	(14.18)	(0.339)	(3.648)
other_patients (30-40)	3.701***	40.48***	3.280***	26.58***
	(0.473)	(19.15)	(0.343)	(9.117)
other_patients (40-50)	3.970***	52.97***	3.536***	34.33***
	(0.474)	(25.12)	(0.375)	(12.86)
other_patients (50-60)	4.128***	62.06***	3.741***	42.14***
	(0.480)	(29.77)	(0.403)	(16.97)
other_patients (>60)	4.607***	100.2***	4.456***	86.16***
	(0.493)	(49.41)	(0.372)	(32.05)
ninteractionspair (1)	(ref)	(ref)	(ref)	(ref)
ninteractionspair (1-5)	0.0509***	1.052***	0.144***	1.155***
	(0.0166)	(0.0175)	(0.0259)	(0.0300)
ninteractionspair (5-10)	0.0508	1.052	0.381***	1.463***
	(0.143)	(0.150)	(0.110)	(0.161)

[31] Appendix 5.5 presents the results using OLS and Logistic Model approach, respectively. These models provide us results that follow the same direction as the Survival and Count Model.

ninteractionspair (10-15)	0.239*	1.270*	0.248	1.282
	(0.123)	(0.156)	(0.172)	(0.220)
ninteractionspair (15-20)	0.466***	1.593***	0.230	1.259
	(0.097)	(0.154)	(0.213)	(0.268)
ninteractionspair (20-25)	0.399***	1.490***	0.009	1.009
	(0.0873)	(0.130)	(0.296)	(0.298)
ninteractionspair (25-30)	0.479***	1.615***	-0.517	0.596
	(0.090)	(0.145)	(0.355)	(0.212)
ninteractionspair (>30)	0.306***	1.358***	0.573***	1.773***
	(0.066)	(0.090)	(0.217)	(0.384)
constant	-1.577***	0.207***	-1.837***	0.159***
	(0.500)	(0.103)	(0.374)	(0.059)
lnalpha	0.827***	2.286***	0.889***	2.432***
	(0.030)	(0.069)	(0.082)	(0.199)
Number of Observations	533,602	533,602	193,629	193,629

Notes:
Robust Standard errors in parentheses.
*, **, and *** denote significance at 10%, 5%, and 1% respectively
Regression includes controls variables for: patient characteristics, healthcare setting, treatment features and year time dummies.

c. Divide the analysis between Primary and Hospital Care

Looking only to primary care facilities, we have that, in comparison with physicians on public exclusivity, only physicians on public job-duality present a positive effect on diffusion. This happens because the private sector does not provide a direct differentiation between primary and hospital care.

Considering hospital care, we have that only physicians on public job-duality present a negative impact on diffusion in comparison with physicians on public exclusivity. Again, this can be related with the undifferentiation of care within the private sector.

Results regarding the principal physician and physician interaction with patients remain positive and are consistent with previous outcomes.

Table 5.12 provides us the Estimates from the Count Model (Negative Binomial Model) for a sample of Primary care vs. Hospital care [32].

[32] Appendix 5.6 presents the results using OLS and Logistic Model approach, respectively. These two models provide us results that follow the same direction as the Survival and Count Model.

Table 5.12 - Estimates from the Count Model (Negative Binomial Model) for a sample of Primary care vs. Hospital care.

	Sample: Only Hospital		Sample: Only Primary Care	
	Coefficient	IRR	Coefficient	IRR
public, exclusive	(ref)	(ref)	(ref)	(ref)
private, exclusive	0.419***	1.521***	-0.349	0.705
	(0.134)	(0.203)	(0.404)	(0.285)
public, jobduality	-0.082	0.921	0.161***	1.175***
	(0.096)	(0.089)	(0.048)	(0.056)
private, jobduality	0.196**	1.217**	-0.141	0.868
	(0.080)	(0.098)	(0.210)	(0.182)
principal physician – ATP	0.257***	1.293***	0.113**	1.119**
	(0.023)	(0.029)	(0.048)	(0.053)
other_patients (1)	(ref)	(ref)	(ref)	(ref)
other_patients (1-10)	0.615*	1.849*	1.426***	4.161***
	(0.331)	(0.613)	(0.513)	(2.134)
other_patients (10-20)	1.565***	4.782***	2.606***	13.55***
	(0.337)	(1.614)	(0.511)	(6.929)
other_patients (20-30)	2.356***	10.55***	3.234***	25.38***
	(0.351)	(3.701)	(0.511)	(12.96)
other_patients (30-40)	3.063***	21.38***	3.484***	32.58***
	(0.350)	(7.478)	(0.511)	(16.63)
other_patients (40-50)	3.345***	28.36***	3.740***	42.12***
	(0.360)	(10.22)	(0.512)	(21.56)
other_patients (50-60)	3.694***	40.22***	3.869***	47.88***
	(0.402)	(16.17)	(0.513)	(24.57)
other_patients (>60)	4.406***	81.90***	4.148***	63.29***
	(0.371)	(30.42)	(0.514)	(32.52)
interactionspair (1)	(ref)	(ref)	(ref)	(ref)
interactionspair (1-5)	0.158***	1.171***	0.0106	1.011
	(0.021)	(0.025)	(0.016)	(0.016)
interactionspair (5-10)	0.292***	1.339***	-0.174	0.841
	(0.097)	(0.130)	(0.206)	(0.173)
interactionspair (10-15)	0.264**	1.302**	0.189	1.208
	(0.125)	(0.163)	(0.149)	(0.180)
interactionspair (15-20)	0.314**	1.369**	0.432***	1.541***
	(0.133)	(0.182)	(0.107)	(0.165)
interactionspair (20-25)	0.304*	1.355*	0.352***	1.421***
	(0.155)	(0.210)	(0.096)	(0.137)
interactionspair (25-30)	0.144	1.155	0.494***	1.639***
	(0.205)	(0.236)	(0.0929)	(0.152)
interactionspair (>30)	0.415***	1.515***	0.316***	1.371***
	(0.106)	(0.161)	(0.079)	(0.108)

constant	-1.683***	0.186***	-1.703***	0.182***
	(0.405)	(0.075)	(0.536)	(0.0978)
lnalpha	1.005***		0.721***	
	(0.057)		(0.027)	
Number of Observations	308,344	308,344	418,887	418,887

Notes:
Robust Standard errors in parentheses.
*, **, and *** denote significance at 10%, 5%, and 1% respectively
Regression includes controls variables for: patient characteristics, healthcare setting, treatment features and year time dummies.

