DISSERTATION FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (Ph.D.)

Determinants of Primary Nonadherence to Prescribed Medications among Adults in Hungary

By Nouh Harsha

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List of abbreviations

ATC: Anatomical Therapeutic Chemical

b: Generalized linear regression coefficient

BC: Before Christ

DWR: Dispensed to Written Ratio

GMP: General Medical Practice

GP: General Practitioner

GPC: General Practice Cluster

IALS: International Adult Literacy Survey

IT: Information technology

NHIF: National Health Insurance Fund

O/E: Observed/Expected

PHC: Primary Health Care

Q1: Quarter 1

RR: Relative risk

SD: Standard Deviation

SDWR: Standardized Dispensed to Written Ratio

SHCP: Swiss Hungarian Cooperation Programme

USA: United States of America

WHO: World Health Organization

95%CI: 95% Confidence Intervals

1 Introduction

1.1 Historical background

Adherence (Latin word “adhaerēre” means cling to or stick to) to prescribed medications is not a new notion. It is deeply rooted in history and goes back to the Hippocratic era (400 BC) when Hippocrates noted that patients did not use their medications properly and complained later that their regimens were ineffective (1). Later on in 1882, when Mycobacterium tuberculosis was identified as the causative agent of tuberculosis (2), Robert Koch noticed that patients with tuberculosis were irresponsible or careless and did not comply with the use of their medications (3). In the 20th century, changes in peoples’ social and cultural factors altered the way noncompliant patients were described and drew more attention to the impact of compliance with doctors' instructions on the therapeutic process (4). A few decades ago, and after predominance of noncommunicable diseases that require long term therapy and strong patient-physician cooperation, more concern was given to the idea after realizing that compliance with therapy is indispensable to achieve optimum therapeutic outcomes (5) and patient involvement in the treatment process is essential to achieve the desired clinical goals (6).

Definition of the concept

The World Health Organization (WHO) described adherence to medications as “the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider” (7). Adherence simply refers to taking medications as described or prescribed by health care providers (3, 8). Adherence is used to reflect the degree to which patients conform or follow instructions and recommendations of health care providers throughout the prescribed treatment course (9, 10). It involves a retrospective memory for remembering the way the medicines are to be used and a prospective memory concerning the time at which the medications are to be used (11). The adherence process entails three main elements: initiation of therapy; implementation of the therapy as prescribed; and persistence on the given therapy for the desired period of time (12-14).

Types of nonadherence

Nonadherence occurs when patients delay or do not dispense medications, do not take the desired dosage, or decide to discontinue their medications prematurely (15). Nonadherence and noncompliance are interchangeably used despite the fact that adherence reflects a more

centered and active role of the patient in the therapeutic process than compliance (16-18). Nonadherence can be classified into two main clinically significant categories: primary and secondary (19).

Primary nonadherence

It refers to a situation when people do not purchase, fill, or dispense new prescriptions written by their health care providers from the beginning of the treatment course (20-22). Although primary adherence to medications is crucial for any successful treatment strategy in both acute and chronic health conditions, less attention has been given to this issue until recently (21, 23). In fact, much less than required is known about frequency, causes, and consequences of primary nonadherence (24, 25).

Secondary nonadherence

It is said to occur when patients either do not follow instructions and guidelines given to them by their health care providers (for instance daily doses) or do not refill the given prescriptions in order to continue the course of their prescribed medications (26, 27).

Unintentional vs. intentional nonadherence

Nonadherence can be either unintentional or intentional. The unintentional nonadherence occurs in a patient who is careless, or who forgets to take their medications correctly and is largely attributed to patient characteristics, physical problems, or treatment complexity. On the other hand, intentional nonadherence is attributed to patients' deliberate decisions or preferences to deviate from the given treatment guidelines and instructions, or probably modifying it to satisfy their needs (28-31).

1.2 Consequences of nonadherence

Nonadherence has been described as a global epidemic (32). The concept has gained increasing attention of economists, health care professionals and stakeholders in the recent years (9) and has become an important public health issue (24, 33). It is likely to affect various patient groups, particularly those with chronic health conditions (34-36). This concern is due to its' role in mediating therapeutic outcome of the prescribed medications (37). Indeed, adherence to medications is considered as the cornerstone in management, control, and prevention of loss of the desired therapeutic outcome, disease progression, and complications (38-40). Several pieces of research attributed higher morbidity and mortality among patients with chronic diseases, premature disability, adverse outcomes, health

disparities, and reduced work and productivity to medications noncompliance (11, 12, 24, 32, 41-48). In addition, nonadherence increases health care costs and hospitalization and is associated with the deterioration of quality of life (20, 49-51). It is estimated that nonadherence to medications in Germany raises health care costs by 10 billion euros per year (52). In the United States (US), it is estimated that more than 125 thousand premature deaths (53) and more than 10% of the hospitalizations occur annually due to improper adherence (54). It is estimated that nonadherence increases health care costs in the United States by 100 to 300 billion US dollars every year (55, 56) and this constitutes 3-10% of the total health care cost (16).

Determinants of nonadherence

Nonadherence has a complex, multifactorial etiology (44, 57, 58). Several factors have been identified to affect patient adherence to prescribed regimens (59, 60). The WHO classified the factors that affect medication adherence into five main categories (7). Those factors include:

- Patients' demographic and socioeconomic factors such as age, sex, education, income, poverty, literacy levels, social support, culture and beliefs (10, 61-65).
- Factors related to patient including cognitive ability, expectations, forgetfulness, lack of motivation, and misunderstanding instructions (51).
- Factors related to medical conditions of the patient such as comorbidity, poly-pharmacy, symptoms severity, and disability (58, 66, 67).
- Factors linked to the health care system like organization, teamwork, provision of services, medications cost/price, insurance, and the patient-physician relationship (66, 68-70).
- Treatment-related issues such as side effects, duration of therapy, and complexity of the prescribed regimens (47, 71, 72).

It is reported that patients' beliefs and attitudes, affected by the cultural and the educational levels, are among the most important determinants that cause adherence or nonadherence to prescribed medications (73, 74).

Measurement of nonadherence

The measurement of nonadherence is challenging (75). The WHO classified the methods used to measure adherence into subjective and objective measures (7). Those methods were described in the literature as direct and indirect methods (69). In general, there is no gold

standard for measuring adherence that fits all situations and use of combined techniques gives more reliable results (76). The direct methods include direct observation of medication use, measurement of the concentration of the drugs, its metabolites in a sample taken directly from body fluids, or through biological markers (77). Although this method provides precise data on drug consumption, some of its drawbacks include being expensive, requiring efforts and health care teams to monitor the process, suitable for patients with single therapy, reporting yes/no results but no usage pattern, and bias is likely since patient may take their medications at the time of the test only leading to a false adherence (48, 73). However, indirect methods assume that patients consume their medications (78). They include patient questionnaires, self-report measures, pill counts and prescriptions refilling rates, clinical response assessment of the patients, electronic monitoring devices, and more recently electronic health records (48, 77). Drawbacks of such methods include distortion and alteration of the results by the patient, high cost like those used in electronic medications monitors, and lack of evidence on actual drug ingestion (31, 69).

1.3 Prevalence of nonadherence

Nonadherence is a global issue (79-81) and is quite common in both developing as well as developed nations (7, 69). A meta-analysis of 20 studies conducted between 1998 and 2010 in Australia, Canada, USA, and Europe to assess the extent of adherence of cardiovascular patients to their regimens indicated that around 50% did not properly adhere to the cardiovascular medications prescribed for preventive purposes (82). A systematic review and meta-analysis of several studies conducted in this field indicated that about one-third of the written prescriptions are not dispensed and around 50% of the dispensed medications are not taken as recommended (71, 83, 84). It is estimated that about half of the patients with chronic diseases do not properly adhere to their prescribed regimens (51, 54). Yet, a meta-analysis of 569 empirical studies, conducted over fifty years period, reported that on average around one-fourth of the patients did not adhere to their regimens (85). A study conducted to assess primary nonadherence in Tayside (Scotland) revealed that 14.5% of the patient did not dispense the given prescriptions from the beginning of their treatment course (86). Furthermore, a study conducted in Quebec (Canada) to assess the incidence of primary nonadherence in the primary health care (PHC) between 2006 and 2009 reported that 31.3% of the written prescriptions were not filled (35).

A study was conducted to investigate compliance to prescribed medications and assess the impact of the social factors across several European countries -including Hungary- using data

obtained from the self-reported "European Social Survey, round 2". In brief, the result indicated that on average 18% of the participants reported nonadherence to prescribed regimens. In addition, the study detected a great variation among the different European countries. Furthermore, sociodemographic and socioeconomic factors studied could not alone explain the detected differences (19). Another proof from the "European Social Survey" indicated that the nonadherence rate to prescribed medications in Hungary was 20.3%, giving it the 4th highest rate of nonadherence among the 24 European countries surveyed (87). This probably indicates the importance of nonadherence as a contributing factor for high amenable mortality in the Hungarian context, which is more than twice the average in the European Union based on the EUROSTAT statistics of 2015 (88).

1.4 Interventions to improve adherence

Several interventions were tried to enhance adherence. Such interventions were usually delivered by number of health professionals including physicians, pharmacists, nurses, and health care workers (71, 89, 90). Interventions delivered by pharmacists were found to be more effective than those delivered by other health care professionals (42, 91, 92). Also, interventions led by non-physician community health workers were found to be effective in increasing adherence to medications in communicable diseases, noncommunicable diseases and in changing lifestyle (93). Furthermore, interventions supported and adopted by governments, academics and other organizations concerned with improving health care showed some positive outcomes in many instances (58). However, interventions made on a large scale are expensive, complex, and consume a lot of resources (14, 53).

Successful interventions require precise knowledge on the utilization of the drugs (94). The interventions should be patient-centered approaches (15, 71). Since adherence is a multifactorial issue, unimodal interventions targeting one aspect of nonadherence are ineffective (9, 48). On the other hand, multifaceted comprehensive approaches with strategies designed and tailored to suit individual patients or groups were found to be the most effective (43, 54, 57). At the same time, the strategies must be simple enough to be integrated into daily practice (12). Interventions targeted the disadvantaged population and people with low socioeconomic status were more likely to show high positive outcomes (24, 61). A key issue in enhancing adherence is the integration of the health care system and services (95).