5.6 Discussion

Doctors respond differently to incentives. Differences in physician outcomes blend differences on each sector's incentives and differences on the physicians' utility function. Exclusivity isolates the between-doctor variation on the exercise of their functions, which considers that differences on physician outcome are caused by differences on each sector's incentives as well as differences on the physicians' utility function.

Portugal allows physicians to practice in more than one health sector [33]. Observing physicians working in both public and private sectors, as well as their prescription behaviour in each sector allows us to separate within-doctor variation in prescription outcomes, associated with differences in incentives between sectors.

This study contributes to observe the impact of different working locations as well as labour regimen as drivers of adoption and diffusion of recent hypoglycaemic agents, in the context of the Portuguese NHS. In particular, the study reports the differences on the adoption and diffusion of recent hypoglycaemic agents produced by physicians working in an exclusivity regimen (public or private health sector) as well as in job-duality (public and private health sector), while controlling for patient characteristics, healthcare sector aspects and treatment features.

This study adds the literature by focusing its attention on physicians working in a single establishment as well as on physicians practicing in more than one workplace. It also focuses on electronic prescription data which are an output of the physician-patient relationship and a direct way to measure health supply, especially on chronic conditions (Abulhaj et al., 2013; Alowi and Kani, 2018; Gönül et al., 2001; Socha, 2010). This is a useful tool to understand how pharmaceuticals reach patients, constituting and appropriate setting to study the effect of job-duality on prescription patterns.

We followed a survival analysis approach that considered time to first prescription (adoption) as the dependent variable. A count model – Negative Binomial using considers quantity (diffusion) as the dependent variable was also considered. A set of control variables for patient, healthcare system and treatment characteristics were used as explanatory variables. Our main variable of interest is the physician location and labour regime: samples: (a) public exclusive, (b) private exclusive, (c) public job-duality and (d)

[33] Section 2 – subsection 2.4 – Physician Workplace and Work Regimen

private job-duality. Physicians who choose to serve exclusively the public healthcare sector are the most frequent group, reason to be considered as our reference group.

The differences on the impact of the physician location across adoption and diffusion of recent drugs are clear.

Adoption, for the all sample, is specially promoted by the private sector when in exclusivity regimens. Job-duality schemes usually require more time to prescribe, in comparison with public exclusive regimes.

When isolating exclusivity schemes, we have that the private sector takes less time to prescribe, thus increasing the pace of adoption. By considering a sample of job-duality, we see thar the public sector is responsible to induce adoption.

Diffusion is promoted by all the other work regimes – private exclusive, public job-duality, private job-duality – in comparison with public exclusivity.

When isolating exclusivity or job-duality regimes, we have a positive effect of private sector over the public sector, i.e., physicians located in this sector are usually associated to more prescriptions containing the drugs of interest.

The literature presents some results regarding prescription differences across health sectors. The exclusivity regimens are the most studied due to its frequency. By considering only physicians associated to an exclusivity contract, our results go in the same direction as previous evidence, i.e., physicians working exclusively in the private sector tend to prescribe more recent drugs (higher levels of diffusion), than those who work in public workplaces. This perspective is showed by Biglaiser and Ma (2007) and Lublóy (2014).

Liu et al. (2011) achieves a different outcome which assumes that in comparison to private providers, physicians who are practicing in public institutions are more likely to prescribe new drugs to their patients.

Job-duality schemes suggest that recent drugs are adopted at a faster speed, in comparison with physician in exclusivity. By isolating the first alternative, we get that the same physician takes less time to adopt a drug in the private health sector. The Public health sector promotes adoption in exclusivity regimes.

Diffusion of the selected drugs is also faster when physicians are dual practitioners. When isolating job-duality, we have different results from adoption by having that the same

physician prescribes more in the public health sector. Private health sector, on the contrary, promotes diffusion.

García Lirola et al. (2000) found that doctors with more than one workplace adopted new drugs earlier than others not directly specifying the workplace. More recently, Lin et al. (2011) believed that the type of medical centre, public or private, affects prescription behaviour due to different degrees of budget control, however the authors assume that the number of current workplaces is irrelevant.

Another opposing view arises with Zhang et al. (2019) that showed that physician demographic and professional characteristics, such as personal and medical training characteristics, risk preference and personality, physician practice style as well as social interactions and practice characteristics, are able to influence prescription as well as are strong predictors of adoption patterns. Still affiliation with public hospitals does not appear to affect the rate of adoption of new drugs.

Brekke and Sogard (2007) assume, on the demand side, that public and private care are (horizontally) differentiated products. The authors developed a theoretical model to argue that allowing physician dual practice will induce physicians to provide less supply or attention in the public sector, which in turn leads to lower overall health provision. They also suggest that allowing dual practice in a mixed health care market may be socially desirable. This view is complemented by Biglaiser and Ma (2007), who develop another model that suggests allowing dual practice always enhances aggregate patients' welfare, even though dual-practice physicians may refer patients to their private practices.

Most health economists agree that this dual practice has both positive and negative side-effects on the delivery of health services. They argue that, on the one hand, allowing dual practice can serve to reduce waiting times for treatment and lead to improvements in access to health services. But, on the other hand, dual providers may have incentives to skimp on work hours or divert patients to private clinics where they have some financial interest, compromising the efficiency and quality of public health provision (González and Macho-Stadler, 2013).

The public sector can introduce treatment rationing. This, associated to dual-practitioners, may introduce the problem of "cream-skimming", where physicians end up referencing their patients or treating the mildest cases from the waiting list in their private practice, attracting patients with higher ability to pay, leaving public hospitals with more complex

patients (Barros and Olivella, 2005; Biglaiser and Ma, 2007; Cheng et al., 2018). Brekke and Sogard (2007) complement this perspective by assuming that physician dual practice 'crowds out' public provision, and results in lower overall health care provision.

We've also decided to introduce the random assignment of patients to physicians. This means that physicians consult different patients, with clinical conditions ranging from the mildest to the most severe.

On the private sector, patients demand for healthcare according to their needs, without the existence of gatekeeping as well as they choose the physician to interact with. Thus, the provision of care tends to keep up with the demand.

Physicians present different motives to engage in dual practice. Some may think that they are driven by self-interest and financial reasons, compromising their vow towards the patient with the pursuit of profit-maximization. Although physicians and their preferences usually go towards the private sector due to higher flexibility and financial reasons that maximize their utility function, this perspective must not be generalized since (i) many physicians remain in the public sector, due to the oopportunity to keep in touch with research centres and new scientific knowledge, other specialties and a multitude of procedures that arise from the multi-dimensional approach of a public hospital and (ii) among those who are engaged in dual practice, many spend comparatively little time in their private practice (García-Prado and González, 2011; Socha, 2010).

Still, due to better income raising opportunities, some dual-practitioners are suspected to concentrate their attention and work effort on the private practice at the expense of the public one (Socha, 2010).

Other factors have been identified such as lack of career development opportunities in the public sector (early stages of their medical careers might decide to undertake some work in the private sector to acquire new skills in preparation and anticipation of a move into full-time private practice in the future), poor infrastructure in public facilities, and greater autonomy in the private sector (Cheng et al., 2018).

Features related with the physicians play an influential role on adoption and diffusion of recent hypoglycemic agents. Warrier et al. (2010) start by considering that there was no difference in innovative drugs' usage between primary care *vs.* specialty physicians. Jones et al. (2001) take a new perspective on the subject and assumes that GPs generally introduce more innovative pharmaceuticals than Specialists, that may have different

inherent attitudes towards new medicines and their costs, as they may have less alternative treatment options

More recently, Nieuwenhuis (2014) also affirms that GPs prescribe a considerable number of total prescriptions to a wide variety of patients, as opposed to medical specialists that normally treat an isolated population of patients. This is a fact, in the sense that GPs are mainly located in primary healthcare facilities which are the first resource that the patient should use in case of need. GPs also work as a gatekeeper which increases the variety of the population that they attend. Also Lublóy (2014) assumes that, physicians are more likely to "*prescribe new drugs in clinical and therapeutic areas where they feel familiar or have special interests*". A literature systematic review provided by the previous author considers that Specialists are seen as innovators and GPs as followers, since specialisation associated to the therapeutic areas where the drugs are introduced positively influences adoption and diffusion.

Our results consider that Specialists, such as Endocrinologists and Internal Medicine physicians are expected to require less time to prescribe the drugs of interest as well as are associated to a higher number of prescriptions containing new drugs in comparison with General Practitioners, i.e, they play an active role on drug diffusion which confirms the innovator perspective. This is due to the extensive presence of this condition in their areas of specialization and acting as well as the higher number of visits from pharmaceutical sales representatives.

Other specialties are also able to prescribe recent drugs, however their interaction with diabetic patients is not common (they prescribe by convenience). For this reason, they may not be extremely aware of recent hypoglycaemic agents introduced in the market for this particular condition, which is represented by a negative sign in comparison with GPs.

The physician responsible for the active treatment as well as their maintenance is considered as the patient's principal physician (Active-Treatment Provider – ATP). The agency relationship built from physician-patient repeated interactions is important since the physician becomes more aware of the context of the patients' health problems, and has more information about the patients' medical history, social circumstances, values and preferences (Culyer and Newhouse, 2000; Saxell, 2014).

Saxell (2014) considers that each patient reacts differently to the suggested drug treatment, and physicians may learn the individual match quality both from their own

experiences and from the treatment choices of the patient's previous doctors (number of signals/feedback). The author also considers that repeated consultations with the same physician are beneficial reducing information asymmetry (Culyer and Newhouse, 2000; Saxell, 2014). Physician becomes more familiar with the patient's disease and their knowledge on the distribution of health effects become more precise. The knowledge and perceptions towards this interaction translate the quality of the match and the ability of physicians to learn from it and adjust their way of making further decisions.

However, the interaction with only one patient limits the information provided to the physician, i.e., the patient needs to me medicated with one of the drugs of interest as well as the information is provided from one solo perspective. For this reason, the learning process may take long. On the contrary, since the principal physician is responsible for treatment maintenance and adjustment, he presents an active behaviour towards diffusing them (hazard ratio below 1 and incidence rate ratio above 1 (1.242)).

The interaction between patients and physicians is important since allows patients to receive medical advice and treatment, while physicians learn from patients' feedback. The higher the number of interactions between the physician and multiple patients the more feedback he gets as well as more diverse. The circle of contacts becomes larger, so they tend to receive more information and a constant update on knowledge level. Having the aspects of this relationship into account, it makes sense to assume that our results show that physicians are more likely to prescribe innovative agents to patients that they see more often, suggesting that physicians are more open to innovation with patients that they know better.

The higher the number of consults the physician gives, the higher the level of interaction with other patients. This increases physician's knowledge about a specific product, reduces uncertainty about new therapeutic agents and enhances the opportunity of introducing new therapeutics (Coscelli and Shum, 2004; Crawford and Shum, 2005). The process of learning through self-experience or the influence of peer- group effects/pharmaceutical sales representatives is also important, however it is not covered within the scope of our study (Coscelli and Shum, 2004; Crawford and Shum, 2005).

This study represents an added-value to the literature on physician workplace as well as it is able to provide further input to decision-makers on how to consider the benefits and disadvantages of the exclusivity hypothesis.