Some interventions tested globally included simple dose adjustment and reducing the number of medications (37, 96), reminders and improved scheduling (97) and educational

interventions (71, 98, 99). Other interventions included more comprehensive and complex strategies such as expansion of the pharmacist role in health care (83), enhancing patient-physician communication (37), provision of services (100), proper description of disease and medications (48, 101), habit analysis and management of side effects (42, 91), patient follow up, social, behavioral support and motivation (57, 58, 71, 102) and acting on patients' feedback (103).

There is no gold standard for a comprehensive approach that can be used to enhance adherence (104). In fact, due to the multidisciplinary nature of nonadherence (57, 105), understanding the context and the real causes are key issues in designing effective interventions (69, 71). Interestingly, the given results of the tested interventions are sometimes unclear or even inconsistent (91). A meta-analysis of many interventions implemented indicated an increase in adherence magnitude by 4 to 11% (84). Approaches that focused on patient follow up and incentives were very effective, particularly among the disadvantaged population (106, 107).

Study context

Despite achieving improvement in some of the health indicators in Hungary in the last few decades such as increasing life expectancy rate at birth for both men and women and successful control of communicable diseases among children, many other health indicators remained poorly controlled, keeping health status of the population inferior to that in majority of the European countries (108). The Hungarian PHC system stands in the weakest third in Europe (109). Furthermore, prevention and health promotion activities are underdeveloped and lack proper coordination and financing (110, 111). The situation is even worse for Roma (112). The Health Care System of Hungary is facing several challenges. The most critical issues include, but not limited to, noncommunicable diseases especially ischemic heart diseases, liver diseases, cancer, socioeconomic and territorial inequalities, unhealthy lifestyle, issues related to health awareness and behavior of the people, weak intersectoral collaboration at local and national level, scarcity of the resources in addition to insufficiency of preventive activities in the PHC (111-114).

1.5 The Swiss Hungarian Cooperation Programme

Reorientation of the Hungarian health care system constitutes a top priority. The Swiss Hungarian Cooperation Programme (SHCP) entitled "Public Health Focused Model Programme for Organizing Primary Care Services Backed by a Virtual Care Service Centre"

was implemented as a pilot project in the disadvantaged and the most disadvantaged areas of the country (111, 115). The programme entailed establishing general practice clusters (GPCs) for expansion and strengthening of the PHC role to include health promotion activities to improve health determinants and equity among the disadvantaged and the most disadvantaged groups, disease prevention, health restoration, and rehabilitation activities in a well-organized and collaborated manner. The concept behind this programme was the support of the PHC team consisting traditionally of one general practitioner (GP) and one practice nurse with other health care professionals as recommended by the WHO (115, 116).

Research rationale

The health status of the Hungarian population is inferior to that in the majority of the European countries. For instance, the mortality rate is more than twice that of the average in the European Union countries (88). Given that adherence to prescribed medications is essential for achieving desired clinical outcomes, reducing morbidity and mortality, prevention of disease progression and complications, reducing health care costs and improving the overall quality of life, studying nonadherence and uncovering its major determinants is essential (38, 48-51). Indeed, primary nonadherence has not been investigated previously in Hungary at the national level. However, the results of the self-reported European Social Surveys reported that Hungary has a big burden of nonadherence (87). Given that high rates of nonadherence is a major contributing factor to the poor health status of the population, studying and understanding nonadherence in Hungary is indispensable.

1.6 Objectives

The aims of our investigations were to:

1. Estimate primary nonadherence to prescribed medications written in the general medical practices (GMPs) among adults in Hungary using the WHO key indicator of patient care “percentage of drugs actually dispensed” (117) to quantify the dispensed medications at the period between 2012 and 2015, and to describe the variation of adherence across GMPs.
2. To determine the effects of GMP structure and patient characteristics on adherence to medications.
3. To evaluate whether operating the GPC model for the purpose of organizing and improving the effectiveness of PHC increases the percentage of drugs actually

dispensed reflecting eventually better patient-physician collaboration necessary for improving the overall health status of the population.

Study hypotheses

We hypothesize that:

1. Primary nonadherence to GP prescribed medications among adults in Hungary is high.
2. Nonadherence varies by patient characteristics (such as age, sex, and eligibility for exemption certificate) and characteristics of the GMP like socioeconomic status marked by standardized patients' relative education, the vacancy of the GP, size of the GMP, settlement type, and county location.
3. The interventions implemented in the SHCP improved primary adherence to the prescribed medications in Hungary.

2 Methods

2.1 Setting

In this study, we performed secondary data analyses. Analysis unit was the prescription written by a GP working in PHC and filled by the patient. Data on prescribed and dispensed prescriptions were obtained from the National Health Insurance Fund (NHIF). The data investigated covered all GMPs running in Hungary for the period between January 2012 and September 2015.

As far as the SHCP is concerned, Hungarian PHC teams working in GMPs (each GMP team consists of one GP and one practice nurse) were invited to establish the GPCs in 2012. The aim of this community-oriented approach was to reorient the PHC system in Hungary in order to improve the general health status and quality of life of the population. In fact, this project is greatly related to the Semmelweis Plan of reforming the national health care system of Hungary to improve health care, the involvement of GPs in preventive services and health promotion, proper allocation of resources, fostering collaboration and integration among GPs, other health care professionals, and health organizations (115).

Four GPCs were established in four districts of Hungary. Each cluster consisted of six GMPs. The GPC was created with the aim of offering preventive services and health promotion interventions besides the usually given acute, curative, and emergency services. The work of the GPC was supported by other health professionals including one community nurse, one dietician, one psychologist, one physiotherapist, two specialists in public health, and twelve health mediators. Details of GPCs structure, operation rules, and functions were reported in previous reports in detail (110, 115). Although the major interventions implemented were focused on the disadvantaged and the most disadvantaged areas of the country especially the Roma population settlements, the goal was to build up methodological suggestions and guidelines helpful to policymakers to improve health care services at the national level.

In 2014, after setting the health care protocol, the establishment of the appropriate infrastructure, and training the staff, the new health care services were initiated. The invitation was given to all adults aged 18 years and above whose GMPs participated in the programme to take part in an organized assessment of health status carried out by the community nurse and the public health specialists. Three new activities –which were not available before- were introduced into primary health care system: assessment of health status at the beginning and at the end of the programme to detect differences in health conditions;

medical risk assessment to estimate significance of risks factors or morbidities evaluated during health status assessment carried out by a GP; and then the GP refers patients to treatment or lifestyle counseling to be offered by dieticians, physiotherapists, psychologists, or public health specialists to manage risk factors, foster health literacy, and motivate patients to adhere to medications and instructions of health professionals (110).

In addition, a new dimension towards rehabilitation was introduced into chronic care services to assist the disabled to achieve social integration through proper collaboration between physicians and other health care providers. Details on health status assessment were discussed in detail in previous papers (118, 119). To achieve the best possible outcomes, all stakeholders and municipal/ local governments were involved in the programme to ensure their commitment.

2.2 Data collection

During medical practice, the NHIF data that cover the whole country were aggregated into four quarters per annum and stratified by patient's sex, age (5-year bands), and holding an exemption certificate (issued for socioeconomically disadvantaged people with chronic health conditions to enable them to obtain medical devices and medications without paying). The prescribed drugs were classified based on the Anatomical Therapeutic Chemical (ATC) Classification proposed by the WHO into 14 groups (120). The data analyses did not encompass antineoplastic and immunomodulating agents, antiparasitic drugs, insecticides and repellents since prescribing those medications were not linked to GMPs as per the Hungarian regulations.

Characteristics of the GMPs were also obtained from the NHIF. The characteristics included information on the vacancy of the GMP as to whether the health care service is provided by a temporary contracted GP available at a specific time and place or a permanent GP available persistently. The GMPs were also classified as being in an urban or rural setting. Size of the locality based on the number of adults to which health care services were provided based on the categorization of the NHIF (less than 800, 801–1200, 1201–1600, 1601–2000, and 2001 or more clients). In addition, geographical location by the county where the GMPs were operating was investigated. Furthermore, the socioeconomic status of clients receiving health care services in a GMP was reflected by their internally standardized relative education estimated by the indirect standardization method. This was completed using gender and age group-specific levels of education of the Hungarian Census of 2011 and the gender and age

group structure of the related GMP clients (121). The national socio-economic status average equals value 1 of the internally standardized relative education.

2.3 Statistical analysis

Outcomes measured (dependent variables)

The outcomes measured were the primary adherence ratios indirectly standardized for sex, age, and possession of exemption certificates. The standardized adherence ratios were obtained by dividing the accumulated GMP-specific numbers of the observed (O) dispensed medications (prescriptions) by the accumulated GMP-specific numbers of the expected (E) dispensed medications (prescriptions).

The NHIF determined the age-, sex-, and exemption certificate-specific number of both the written and the dispensed prescriptions and proportion of drugs actually dispensed (dispensed to written ratio, DWR) (117) as an indicator of primary adherence for each ATC group of drugs studied during the entire period of investigation for the whole country.

The expected number of dispensed prescriptions was estimated for each GMP using the age-, sex-, and exemption certificate-specific number of the written prescriptions and the national reference DWRs (summing up the expected number of medications dispensed in all strata). The ratio of the registered number of dispensed prescriptions in a GMP and the estimated GMP-specific expected number of dispensed prescriptions was calculated to indicate GMP-specific standardized dispensed to written ratios (SDWRs) for each ATC group studied.

SDWR values obtained were tested for normal distribution. Results of the Kolmogorov-Smirnov test showed that these data were not normally distributed. To describe their distribution, median values and interquartile ranges were used. Given that the SDWR values were positive numbers, Box-Cox transformation was used to transform and normalize the data (122). Histograms of the original and normalized SDWRs are presented under the results section.

Generalized linear regression modeling

In order to identify the major determinants of the SDWRs while controlling for the time, generalized linear regression modeling was performed. We calculated generalized linear regression coefficients (b) along with their corresponding 95% confidence intervals (95%CI). Both vacancy of GMP and type of settlement were inserted into the model as binary parameters. However, county location and size of the GMP were inserted into the model as

dummy variables with Budapest as a reference category for county location and size of the GMP serving 1601-2000 clients as a reference category for GMP size. Pearson chi-square goodness of fit was used to indicate regression modeling performance. The significance level was set at 95% ($p<0.05$). SPSS version 20 was used to analyze the data.

2.4 Evaluation of the SHCP

The effectiveness of the intervention has been evaluated by before-after analyses of the programme. We aggregated data of the number of prescriptions written by the GPs and dispensed by the clients and calculated the DWRs in the first quarter of 2012 (2012Q1, before the intervention) and in the third quarter of 2015 (2015Q3, after the intervention) for both the intervention area and the whole country. The DWRs for the aggregated intervention population were calculated by age, sex, and exemption certificate eligibility and compared with the DWRs of the whole country before and after the intervention programme. In addition, SDWRs (calculated by dividing the total observed number of dispensed prescriptions by the total number of expected dispensed prescriptions) for each ATC group was calculated and compared. Relative dispensing ratios (RRs) for 2015Q3 and 2012Q1 were calculated for each ATC group using 95% CI of the measures to indicate the impact of the programme on the DWRs.

Ethical considerations

This research involved secondary data analyses. It did not reflect any personal information or identifier. In line with the Hungarian rules and regulations, no ethical approval is required to carry out this type of study analysis.

3 Results

3.1 Prevalence of primary nonadherence among adults in Hungary

Characteristics of the GMPs running across Hungary

Table 1 below summarizes characteristics of the GMPs operating in Hungary. Overall, 4,856 GMPs were running around the country. 3.3% of the GMPs were vacant, two-third of the GMPs were located in urban areas. Majority of the GMPs were running in localities serving more than 1200 clients. 18% of the GMPs were running in Budapest County which is used as a reference category in our analysis, 5.1% were in Hajdú-Bihar, 4.0% were in Fejér, and 2.9% were operating in Zala County. The mean relative education of clients was 1.00 (SD±0.10) using the internally standardized approach.

Table 1. Distribution and characteristics of general medical practices in Hungary

Variable name		**Number of GMP (%)**
Vacancy of general practitioner	Vacant	160 (3.3)
	Fulfilled	4,696 (96.7)
Type of settlement	Rural	1,683 (34.7)
	Urban	3,173 (65.3)
Size of GMP	< 800	158 (3.3)
	800-1200	677 (13.9)
	1201-1600	1,481 (30.5)
	1601-2000	1,541 (31.7)
	>2000	999 (20.6)
County	Budapest	875 (18.0)
	Baranya	209 (4.3)
	Bács-Kiskun	256 (5.3)
	Békés	191 (3.9)
	Borsod-Abaúj-Zemplén	377 (7.8)
	Csongrád	205 (4.2)
	Fejér	196 (4.0)
	Győr	205 (4.2)
	Hajdú-Bihar	246 (5.1)
	Heves	161 (3.3)
	Komárom-Esztergom	146 (3.0)
	Nógrád	109 (2.2)
	Pest	477 (9.8)
	Somogy	177 (3.6)
	Szabolcs-Szatmár-Bereg	267 (5.5)
	Jász-Nagykun-Szolnok	194 (4.0)
	Tolna	121 (2.5)
	Vas	134 (2.8)
	Veszprém	169 (3.5)
	Zala	141 (2.9)
Total number of GMPs		4,856 (100.0)

Proportion of drugs actually dispensed by patient characteristics for total practice.

Overall, percentage of prescriptions dispensed for the entire GMPs was 64.1% (Table 2). The DWR showed significant variation across age groups with better adherence of 65.8% reported for elderly adults aged 65 years and above. Slight differences (with no practical importance) by gender were reported with 64.5% for females and 63.6% for males. Remarkable differences (practically important) by exemption certificates were reported (DWR was 78.3% for patients with exemption certificates and 62.4% for patients without exemption certificates). Differences observed were statistically significant when checked by the Chi-square test ($p<0.001$).

Table 2. Dispensed to written prescription ratios by patient characteristics for total practice between January 2012 and September 2015 in Hungary

Patient characteristics		**Written prescriptions**	**Dispensed prescriptions**	**Dispensed percentage**	**P-value***
Age groups (years)	18-44	39,971,036	25,539,871	63.9	<0.001
	45-64	171,996,562	106,753,470	62.1	
	65 and above	226,646,402	149,022,045	65.8	
Sex	Male	172,358,931	109,603,855	63.6	<0.001
	Female	266,255,069	171,711,531	64.5	
Exemption certificate	Yes	47,960,440	37,548,944	78.3	<0.001
	No	390,653,560	243,766,442	62.4	
Total		438,614,000	281,315,386	64.1	-

**** Chi-square test***

Indeed, variation in the distribution of adherence by sex and exemption certificate has been detected in each ATC group investigated. However, variation by age groups differed by the ATC group. Tables (3-14) show the distribution of DWRs by the ATC group of drugs.

Proportion of drugs actually dispensed by patient characteristics for ATC A (alimentary tract and metabolism drugs) group.

Differences among age groups (range 66.5% to 69.7%), slight differences by gender, and remarkable difference by exemption certificate were noted ($p<0.001$). Overall adherence for ATC A group was 4.5% higher than adherence reported for the total practice as listed in Table 3.

Table 3. Dispensed to written prescription ratios by patient characteristics for ATC A group (alimentary tract and metabolism drugs) between January 2012 and September 2015

Patient characteristics		**Written prescriptions**	**Dispensed prescriptions**	**Dispensed percentage**	**P-value***
Age groups (years)	18-44	6,174,881	4,104,388	66.5	<0.001
	45-64	27,880,143	18,857,038	67.6	
	65 and above	37,681,316	26,247,298	69.7	
Sex	Male	26,771,874	18,416,334	68.8	<0.001
	Female	44,964,466	30,792,390	68.5	
Exemption certificate	Yes	9,362,841	7,377,434	78.8	<0.001
	No	62,373,499	41,831,290	67.1	
Total		71,736,340	49,208,724	68.6	-

**** Chi-square test***

Proportion of drugs actually dispensed by patient characteristics for ATC B (blood and blood-forming organs agents) group.

Remarkable differences across age groups (range 63.5% - 70.9%), slight differences within gender, and significant difference by exemption certificate were observed ($p<0.001$). Overall adherence for this group is 5.1% higher than adherence reported for the total practice (Table 4).

Table 4. Dispensed to written prescription ratios by patient characteristics for ATC B drugs (blood and blood-forming organs agents) between January 2012 and September 2015

Patient characteristics		**Written prescriptions**	**Dispensed prescriptions**	**Dispensed percentage**	**P-value***
Age groups (years)	18-44	1,707,816	1,084,488	63.5	<0.001
	45-64	10,733,646	7,219,083	67.3	
	65 and above	17,796,395	12,617,489	70.9	
Sex	Male	13,094,524	9,091,791	69.4	<0.001
	Female	17,143,333	11,829,269	69.0	
Exemption certificate	Yes	3,357,110	2,682,641	79.9	<0.001
	No	26,880,747	18,238,419	67.8	
Total		30,237,857	20,921,060	69.2	-

**** Chi-square test***

Proportion of drugs actually dispensed by patient characteristics for ATC C (cardiovascular system agents) group.

Remarkable differences across age groups (range 54.8% - 61.8%), slight differences within gender, and significant difference by exemption certificate were noted ($p<0.001$). Adherence was the lowest for this important group of drugs with 4.7% lower than the adherence reported for the total practice (Table 5).

Table 5. Dispensed to written prescription ratios by patient characteristics for ATC C drugs (cardiovascular system agents) between January 2012 and September 2015

Patient characteristics		**Written prescriptions**	**Dispensed prescriptions**	**Dispensed percentage**	**P-value***
Age groups (years)	18-44	12,904,985	7,072,587	54.8	<0.001
	45-64	91,945,735	52,144,529	56.7	
	65 and above	123,374,490	76,271,970	61.8	
Sex	Male	92,185,977	54,097,172	58.7	<0.001
	Female	136,039,233	81,391,914	59.8	
Exemption certificate	Yes	18,623,266	14,488,200	77.8	<0.001
	No	209,601,944	121,000,886	57.7	
Total		228,225,210	135,489,086	59.4	-

**** Chi-square test***

Proportion of drugs actually dispensed by patient characteristics for ATC D (dermatological agents) group.

Differences across age groups (range 60.7% - 63.4%) were observed with young adults aged 18-44 years old reported the highest adherence. Slight differences within gender and significant difference by exemption certificates were noted ($p<0.001$). Adherence is 2.3% lower than adherence for the total practice (Table 6).

Table 6. Dispensed to written prescription ratios by patient characteristics for ATC D drugs (dermatological agents) between January 2012 and September 2015

Patient characteristics		**Written prescriptions**	**Dispensed prescriptions**	**Dispensed percentage**	**P-value***
Age groups (years)	18-44	1,007,238	639,052	63.4	<0.001
	45-64	1,736,860	1,074,165	61.8	
	65 and above	1,638,087	993,894	60.7	
Sex	Male	1,717,976	1,054,609	61.4	<0.001
	Female	2,664,209	1,652,502	62.0	
Exemption certificate	Yes	856,917	590,367	68.9	<0.001
	No	3,525,268	2,116,744	60.0	
Total		4,382,185	2,707,111	61.8	-

**** Chi-square test***

Proportion of drugs actually dispensed by patient characteristics for ATC G (genitourinary system and sex hormones agents) group.

Remarkable differences across age groups (range 66.0% - 72.6%), slight differences within gender and significant difference by exemption certificate were noted (p<0.001). Adherence is 3.3% higher than adherence for the total practice (Table 7).

Table 7. Dispensed to written prescription ratios by patient characteristics for ATC G drugs (genitourinary system and sex hormones agents) between January 2012 and September 2015

Patient characteristics		**Written prescriptions**	**Dispensed prescriptions**	**Dispensed percentage**	**P-value***
Age groups (years)	18-44	226,801	164,769	72.6	<0.001
	45-64	821,421	541,791	66.0	
	65 and above	2,348,702	1,583,028	67.4	
Sex	Male	2,252,287	1,521,759	67.6	<0.001
	Female	1,144,637	767,829	67.1	
Exemption certificate	Yes	434,919	337,760	77.7	<0.001
	No	2,962,005	1,951,828	65.9	
Total		3,396,924	2,289,588	67.4	-

**** Chi-square test***

Proportion of drugs actually dispensed by patient characteristics for ATC H (systemic hormonal preparations, excluding sex hormones and insulins) group.