5.7 Concluding Remarks

The aim of this study is to analyse to what extent the adoption and diffusion of recent hypoglycaemic agents varies with physicians working in a single establishment (public *vs.* private sector) and those working in both public and private entities. We also analyze the importance of interaction with patients in the adoption of innovation.

Having into account a large longitudinal matched physician-prescription-patient dataset for all Portuguese e-prescriptions for the period between January 2015 and October 2019, we identified the time required to prescribe for the first time the drugs of interest as well as we count prescriptions containing recent hypoglycaemic agents according to physician's job situation, especially when located in both public and private sector.

Approximately 22% of physicians in our data work in job-duality schemes, with their primary job location being mainly public, and they are responsible for a third of the available prescriptions.

Our results suggest that there are differences across health sectors and work regimes.

Adoption, for the all sample, is specially promoted by the private sector when in exclusivity regimens. Job-duality schemes usually require more time to prescribe, in comparison with public exclusive regimes.

When isolating exclusivity schemes, we have that the private sector is expected to takes less time to prescribe, thus increasing the pace of adoption. By considering a sample of job-duality, we see thar the public sector is responsible to induce adoption.

Diffusion is promoted by all the other work regimes – private exclusive, public job-duality, private job-duality – in comparison with public exclusivity.

When isolating exclusivity or job-duality regimes, we have a positive effect of private sector over the public sector, i.e., physicians located in this sector are usually associated to more prescriptions containing the drugs of interest.

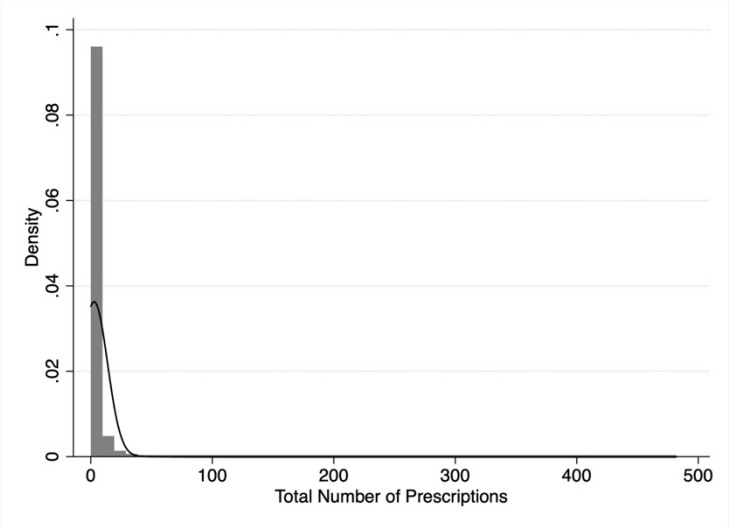
Their job location will generate variation in their medical practice. Although they aim to maximize patient's health condition, they are subject to different motivations provided by the different health sectors, which may affect physicians' labour supply, volume of health care production as well as quality of health care services as they can work in the private or public sectors.

With this study we observe physicians working in both public and private sectors, as well as their prescription behaviour in each sector. This way, we separate within-doctor

variation in prescription outcomes, associated with differences in incentives between sectors, which allowed us to assume that in non-exclusivity situations, the presence of the physician in the private sector makes them prescribe more of these new pharmaceuticals.

5.8 Appendix

Appendix 5.1 – Histogram on the Dependent Variable: Number of Prescriptions



Appendix 5.2 – Statistics on the Dependent Variable: Number of Prescriptions

	N	Mean	Std. Dev.	Variance	Minimum	Maximum
Number of Prescriptions	1,363,778	2.714	10.981	120.588	0	482

Appendix 5.3 - Robustness Check I and IIa: Determinants of diffusion considering public vs. private and exclusivity vs. job-duality – OLS Model approach

	Sample: All	Sample: Only Public	Sample: Only Private	Sample: Only Job-Duality	Sample: Only Exclusivity
	Coefficient	Coefficient	Coefficient	Coefficient	Coefficient
public, exclusive	(ref)	(ref)	-	-	(ref)
private, exclusive	2.323***	-	(ref)	-	2.148***
	(0.049)				(0.093)
public, jobduality	-0.126***	0.411***	-	(ref)	-
	(0.029)	(0.016)			
private, jobduality	1.339***	-	-1.968***	1.278***	-
	(0.053)		(0.092)	(0.079)	
physician_gp	(ref)	(ref)	(ref)	(ref)	(ref)
physician_end	7.820***	1.946***	10.67***	4.608***	14.15***
	(0.075)	(0.585)	(0.459)	(0.176)	(0.639)
physician_im	1.355***	0.569***	0.530***	1.335***	1.344***
	(0.054)	(0.219)	(0.068)	(0.079)	(0.071)
physician_other	0.380***	0.013	0.021	0.523***	0.308***
	(0.049)	(0.194)	(0.042)	(0.059)	(0.041)
principal physician – ATP	0.856***	0.478***	1.315***	0.916***	0.816***
	(0.033)	(0.056)	(0.139)	(0.061)	(0.054)
other_patients (1)	(ref)	(ref)	(ref)	(ref)	(ref)
other_patients (1-10)	0.638***	0.0512	0.780***	-0.481**	0.409***
	(0.097)	(0.085)	(0.212)	(0.242)	(0.028)
other_patients (10-20)	1.466***	0.914***	1.093***	0.186	1.094***
	(0.100)	(0.087)	(0.226)	(0.243)	(0.031)
other_patients (20-30)	2.433***	1.788***	2.081***	1.245***	1.916***
	(0.103)	(0.087)	(0.243)	(0.244)	(0.0340
other_patients (30-40)	3.139***	2.374***	3.245***	1.986***	2.555***
	(0.105)	(0.088)	(0.267)	(0.245)	(0.038)
other_patients (40-50)	3.821***	2.943***	4.654***	2.938***	2.950***
	(0.107)	(0.089)	(0.273)	(0.247)	(0.046)
other_patients (50-60)	4.462***	3.436***	6.397***	3.876***	3.277***
	(0.111)	(0.090)	(0.315)	(0.262)	(0.050)
other_patients (>60)	7.379***	4.785***	12.75***	5.735***	7.844***
	(0.107)	(0.089)	(0.263)	(0.252)	(0.118)
ninteractionspair (1)	(ref)	(ref)	(ref)	(ref)	(ref)
ninteractionspair (1-5)	0.201***	0.185***	0.741***	0.139***	0.247***
	(0.029)	(0.017)	(0.117)	(0.044)	(0.029)
ninteractionspair (5-10)	0.045	0.569***	0.313	-0.267***	0.114**
	(0.087)	(0.068)	(0.216)	(0.076)	(0.044)
ninteractionspair (10-15)	0.009	0.517***	0.263	0.137*	0.013
	(0.076)	(0.050)	(0.221)	(0.081)	(0.054)

ninteractionspair (15-20)	0.279***	0.817***	0.211	-0.098	0.359***
	(0.074)	(0.047)	(0.235)	(0.086)	(0.056)
ninteractionspair (20-25)	0.202***	0.670***	0.467*	0.047	0.315***
	(0.077)	(0.047)	(0.251)	(0.092)	(0.058)
ninteractionspair (25-30)	0.386***	1.086***	0.294	0.181*	0.534***
	(0.082)	(0.051)	(0.259)	(0.110)	(0.065)
ninteractionspair (>30)	0.735***	1.107***	1.295***	0.635***	0.802***
	(0.059)	(0.039)	(0.181)	(0.099)	(0.101)
constant	2.689***	3.658***	4.613***	4.107***	3.031**
	(0.300)	(0.192)	(1.044)	(0.700)	(1.284)
R-squared	0.131	0.210	0.145	0.191	0.119
Number of Observations	727,231	544,234	182,997	246,778	480,453

Notes:
Robust Standard errors in parentheses;
*, **, and *** denote significance at 10%, 5%, and 1% respectively
Regression includes controls variables for: patient characteristics, healthcare setting, treatment features and year time dummies.

Appendix 5.4 - Robustness Check I and IIa: Determinants of diffusion considering public vs. private and exclusivity vs. job-duality – Logistic Model approach

	Sample: All		Sample: Only Public		Sample: Only Private		Sample: Only Job-Duality		Sample: Only Exclusivity	
	Coefficient	Marginal Effects	Coefficient	Marginal Effects	Coefficient	Marginal Effects	Coefficient	Marginal Effects	Coefficient	Marginal Effects
public, exclusive	(ref)	(ref)	(ref)	(ref)	-	-	-	-	(ref)	(ref)
private, exclusive	0.019	0.001	-	-	(ref)	(ref)	-	-	-0.0002	-8.75e-06
	(0.026)	(0.001)							(0.029)	(0.001)
public, jobduality	0.102***	0.004***	0.145***	0.006***	-	-	(ref)	(ref)	-	-
	(0.015)	(0.001)	(0.015)	(0.001)						
private, jobduality	0.209***	0.009***	-	-	0.105***	0.004***	0.125***	0.005***	-	-
	(0.025)	(0.001)			(0.027)	(0.001)	(0.030)	(0.001)		
physician_gp	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)
physician_end	0.179***	0.007***	-0.275**	-0.011***	0.242***	0.008***	0.148***	0.006***	0.257***	0.010***
	(0.031)	(0.001)	(0.113)	(0.004)	(0.046)	(0.002)	(0.045)	(0.002)	(0.047)	(0.002)
physician_im	0.184***	0.008***	-0.143	-0.006	0.122***	0.004***	0.315***	0.015***	0.101***	0.004***
	(0.027)	(0.001)	(0.096)	(0.004)	(0.039)	(0.001)	(0.039)	(0.002)	(0.036)	(0.001)
physician_other	0.185***	0.008***	-0.317***	-0.012***	0.433***	0.016***	0.330***	0.015***	0.123***	0.005***
	(0.027)	(0.001)	(0.105)	(0.004)	(0.035)	(0.001)	(0.044)	(0.002)	(0.036)	(0.001)
principal physician - ATP	0.220***	0.009***	0.235***	0.009***	0.140***	0.005***	0.167***	0.008***	0.259***	0.010***
	(0.017)	(0.01)	(0.035)	(0.002)	(0.033)	(0.001)	(0.027)	(0.001)	(0.023)	(0.01)
other_patients (1)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)
other_patients (1-10)	0.029	0.001	-0.175**	-0.007**	0.215***	0.006***	-1.213***	-0.056***	0.135**	0.0043**
	(0.055)	(0.002)	(0.084)	(0.003)	(0.073)	(0.002)	(0.178)	(0.011)	(0.058)	(0.002)
other_patients (10-20)	0.231***	0.008***	0.029	0.001	0.352***	0.009***	-0.865***	-0.044***	0.291***	0.009***
	(0.056)	(0.002)	(0.085)	(0.003)	(0.077)	(0.002)	(0.177)	(0.011)	(0.060)	(0.002)