Slight difference across age groups (range 73.8% - 75.0%), slight differences within gender and significant difference by exemption certificate were noted (p<0.001). Adherence is 10.0% higher than adherence for the total practice (Table 8).

Table 8. Dispensed to written prescription ratios by patient characteristics for ATC H drugs (systemic hormonal preparations, excluding sex hormones and insulins) between January 2012 and September 2015

Patient characteristics		**Written prescriptions**	**Dispensed prescriptions**	**Dispensed percentage**	**P-value***
Age groups (years)	18-44	881,132	660,897	75.0	<0.001
	45-64	2,088,223	1,542,626	73.9	
	65 and above	1,852,727	1,367,234	73.8	
Sex	Male	790,899	570,827	72.2	<0.001
	Female	4,031,183	2,999,930	74.4	
Exemption certificate	Yes	434,500	339,267	78.1	<0.001
	No	4,387,582	3,231,490	73.7	
Total		4,822,082	3,570,757	74.1	-

**** Chi-square test***

Proportion of drugs actually dispensed by patient characteristics for ATC J (anti-infective agents for systemic use) group.

Remarkable differences across age groups (range 74.9% - 83.8%), slight differences within gender and significant difference by exemption certificate were noted ($p<0.001$). Adherence for this group is 15.0% higher than adherence for the total practice (Table 9).

Table 9. Dispensed to written prescription ratios by patient characteristics for ATC J drugs (anti-infective agents for systemic use) between January 2012 and September 2015

Patient characteristics		**Written prescriptions**	**Dispensed prescriptions**	**Dispensed percentage**	**P-value***
Age groups (years)	18-44	6,072,287	4,545,158	74.9	<0.001
	45-64	4,500,908	3,690,082	82.0	
	65 and above	2,775,185	2,324,755	83.8	
Sex	Male	4,779,654	3,708,273	77.6	<0.001
	Female	8,568,726	6,851,722	80.0	
Exemption certificate	Yes	1,319,135	1,124,071	85.2	<0.001
	No	12,029,245	9,435,924	78.4	
Total		13,348,380	10,559,995	79.1	-

**** Chi-square test***

Proportion of drugs actually dispensed by patient characteristics for ATC M (musculoskeletal system agents) group.

Remarkable differences across age groups (range 66.5% - 70.4%), slight differences within gender and significant difference by exemption certificate were noted (p<0.001). Adherence is 4.8% higher than adherence for total practice (Table 10).

Table 10. Dispensed to written prescription ratios by patient characteristics for ATC M drugs (musculoskeletal system agents) between January 2012 and September 2015

Patient characteristics		**Written prescriptions**	**Dispensed prescriptions**	**Dispensed percentage**	**P-value***
Age groups (years)	18-44	3,695,766	2,456,246	66.5	<0.001
	45-64	12,483,264	8,487,634	68.0	
	65 and above	13,641,757	9,597,219	70.4	
Sex	Male	12,456,342	8,517,643	68.4	<0.001
	Female	17,364,445	12,023,456	69.2	
Exemption certificate	Yes	4,669,932	3,738,666	80.1	<0.001
	No	25,150,855	16,802,433	66.8	
Total		29,820,787	20,541,099	68.9	-

**** Chi-square test***

Proportion of drugs actually dispensed by patient characteristics for ATC N (nervous system agents) group.

Differences across age groups (range 68.6% - 72.0%), slight differences within gender and significant difference by exemption certificate were observed (p<0.001). Adherence is 6.6% higher than adherence for the total practice (Table 11).

Table 11. Dispensed to written prescription ratios by patient characteristics for ATC N drugs (nervous system agents) between January 2012 and September 2015

Patient characteristics		**Written prescriptions**	**Dispensed prescriptions**	**Dispensed percentage**	**P-value***
Age groups (years)	18-44	2,599,090	1,870,767	72.0	<0.001
	45-64	9,879,005	6,779,307	68.6	
	65 and above	15,859,815	11,390,583	71.8	
Sex	Male	8,716,855	6,215,523	71.3	<0.001
	Female	19,621,055	13,825,134	70.5	
Exemption certificate	Yes	4,700,421	3,689,171	78.5	<0.001
	No	23,637,489	16,351,486	69.2	
Total		28,337,910	20,040,657	70.7	-

**** Chi-square test***

Proportion of drugs actually dispensed by patient characteristics for ATC R (respiratory system agents) group.

Remarkable differences across age groups (range 62.3% - 68.8%), slight differences within gender and significant difference by exemption certificate were noted (p<0.001). Adherence is 1.7% higher than adherence for the total practice (Table 12).

Table 12. Dispensed to written prescription ratios by patient characteristics for ATC R drugs (respiratory system agents) between January 2012 and September 2015

Patient characteristics		**Written prescriptions**	**Dispensed prescriptions**	**Dispensed percentage**	**P-value***
Age groups (years)	18-44	4,239,364	2,641,667	62.3	<0.001
	45-64	9,121,470	5,890,282	64.6	
	65 and above	8,469,307	5,825,171	68.8	
Sex	Male	8,666,122	5,800,762	66.9	<0.001
	Female	13,164,019	8,556,358	65.0	
Exemption certificate	Yes	3,710,124	2,832,161	76.3	<0.001
	No	18,120,017	11,524,959	63.6	
Total		21,830,141	14,357,120	65.8	-

**** Chi-square test***

Proportion of drugs actually dispensed by patient characteristics for ATC S (sensory organs agents) group.

Remarkable differences across age groups (range 66.4% - 70.1%), no differences within gender, and significant differences by exemption certificates were reported. Differences by age and exemption certificates were statistically significant ($p<0.001$). Adherence is 4.4% higher than adherence for total practice (Table 13).

Table 13. Dispensed to written prescription ratios by patient characteristics for ATC S drugs (sensory organs agents) between January 2012 and September 2015

Patient characteristics		**Written prescriptions**	**Dispensed prescriptions**	**Dispensed percentage**	**P-value***
Age groups (years)	18-44	344,379	228,643	66.4	<0.001
	45-64	536,539	362,283	67.5	
	65 and above	745,722	522,697	70.1	
Sex	Male	543,743	372,326	68.5	0.912
	Female	1,082,897	741,297	68.5	
Exemption certificate	Yes	265,041	198,547	74.9	<0.001
	No	1,361,599	915,076	67.2	
Total		1,626,640	1,113,623	68.5	-

**** Chi-square test***

Proportion of drugs actually dispensed by patient characteristics for ATC V (various agents) group.

No statistical difference across age groups (range 60.6% - 61.1%), slight differences within gender and significant difference by exemption certificate were noted. Differences by gender and exemption certificates were statistically significant (p<0.001). Adherence is 3.3% lower than adherence for total practice (Table 14).

Table 14. Dispensed to written prescription ratios by patient characteristics for ATC V drugs (various agents) between January 2012 and September 2015

Patient characteristics		**Written prescriptions**	**Dispensed prescriptions**	**Dispensed percentage**	**P-value***
Age groups (years)	18-44	117,297	71,209	60.7	0.118
	45-64	269,348	164,650	61.1	
	65 and above	462,899	280,707	60.6	
Sex	Male	382,678	236,836	61.9	<0.001
	Female	466,866	279,730	59.9	
Exemption certificate	Yes	226,234	150,659	66.6	<0.001
	No	623,310	365,907	58.7	
Total		849,544	516,566	60.8	-

**** Chi-square test***

Proportion of drugs actually dispensed by ATC groups.

Wide variation of DWRs by drug class was reported (Table 15). The lowest DWR among ATC groups was reported for agents used for the cardiovascular system at 59.4%. The highest DWR was detected for anti-infective drugs for systemic use with 79.1%.

Table 15. Dispensed to written prescription ratio by ATC group between January 2012 and September 2015

ATC drug class	**Written prescriptions**	**Dispensed prescriptions**	**Dispensed percentage**
Alimentary tract and metabolism (A-group)	71,736,340	49,208,724	68.6
Blood and blood forming organs (B-group)	30,237,857	20,921,060	69.2
Cardiovascular system (C-group)	228,225,210	135,489,086	59.4
Dermatologicals (D-group)	4,382,185	2,707,111	61.8
Genitourinary system and sex hormones (G-group)	3,396,924	2,289,588	67.4
Systemic hormonal preparations* (H-group)	4,822,082	3,570,757	74.1
Antiinfectives for systemic use (J-group)	13,348,380	10,559,995	79.1
Musculoskeletal system (M-group)	29,820,787	20,541,099	68.9
Nervous system (N-group)	28,337,910	20,040,657	70.7
Respiratory system (R-Group)	21,830,141	14,357,120	65.8
Sensory organs (S-group)	1,626,640	1,113,623	68.5
Various (V-group)	849,544	516,566	60.8
Altogether^	438,614,000	281,315,386	64.1

**** Sex hormones and insulin were excluded***

^ ***Antineoplastic, immunomodulating agents, antiparasitic products, repellents, and insecticides, were not included in the data analysis.***

Distribution of dispensed to written ratios of prescribed medications by ATC groups.

Table 16 below shows distribution of DWRs of the prescribed medications by the ATC drug groups. Since data were not normally distributed, median and interquartile ranges were used in the description. Median was 1.09 for alimentary tract and metabolism drugs, blood and blood-forming agents, and cardiovascular system drugs with corresponding interquartile range 34%, 36%, and 42%, respectively. Median was 1.04 for anti-infective drugs for systemic use and the interquartile range was 14%.

Table 16. Distribution of dispensed to written ratios of prescribed medications by ATC groups between January 2012 and September 2015 in Hungary

ATC group	Median	Limits of interquartile range	Interquartile range
Alimentary tract and metabolism (A-group)	1.09	0.88 - 1.22	0.34
Blood and blood forming organs (B-group)	1.09	0.86 - 1.22	0.36
Cardiovascular system (C-group)	1.09	0.84 - 1.26	0.42
Dermatologicals (D-group)	1.08	0.88 - 1.25	0.37
Genitourinary system and sex hormones (G-group)	1.07	0.83 - 1.24	0.41
Systemic hormonal preparations* (H-group)	1.06	0.93 - 1.16	0.23
Antiinfectives for systemic use (J-group)	1.04	0.96 - 1.10	0.14
Musculoskeletal system (M-group)	1.07	0.89 - 1.18	0.29
Nervous system (N-group)	1.07	0.87 - 1.19	0.32
Respiratory system (R-Group)	1.07	0.88 - 1.20	0.32
Sensory organs (S-group)	1.05	0.84 - 1.22	0.38
Various (V-group)	1.10	0.79 - 1.43	0.64
Altogether^	1.08	0.87 - 1.22	0.35

**** Sex hormones and insulin were excluded.***

^ "Antineoplastic and immunomodulating agents" and "Antiparasitic products, insecticides, and repellents" were not investigated.

Results of the Kolmogorov-Smirnov test and data transformation.

Kolmogorov-Smirnov test of normality is presented in Table 17. It shows deviations of SDWRs from the normal distribution before and after data transformation. Before transformation p-value was less than 0.05 for all ATC groups indicating a difference in their distribution from the normal distribution. However, after data transformation, the P-value for the majority of ATC groups became more than 0.05 indicating no differences in their distribution from the normal distribution. For the total practice deviation (D) was 0.096, p<0.001 before transformation. After transformation D became 0.002, p=0.200 indicating a normal distribution for the transformed data.

Table 17. Kolmogorov-Smirnov test of normality for various ATC drug groups with deviations of distribution of SDWRs parameters from normal distribution before and after transformation

ATC group	Non-transformed SDWR		Box-Cox transformed SDWR	
	D	p-value	D	p-value
Alimentary tract and metabolism (A-group)	0.097543	<0.001	0.001973	0.200
Blood and blood forming organs (B-group)	0.099504	<0.001	0.002017	0.200
Cardiovascular system (C-group)	0.088931	<0.001	0.002375	0.200
Dermatologicals (D-group)	0.049958	<0.001	0.004532	0.004
Genitourinary system and sex hormones (G-group)	0.071367	<0.001	0.006203	<0.001
Systemic hormonal preparations* (H-group)	0.106909	<0.001	0.004013	0.019
Antiinfectives for systemic use (J-group)	0.171842	<0.001	0.001804	0.200
Musculoskeletal system (M-group)	0.090163	<0.001	0.001888	0.200
Nervous system (N-group)	0.100263	<0.001	0.002051	0.200
Respiratory system (R-Group)	0.078050	<0.001	0.002256	0.200
Sensory organs (S-group)	0.059144	<0.001	0.008493	<0.001
Various (V-group)	0.037208	<0.001	0.021532	<0.001
Altogether^	0.095995	<0.001	0.002128	0.200

**** Sex hormones and insulin were excluded.***

^ "Antineoplastic and immunomodulating agents" and "Antiparasitic products, insecticides, and repellents" were not investigated.

Histograms of the standardized written to dispensed ratios before and after Box-Cox data transformation by ATC group for adults in Hungary for the period 2012-2015.