other_patients (20-30)	0.317***	0.012***	0.098	0.004	0.461***	0.014***	-0.680***	-0.037***	0.343***	0.011***
	(0.057)	(0.002)	(0.085)	(0.003)	(0.082)	(0.002)	(0.178)	(0.011)	(0.061)	(0.002)
other_patients (30-40)	0.393***	0.015***	0.088	0.004	0.986***	0.035***	-0.505***	-0.028**	0.355***	0.012***
	(0.058)	(0.002)	(0.086)	(0.003)	(0.086)	(0.003)	(0.179)	(0.011)	(0.063)	(0.002)
other_patients (40-50)	0.366***	0.014***	0.085	0.004	0.804***	0.027***	-0.605***	-0.033***	0.378***	0.013***
	(0.059)	(0.002)	(0.086)	(0.004)	(0.088)	(0.003)	(0.179)	(0.011)	(0.064)	(0.002)
other_patients (50-60)	0.347***	0.013***	0.037	0.002	0.976***	0.034***	-0.549***	-0.031***	0.272***	0.009***
	(0.061)	(0.002)	(0.088)	(0.004)	(0.097)	(0.004)	(0.181)	(0.011)	(0.068)	(0.002)
other_patients (>60)	0.468***	0.018***	0.149*	0.006*	0.965***	0.034***	-0.535***	-0.029***	0.529***	0.019***
	(0.058)	(0.002)	(0.087)	(0.004)	(0.084)	(0.003)	(0.179)	(0.011)	(0.064)	(0.002)
ninteractionspair (1)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)
ninteractionspair (1-5)	0.081***	0.004***	0.103***	0.005***	0.017	0.001	0.122***	0.006***	0.053***	0.002***
	(0.015)	(0.001)	(0.016)	(0.001)	(0.033)	(0.001)	(0.024)	(0.001)	(0.019)	(0.001)
ninteractionspair (5-10)	-0.331***	-0.013***	-0.225***	-0.009***	-0.316***	-0.011***	-0.140	-0.006	-0.407***	-0.015***
	(0.052)	(0.002)	(0.076)	(0.003)	(0.075)	(0.003)	(0.101)	(0.004)	(0.060)	(0.002)
ninteractionspair (10-15)	-0.377***	-0.014***	-0.468***	-0.017***	-0.162**	-0.006**	-0.0277	-0.001	-0.495***	-0.017***
	(0.043)	(0.002)	(0.054)	(0.002)	(0.072)	(0.003)	(0.093)	(0.004)	(0.049)	(0.002)
ninteractionspair (15-20)	-0.568***	-0.020***	-0.549***	-0.019***	-0.614***	-0.019***	-0.507***	-0.019***	-0.639***	-0.021***
	(0.041)	(0.001)	(0.048)	(0.002)	(0.086)	(0.003)	(0.099)	(0.003)	(0.047)	(0.001)
ninteractionspair (20-25)	-0.497***	-0.018***	-0.553***	-0.019***	-0.266***	-0.009***	-0.323***	-0.013***	-0.591***	-0.020***
	(0.041)	(0.001)	(0.047)	(0.002)	(0.089)	(0.003)	(0.084)	(0.003)	(0.049)	(0.002)
ninteractionspair (25-30)	-0.464***	-0.017***	-0.470***	-0.017***	-0.357***	-0.013***	-0.431***	-0.017***	-0.513***	-0.018***
	(0.043)	(0.001)	(0.049)	(0.002)	(0.091)	(0.003)	(0.082)	(0.003)	(0.052)	(0.0012
ninteractionspair (>30)	-0.689***	-0.023***	-0.710***	-0.024***	-0.568***	-0.019***	-0.549***	-0.021***	-0.807***	-0.026***
	(0.032)	(0.001)	(0.039)	(0.001)	(0.057)	(0.002)	(0.049)	(0.002)	(0.0423)	(0.001)
constant	-7.027***		-6.670***		-6.543***		-5.509***		-7.657***	
	(0.196)		(0.250)		(0.333)		(0.294)		(0.331)	

Number of Observations	727,231	727,231	544,234	544,234	182,946	182,946	246,731	246,731	480,453	480,453

Notes:
Robust Standard errors in parentheses;
*, **, and *** denote significance at 10%, 5%, and 1% respectively
Regression includes controls variables for: patient characteristics, healthcare setting, treatment features and year time dummies.

Appendix 5.5 - Robustness Check IIb: Determinants of diffusion considering General Practitioner vs. Specialist – OLS and Logistic Model approach

	Sample: GP (OLS)	Sample: GP (Logistic Model)		Sample: Specialists (OLS)	Sample: Specialists (Logistic Model)	
	Coefficient	Coefficient	Marginal Effects	Coefficient	Coefficient	Marginal Effects
public, exclusive	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)
private, exclusive	0.202**	-0.360***	-0.012***	2.986***	0.193***	0.008***
	(0.079)	(0.069)	(0.002)	(0.133)	(0.035)	(0.002)
public, jobduality	0.280***	0.110***	0.004***	-1.121***	0.126***	0.005***
	(0.020)	(0.017)	(0.001)	(0.069)	(0.030)	(0.001)
private, jobduality	0.224***	-0.152**	-0.006**	0.766***	0.379***	0.017***
	(0.079)	(0.070)	(0.003)	(0.096)	(0.034)	(0.002)
principal physician - ATP	0.571***	0.315***	0.012***	1.391***	0.019	0.0008
	(0.023)	(0.021)	(0.001)	(0.137)	(0.032)	(0.001)
other_patients (1)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)
other_patients (1-10)	0.452***	0.271	0.009*	1.011***	-0.073	-0.003
	(0.175)	(0.172)	(0.005)	(0.069)	(0.060)	(0.002)
other_patients (10-20)	1.547***	0.249	0.008	1.391***	0.228***	0.009***
	(0.174)	(0.172)	(0.005)	(0.084)	(0.064)	(0.003)
other_patients (20-30)	2.482***	0.332*	0.011**	1.729***	0.243***	0.009***
	(0.175)	(0.172)	(0.005)	(0.084)	(0.069)	(0.003)
other_patients (30-40)	3.027***	0.334*	0.011**	3.533***	0.793***	0.039***
	(0.175)	(0.172)	(0.005)	(0.095)	(0.073)	(0.003)
other_patients (40-50)	3.751***	0.331*	0.011**	4.109***	0.664***	0.031***
	(0.175)	(0.172)	(0.005)	(0.107)	(0.077)	(0.004)
other_patients (50-60)	4.466***	0.356**	0.012**	4.584***	0.408***	0.018***
	(0.176)	(0.173)	(0.005)	(0.146)	(0.085)	(0.004)
other_patients (>60)	5.909***	0.465***	0.017***	12.480***	0.571***	0.026***
	(0.176)	(0.172)	(0.005)	(0.218)	(0.071)	(0.003)
ninteractionspair (1)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)
ninteractionspair (1-5)	0.160***	0.096***	0.004***	0.232***	0.012	0.002
	(0.021)	(0.018)	(0.001)	(0.071)	(0.026)	(0.001)
ninteractionspair (5-10)	0.594***	-0.732***	-0.024***	-0.549***	-0.173***	-0.008***
	(0.087)	(0.101)	(0.003)	(0.096)	(0.064)	(0.003)
ninteractionspair (10-15)	0.535***	-0.415***	-0.015***	-1.243***	-0.356***	-0.015***
	(0.057)	(0.054)	(0.002)	(0.132)	(0.069)	(0.003)
ninteractionspair (15-20)	0.663***	-0.543***	-0.019***	-1.645***	-0.950***	-0.033***
	(0.051)	(0.047)	(0.001)	(0.148)	(0.101)	(0.003)
ninteractionspair (20-25)	0.507***	-0.501***	-0.017***	-1.427***	-1.011***	-0.035***

	(0.051)	(0.045)	(0.001)	(0.153)	(0.144)	(0.004)
ninteractionspair (25-30)	0.686***	-0.478***	-0.017***	-1.943***	-1.230***	-0.039***
	(0.053)	(0.046)	(0.002)	(0.165)	(0.190)	(0.004)
ninteractionspair (>30)	0.915***	-0.694***	-0.023***	0.090	-0.845***	-0.031***
	(0.039)	(0.036)	(0.001)	(0.337)	(0.078)	(0.002)
constant	3.825***	-7.196***		6.784***	-7.161***	
	(0.360)	(0.491)		(1.116)	(0.237)	
R-squared	0.171			0.133		
Number of Observations	533,602	533,487	533,487	193,629	193,629	193,629

Notes:
Robust Standard errors in parentheses;
*, **, and *** denote significance at 10%, 5%, and 1% respectively
Regression includes controls variables for: patient characteristics, healthcare setting, treatment features and year time dummies.

Appendix 5.6 - Robustness Check IIc: Determinants of diffusion considering Primary care vs. Hospital care – OLS and Logistic Model approach

	Sample: Primary Care (OLS)	Sample: Primary Care (Logistic Model)		Sample: Hospital (OLS)	Sample: Hospital (Logistic Model)	
	Coefficient	Coefficient	Marginal Effects	Coefficient	Coefficient	Marginal Effects
public, exclusive	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)
private, exclusive	0.130*	-0.509*	-0.016**	2.199***	0.102***	0.004***
	(0.079)	(0.291)	(0.008)	(0.086)	(0.028)	(0.001)
public, jobduality	0.430***	0.119***	0.005***	-1.080***	0.114***	0.005***
	(0.019)	(0.017)	(0.001)	(0.063)	(0.027)	(0.001)
private, jobduality	-0.531***	0.361	0.016	0.815***	0.228***	0.009***
	(0.087)	(0.291)	(0.014)	(0.057)	(0.028)	(0.001)
principal physician - ATP	0.597***	0.325***	0.013***	0.996***	0.106***	0.004***
	(0.024)	(0.024)	(0.001)	(0.091)	(0.026)	(0.001)
other_patients (1)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)
other_patients (1-10)	0.307*	0.172	0.006	0.781***	0.007	0.0002
	(0.170)	(0.322)	(0.011)	(0.046)	(0.056)	(0.002)
other_patients (10-20)	1.522***	0.155	0.006	1.120***	0.218***	0.008***
	(0.170)	(0.320)	(0.011)	(0.054)	(0.058)	(0.002)
other_patients (20-30)	2.346***	0.248	0.009	1.869***	0.258***	0.009***
	(0.171)	(0.320)	(0.011)	(0.062)	(0.062)	(0.002)
other_patients (30-40)	2.787***	0.183	0.007	3.204***	0.682***	0.029***
	(0.171)	(0.320)	(0.011)	(0.071)	(0.065)	(0.003)
other_patients (40-50)	3.402***	0.194	0.007	4.098***	0.562***	0.023***
	(0.172)	(0.320)	(0.011)	(0.079)	(0.067)	(0.003)
other_patients (50-60)	3.915***	0.195	0.007	5.332***	0.501***	0.019***
	(0.174)	(0.321)	(0.011)	(0.159)	(0.073)	(0.003)
other_patients (>60)	4.661***	0.281	0.011	11.37***	0.619***	0.025***
	(0.174)	(0.320)	(0.011)	(0.159)	(0.064)	(0.002)
ninteractionspair (1)	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)
ninteractionspair (1-5)	0.074***	0.110***	0.005***	0.263***	0.013	0.001
	(0.017)	(0.019)	(0.001)	(0.053)	(0.022)	(0.001)
ninteractionspair (5-10)	1.088***	-1.145***	-0.033***	-0.269***	-0.252***	-0.010***
	(0.057)	(0.227)	(0.004)	(0.067)	(0.056)	(0.002)
ninteractionspair (10-15)	0.486***	-0.404***	-0.015***	-0.565***	-0.382***	-0.015***
	(0.039)	(0.064)	(0.002)	(0.086)	(0.058)	(0.002)
ninteractionspair (15-20)	0.589***	-0.531***	-0.019***	-0.589***	-0.808***	-0.027***
	(0.039)	(0.053)	(0.002)	(0.094)	(0.074)	(0.002)

ninteractionspair (20-25)	0.410***	-0.605***	-0.021***	-0.413***	-0.391***	-0.015***
	(0.043)	(0.051)	(0.002)	(0.097)	(0.078)	(0.003)
ninteractionspair (25-30)	0.807***	-0.539***	-0.019***	-0.580***	-0.472***	-0.018***
	(0.057)	(0.052)	(0.002)	(0.101)	(0.083)	(0.003)
ninteractionspair (>30)	0.929***	-0.748***	-0.024***	0.514***	-0.675***	-0.024***
	(0.053)	(0.043)	(0.001)	(0.146)	(0.048)	(0.002)
constant	3.053***	-7.874***		3.207***	-6.757***	
	(0.371)	(0.669)		(1.038)	(0.211)	
R-squared	0.206			0.131		
Number of Observations	418,887	418,815	418,815	308,344	308,344	308,344

Notes:
Robust Standard errors in parentheses;
*, **, and *** denote significance at 10%, 5%, and 1% respectively
Regression includes controls variables for: patient characteristics, healthcare setting, treatment features and year time dummies.