Figure 1 ATC A (Alimentary tract and metabolism) group of drugs

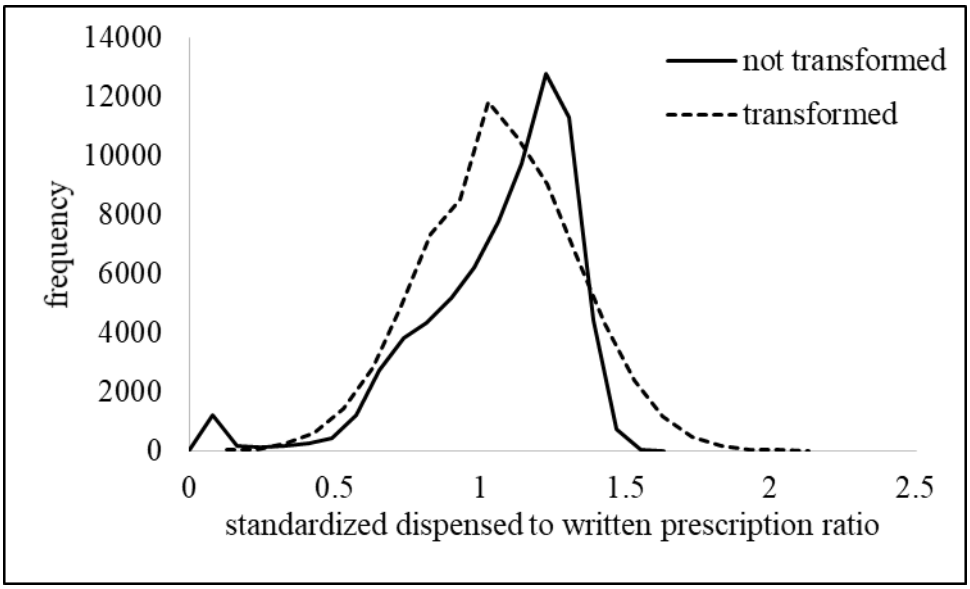


Figure 2 ATC B (Blood and blood-forming organs) group of drugs

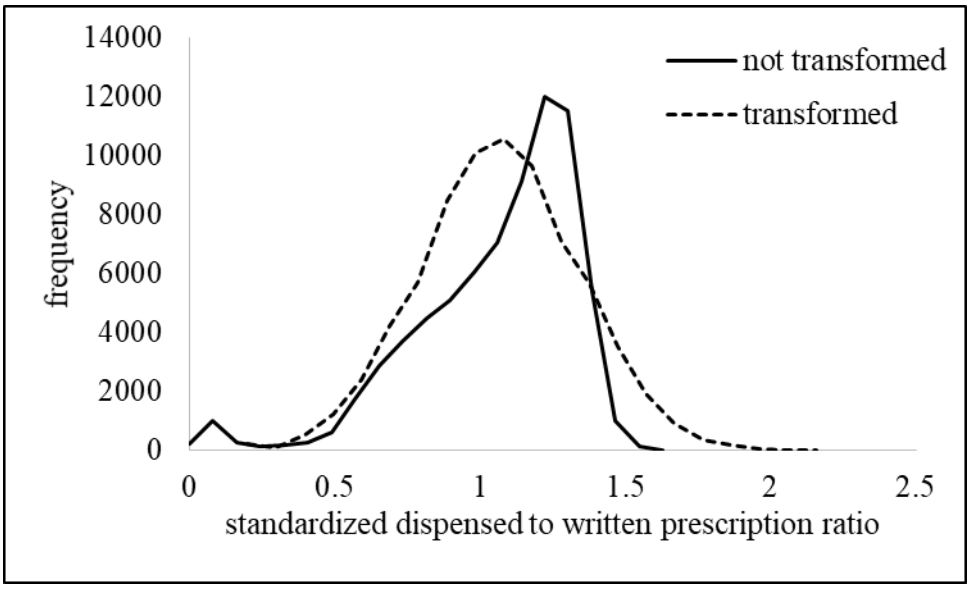


Figure 3 ATC C (Cardiovascular system) group of drugs

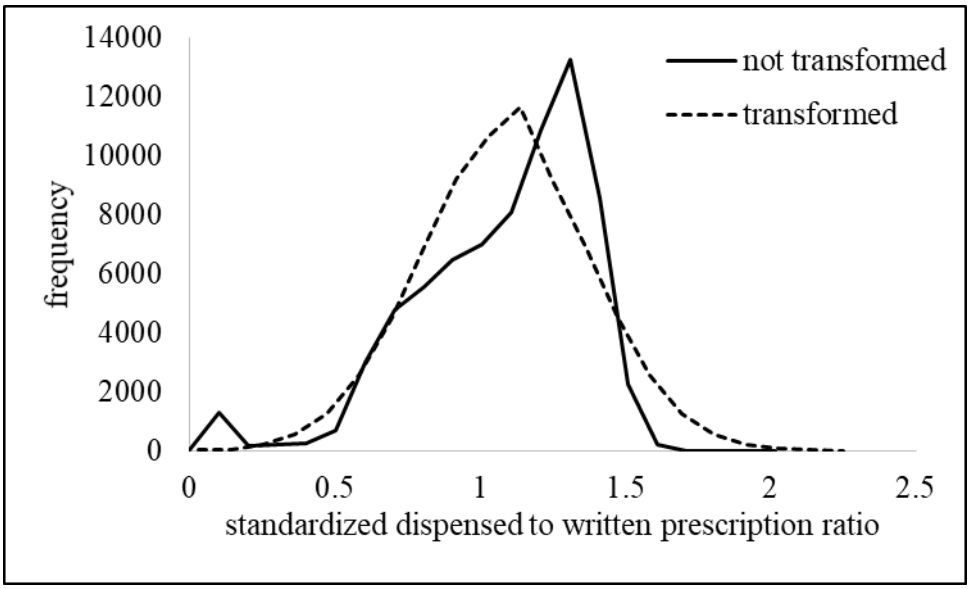


Figure 4 ATC D (Dermatologicals) group of drugs

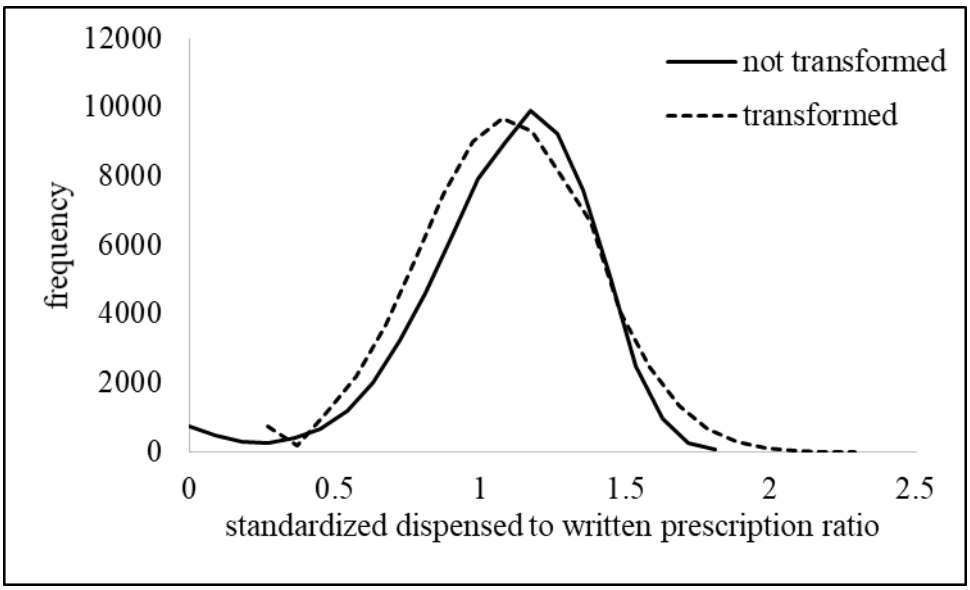


Figure 5 ATC G (Genitourinary system and sex hormones) group of drugs

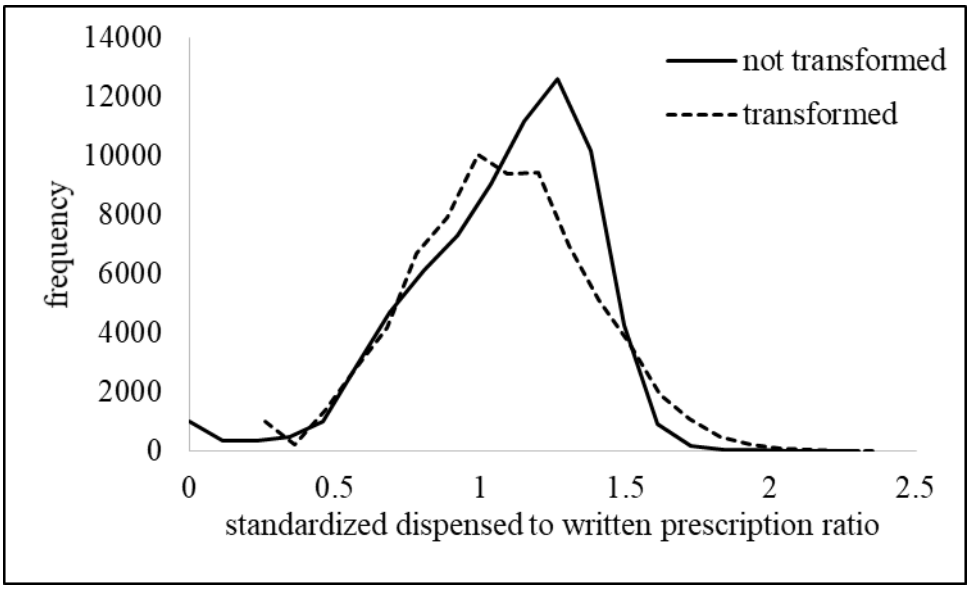
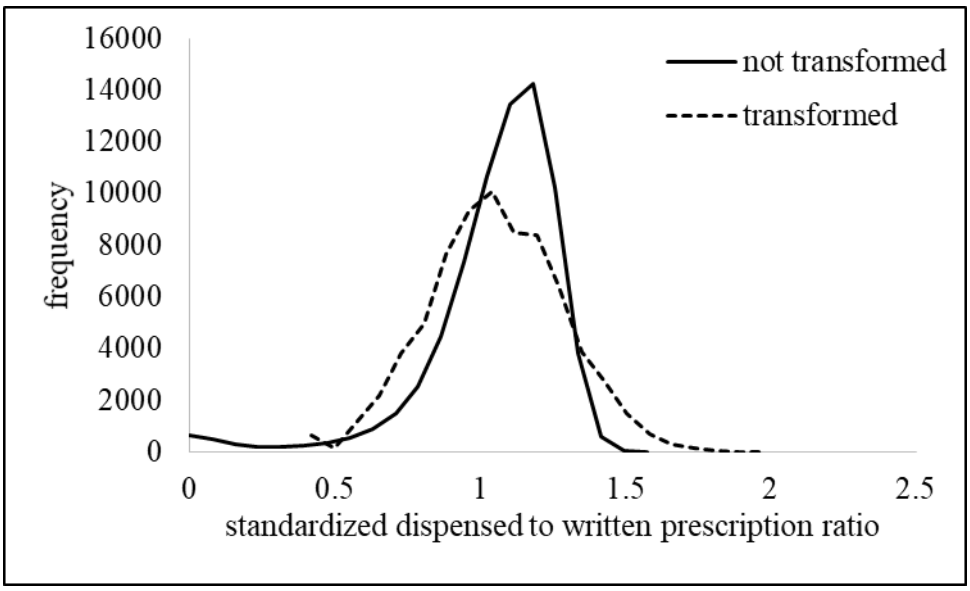


Figure 6 ATC H (Systemic hormonal preparations*) group of drugs



** Sex hormones and insulin were excluded*

Figure 7 ATC J (Antiinfectives for systemic use) group of drugs

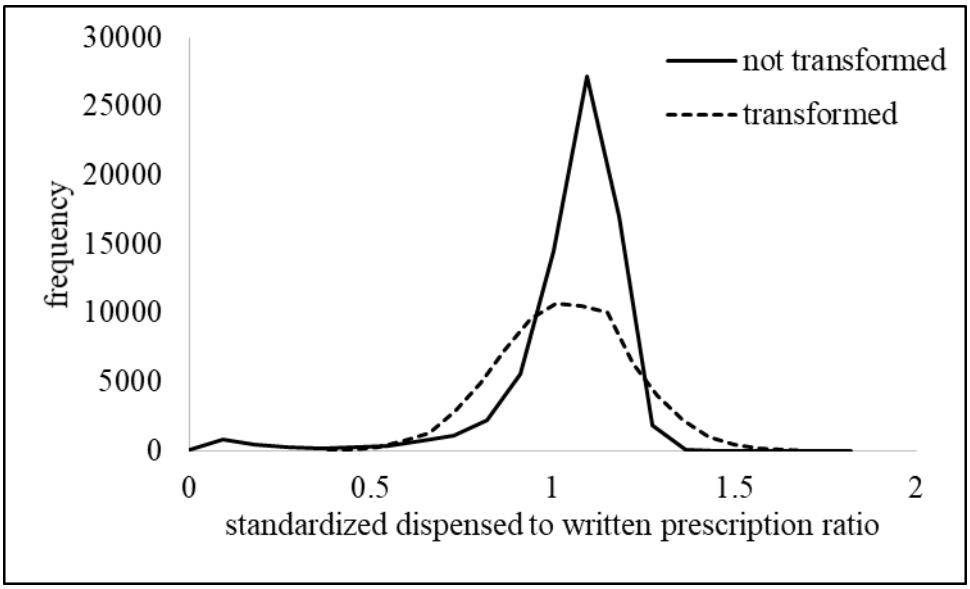


Figure 8 ATC M (Musculoskeletal system) group of drugs

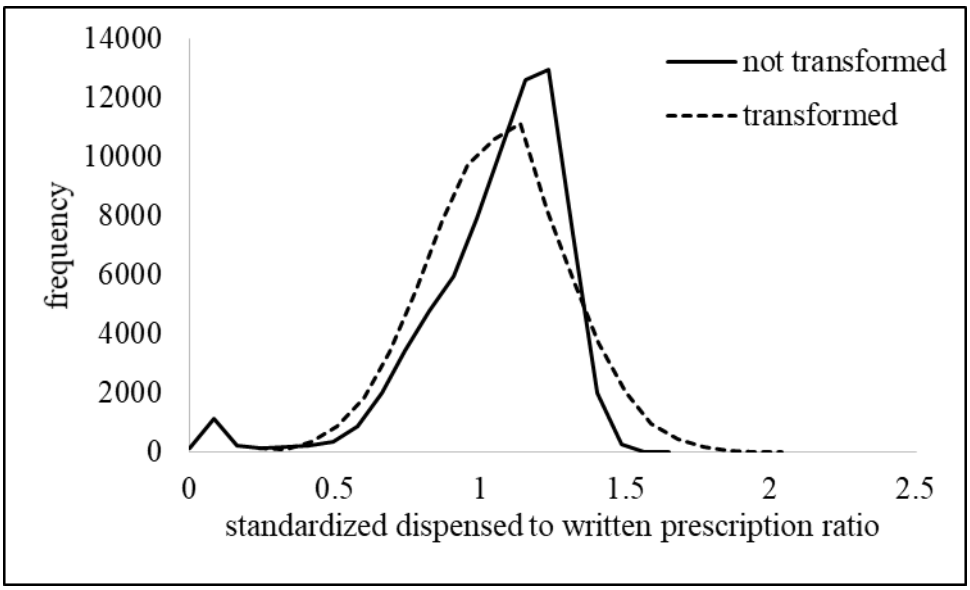


Figure 9 ATC N (Nervous system) group of drugs

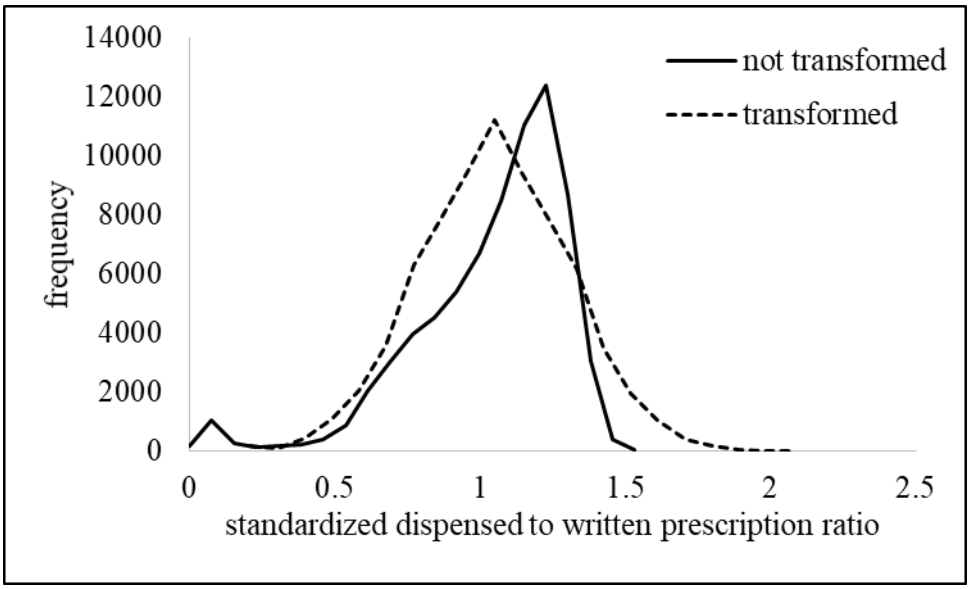


Figure 10 ATC R (Respiratory system) group of drugs

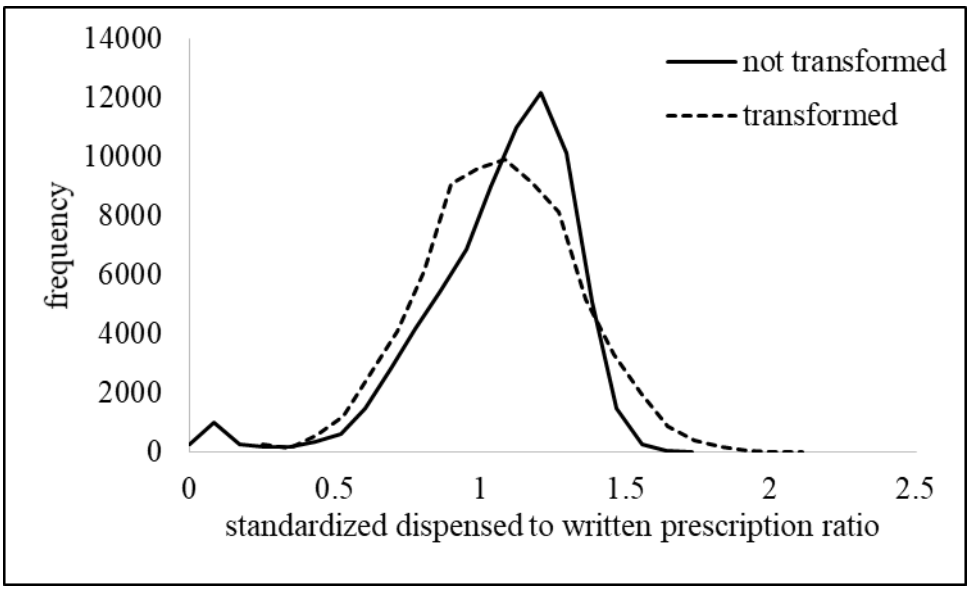


Figure 11 ATC S (Sensory organs) group of drugs

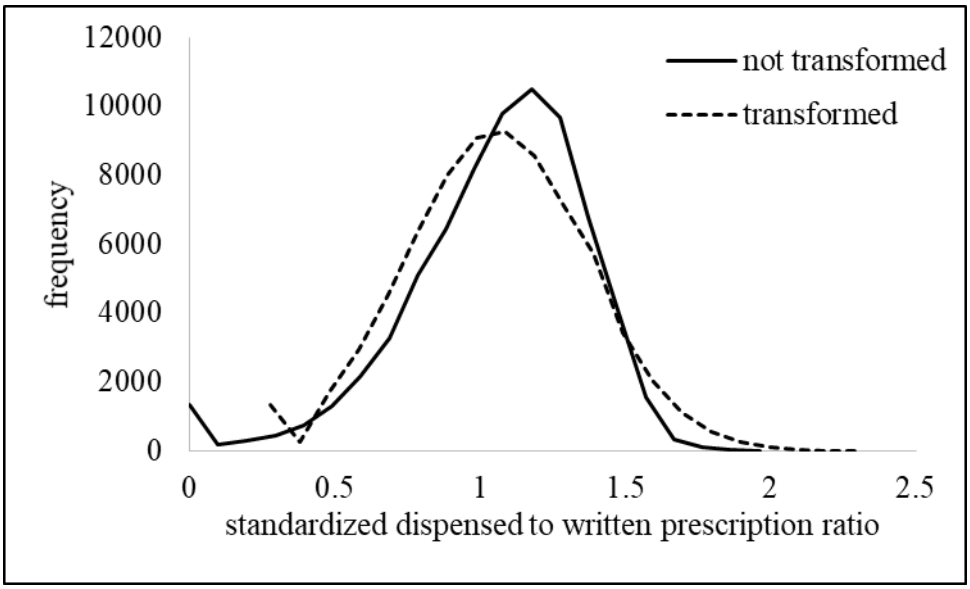


Figure 12 ATC V (Various) group of drugs

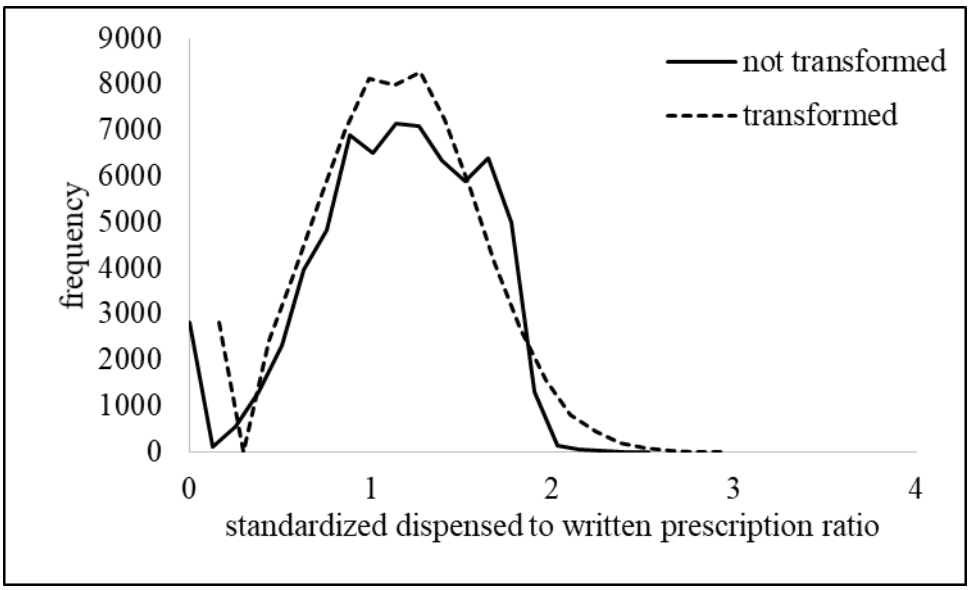
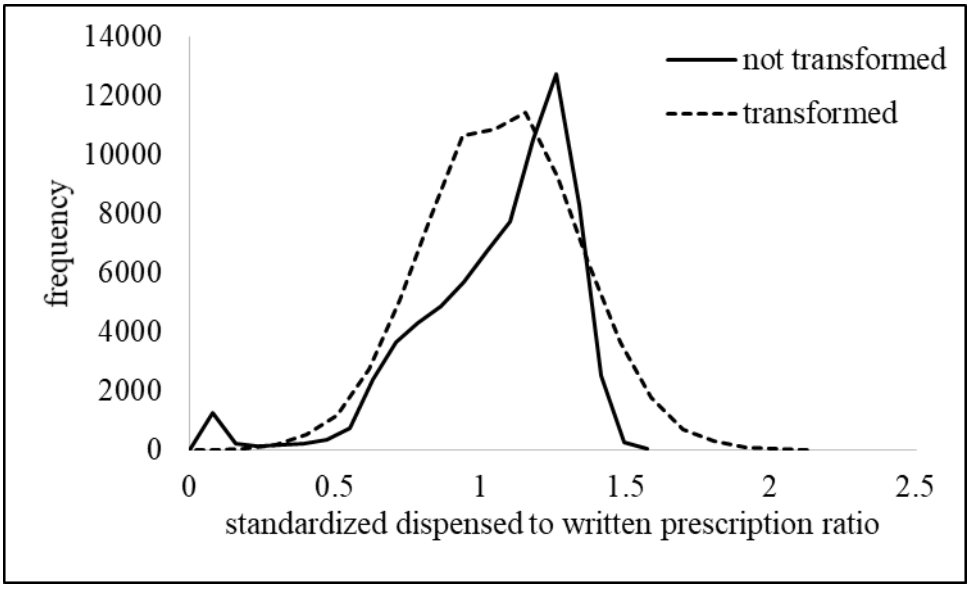


Figure 13 All ATC groups (total practice) of medicines excluding “Antineoplastic and immunomodulating agents” and “Antiparasitic products, insecticides, and repellents”



3.2 Predictors of nonadherence among adults for the total practice in Hungary

Table 18 summarizes results of the generalized linear regression model. The results showed that there was an inverse association between SDWRs and relative education of patients [b=-0.440, 95%CI: -0.468;-0.413], vacancy of the GMP [b= -0.193, 95%CI: -0.204;-0.182], and living in urban areas [b= -0.099, 95%CI: -0.103;-0.094]. A better SDWRs was noted for GMPs running in a relatively smaller localities [$b_{X\text{-}800}$= 0.052, 95%CI: 0.041; 0.063, $b_{801\text{-}1200}$= 0.031, 95%CI: 0.025; 0.037, $b_{1201\text{-}1600}$= 0.017, 95%CI: 0.013; 0.022] compared to those running in larger localities [$b_{2001\text{-}X}$= -0.014, 95%CI: -0.019;-0.009]. The geographical location of the county was an important determinant. The generalized linear regression coefficient showed that living in urban areas, vacancy of the GMP, and higher levels of education of the clients were the major determinants associated with reduced levels of SDWRs.