6 Conclusion

Electronic prescriptions provided the opportunity to study and understand the drivers of prescription by a physician, and of treatment adherence by patients.

This dissertation developed three related topics that aim to add evidence on questions about treatment adherence, job duality, and innovation diffusion, while considering a large longitudinal matched physician-prescription-patient dataset for all Portuguese e-prescriptions containing information on prescription and dispensing, for the period between January 2015 and October 2019 for all regions in Portugal.

Adherence levels are influenced by the physician-patient interaction and healthcare setting, but they may also affect patient's health outcomes. Approximately 82.1% of prescriptions contain at least one drug that was dispensed and the average adherence rate for the selected period is 68.9%.

Considering the first matter, we build on the framework of a physician-patient agency relationship and use a Fractional Regression Model as our principal econometric approach. We provide key contributions to the current literature on the field of physician-patient relationship as well as the had the opportunity to focus our attention on the determinants of primary adherence in a large Portuguese population. This study provides evidence of an increase on the adherence levels when the prescription is issued by the principal physician. It also shows that the number of interactions between both parties has a positive but small effect on adherence which tends to increase and stabilize on further visits. This suggests that the levels of trust between the patient and the provider require time to be built and remain stable. Adherence can also be influenced by the setting where this interaction is established. The public health setting as well as the presence of the principal physician in the public health setting, provided by the interaction between the two variables, presents a negative impact on the adherence levels.

The positive influence of the principal physician on patients' health behaviour and the decision to follow the recommended therapy supports the need for customized interventions and the increase in the number of 'Family Doctors' within the NHS.

These strategies should also be focusing their attention on the public health setting, where the majority of interactions occurs, due to their negative impact on adherence.

An increase on the number of 'Family Doctors' would introduce several benefits to the NHS. First, it would reduce the number of patients that are not assigned to a specific

physician. This would give the opportunity to increase the follow-up levels and introduce long-term relationships. Second, it would reduce the ratio of patients per physician leading to higher levels of attention given to the patient on each interaction. This would give more time per visit as well as it would improve communication and trust levels within the interaction.

The suggested benefits were able to improve adherence as well as reduce indirect costs to the health service, such as worst health outcomes and unnecessary hospitalizations.

For this reason, we have decided to analyse and provide additional evidence on the effect of adherence on improved outcomes, especially regarding disease progression associated to Diabetes. We build on the framework of the three levels of therapeutic guidelines followed by physicians and use a Fixed Effects Ordered Logit Model as our principal econometric approach.

Our contributions to the current literature are focused on the outcomes of primary adherence on disease progression in a large Portuguese population. We provide evidence that higher levels of adherence increase the probability of disease control avoiding the need to introduce more complex therapeutic regimes. Also, this process can be influenced by the health setting where the patient is associated to with the public sector providing better health outcomes.

It is especially important to find a way of maximizing patient's health while reduce all the negative impact of a non-controlled condition on the individual and on the health system. Efforts should be made to provide an incentive to adherence putting the patient as a central focus of attention. These incentives should be done (i) by promoting a proper match among the patient and the physician, previously considered in out study of adherence and the physician-patient agency relationship or (ii) by incentivize pharmacies to actively participate on this matter.

These strategies should also be focusing their attention on the public health setting to continue to improve disease control as well as reduce indirect costs to the health service, such as worst health outcomes and unnecessary hospitalizations.

Prescriptions not only translate the patient behaviour but also the physician performance. We've decided to consider the physician approach towards pharmaceuticals and analyse to what extent the adoption and diffusion of recent hypoglycaemic agents varies with physicians working in a single establishment (public *vs.* private sector) and those working

in both public and private entities. This seems a good approach since approximately 22% of physicians in our data work in job-duality schemes, with their primary job location being mainly public, and they are responsible for a third of the available prescriptions.
We identified the time required to prescribe for the first time the drugs of interest (adoption) as well as we count prescriptions containing recent hypoglycaemic agents (diffusion) according to physician's job situation, especially when located in both public and private sector.
Our results suggest that there are differences across health sectors and work regimes.
Adoption, for the all sample, is specially promoted by the private sector when in exclusivity regimens. Job-duality schemes usually require more time to prescribe, in comparison with public exclusive regimes.
When isolating exclusivity schemes, we have that the private sector takes less time to prescribe, thus increasing the pace of adoption. By considering a sample of job-duality, we see thar the public sector is responsible to induce adoption.
Diffusion is promoted by all the other work regimes – private exclusive, public job-duality, private job-duality – in comparison with public exclusivity.
When isolating exclusivity or job-duality regimes, we have a positive effect of private sector over the public sector, i.e., physicians located in this sector are usually associated to more prescriptions containing the drugs of interest.
Their job location will generate variation in their medical practice. Although they aim to maximize patient's health condition, they are subject to different motivations provided by the different health sectors, which may affect physicians' labour supply, volume of health care production as well as quality of health care services as they can work in the private or public sectors.
With this study we observe physicians working in both public and private sectors, as well as their prescription behaviour in each sector. This way, we separate within-doctor variation in prescription outcomes, associated with differences in incentives between sectors. This study provides interesting findings as several systems, including the Portuguese, consider legislate towards making exclusivity contracts mandatory. For this reason, it is helpful to understand the mechanisms associated to prescription patterns in exclusivity vs. job-duality scheme.

This dissertation provides great input on adding new content to pre-existing evidence, complementing the evidence gaps provided by previous studies as well as it has the chance to be considered by stakeholders decisions.

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