Table 18. Generalized linear regression modeling^ to assess the associations between general medical practice (GMP) characteristics and SDWRs* among Hungarian adults for the period from January 2012 to September 2015

Variables	**Regression coefficient [95%CI]**
Standardized relative education**	-0.440 [-0.468;-0.413]
Vacant GP position / filled GP position	-0.193 [-0.204;-0.182]
Urban / rural	-0.099 [-0.103;-0.094]
X-800 GMP size / 1601-2000 GMP size	0.052 [0.041;0.063]
801-1200 GMP size / 1601-2000 GMP size	0.031 [0.025;0.037]
1201-1600 GMP size / 1601-2000 GMP size	0.017 [0.013;0.022]
2001-X GMP size / 1601-2000 GMP size	-0.014 [-0.019;-0.009]
Baranya county / Budapest	0.083 [0.072;0.093]
Bács-Kiskun county / Budapest	0.056 [0.046;0.067]
Békés county / Budapest	0.023 [0.012;0.033]
Borsod-Abaúj-Zemplén county / Budapest	-0.015 [-0.024;-0.006]
Csongrád county / Budapest	0.021 [0.011;0.032]
Fejér county / Budapest	-0.132 [-0.142;-0.121]
Győr-Moson-Sopron county / Budapest	-0.002 [-0.012;0.008]
Hajdú-Bihar county / Budapest	-0.035 [-0.045;-0.025]
Heves county / Budapest	-0.033 [-0.044;-0.021]
Jász-Nagykun-Szolnok county / Budapest	0.044 [0.033;0.055]
Komárom-Esztergom county / Budapest	0.072 [0.060;0.084]
Nógrád county / Budapest	-0.028 [-0.042;-0.015]
Pest county / Budapest	-0.002 [-0.01;0.006]
Somogy county / Budapest	0.079 [0.068;0.090]
Szabolcs-Szatmár-Bereg county / Budapest	0.074 [0.064;0.084]
Tolna county / Budapest	0.060 [0.047;0.073]
Vas county / Budapest	0.103 [0.091;0.115]
Veszprém county / Budapest	0.006 [-0.006;0.017]
Zala county / Budapest	0.017 [0.005;0.029]

**** Box-Cox transformation***

***** Relative education was used as a standardized continuous parameter***

^ p=0.060 (Pearson chi-square goodness-of-fit test)

Predictors of nonadherence among adults by ATC group in Hungary

Table 19 represents results of the generalized linear regression model (controlled for time) by the ATC group of drugs. It shows effects of characteristics of patients' and GMPs on the SDWRs) between January 2012 and September 2015 among adults in Hungary, indicated by the generalized linear regression coefficient (b) and the corresponding 95%CI. Standardized relative education, vacancy of the GMP, and living in urban areas showed a significant negative association with SDWRs across all ATC groups for the entire period studied. The smaller the size of the population where GMP is operating, the better the SDWRs reported.

Effect of the geographic location of the county on SDWRs across ATC groups was not clear. For instance, a positive association with SDWRs was reported for the entire study period in both Komárom-Esztergom county (with b ranging between 0.019 [95%CI: 0.011; 0.028] for ATC J group and 0.116 [95%CI: 0.102; 0.130] for ATC G group) and Somogy county (with b ranging between 0.058 [95%CI: 0.045; 0.071] for ATC C group and 0.139 [95%CI: 0.126; 0.152] for ATC D group).

In contrast, in Fejér county a significant negative association was reported across all ATC groups for the entire period investigated (with b ranging between -0.066 [95%CI: -0.074;-0.058] for ATC J group and -0.150 [95%CI: -0.162;-0.138] for ATC C group). Yet, other counties reported intermixed results with different ATC groups. For example, in Hajdú-Bihar county, negative association was reported for ATC A, ATC B, ATC C, ATC D, ATC J, ATC M, ATC N, ATC R, and ATC S groups (with b ranging between -0.002 [95%CI: -0.012; 0.008] for ATC B group and -0.061 [95%CI: -0.072;-0.050] for ATC C group). However, a positive association was detected in Hajdú-Bihar county for ATC G, ATC H, and ATC V groups (with b ranging between 0.008 [95%CI: -0.009; 0.026] for ATC V group and 0.012 [95%CI: 0.004; 0.021] for ATC H group).

Table 19. Generalized linear regression model (controlled for time) by ATC group showing effects of characteristics of patients' and GMPs on the standardized* dispensed to written ratios (SDWRs) between January 2012 and September 2015 among adults in Hungary (presented by the generalized linear regression coefficient (b) and the 95% confidence intervals).

Variables	ATC A	ATC B	ATC C	ATC D	ATC G	ATC H	ATC J	ATC M	ATC N	ATC R	ATC S	ATC V
Relative education (standardized continuous parameter)	-0.442 -0.469 -0.415	-0.470 -0.498 -0.442	-0.487 -0.518 -0.457	-0.216 -0.247 -0.184	-0.493 -0.525 -0.461	-0.309 -0.334 -0.285	-0.091 -0.111 -0.072	-0.320 -0.346 -0.295	-0.456 -0.482 -0.430	-0.446 -0.473 -0.419	-0.299 -0.332 -0.266	-0.266 -0.316 -0.216
Vacant GP position / filled GP position	-0.186- 0.197 -.0.176	-0.184 -0.195 -0.172	-0.211 -0.223 -0.199	-0.190 -0.202 -0.177	-0.182 -0.195 -0.170	-0.134 -0.144 -0.125	-0.128 -0.136 -0.120	-0.178 -0.188 -0.168	-0.179 -0.189 -0.168	-0.185 -0.196 -0.174	-0.196 -0.209 -0.182	-0.171 -0.192 -0.151
Urban / rural	-.099 -0.104 -0.095	-0.090 -0.094 -0.085	-0.100 -0.105 -0.095	-0.078 -0.084 -0.073	-0.081 -0.086 -0.075	-0.050 -0.054 -0.046	-0.030 -0.033 -0.026	-0.093 -0.097 -0.088	-0.099 -0.104 -0.095	-0.096 -0.101 -0.092	-0.075 -0.081 -0.069	-0.050 -0.059 -0.042
X-800 GMP size / 1601-2000 GMP size	0.051 0.040 0.062	0.027 0.016 0.038	0.058 0.046 0.070	0.046 0.033 0.059	0.031 0.018 0.045	0.021 0.011 0.031	-0.016 -0.024 -0.008	0.049 0.039 0.059	0.045 0.034 0.055	0.045 0.34 0.056	0.027 0.013 0.041	0.008 -0.014 0.030
801-1200 GMP size / 1601-2000 GMP size	0.028 0.022 0.034	0.017 0.011 0.023	0.034 0.028 0.041	0.022 0.015 0.028	0.030 0.023 0.037	0.026 0.021 0.032	-0.012 -0.017 -0.008	0.025 0.020 0.031	0.029 0.023 0.035	0.029 0.023 0.035	0.015 0.008 0.022	0.016 0.005 0.027
1201-1600 GMP size / 1601-2000 GMP size	0.016 0.012 0.021	0.011 0.006 0.015	0.021 0.016 0.026	0.015 0.009 0.020	0.016 0.011 0.021	0.015 0.011 0.019	-0.006 -0.009 -0.002	0.012 0.008 0.016	0.014 0.010 0.018	0.014 0.010 0.019	0.013 0.008 0.019	0.022 0.014 0.030
2001-X GMP size / 1601-2000 GMP size	-0.016 -0.021	-0.013 -0.018	-0.013 -0.018	-0.027 -0.033	-0.022 -0.028	-0.015 -0.020	-0.004 -0.007	-0.013 -0.018	-0.014 -0.019	-0.017 -0.023	-0.019 -0.025	-0.013 -0.022

Variables	ATC A	ATC B	ATC C	ATC D	ATC G	ATC H	ATC J	ATC M	ATC N	ATC R	ATC S	ATC V
	-0.011	-0.008	-0.007	-0.021	-0.016	-0.011	0.000	-0.008	-0.009	-0.012	-0.012	-0.004
Baranya county / Budapest	0.080 0.070 0.091	0.108 0.097 0.119	0.089 0.078 0.101	0.024 0.012 0.037	0.074 0.062 0.086	0.014 0.005 0.023	0.021 0.013 0.029	0.077 0.067 0.086	0.079 0.069 0.089	0.023 0.013 0.033	-0.008 -0.021 0.005	-0.020 -0.039 -0.002
Bács-Kiskun county / Budapest	0.059 0.049 0.069	0.066 0.056 0.076	0.044 0.032 0.055	0.078 0.066 0.090	0.047 0.035 0.059	0.066 0.057 0.075	0.089 0.082 0.097	0.073 0.063 0.086	0.057 0.047 0.067	0.055 0.045 0.065	0.053 0.041 0.065	0.012 -0.006 0.031
Békés county / Budapest	0.052 0.041 0.063	0.054 0.042 0.065	-0.000 -0.013 0.012	0.083 0.071 0.096	0.049 0.036 0.061	0.052 0.042 0.061	0.053 0.045 0.061	0.049 0.039 0.060	0.043 0.033 0.054	0.011 0.001 0.022	0.040 0.027 0.053	0.083 0.063 0.103
Borsod-Abaúj-Zemplén county / Budapest	0.010 0.001 0.018	0.035 0.026 0.044	-0.031 -0.040 -0.021	-0.054 -0.064 -0.044	0.031 0.020 0.041	-0.017 -0.025 -0.009	-0.029 -0.036 -0.023	0.004 -0.004 0.012	0.003 -0.006 0.011	-0.027 -0.035 -0.018	-0.018 -0.029 -0.007	-0.040 -0.056 -0.024
Csongrád county / Budapest	0.029 0.019 0.039	0.030 0.020 0.041	0.010 -0.001 0.022	-0.031 -0.043 -0.019	0.013 0.000 0.025	0.037 0.027 0.046	0.049 0.042 0.057	0.038 0.028 0.047	0.026 0.016 0.036	0.021 0.011 0.031	0.027 0.014 0.039	0.043 0.024 0.061
Fejér county / Budapest	-0.128- 0.139 -0.118	-0.119 -0.130 -0.108	-0.150 -0.162 -0.138	-0.091 -0.104 -0.079	-0.114 -0.126 -0.101	-0.088 -0.097 -0.079	-0.066 -0.074 -0.058	-0.103 -0.113 -0.093	-0.112 -0.122 -0.102	-0.131 -0.142 -0.121	-0.091 -0.104 -0.078	-0.127 -0.146 -0.107
Győr-Moson-Sopron county / Budapest	0.014 0.004 0.024	0.022 0.0110.03 2	-0.030 -0.041 -0.018	0.012 0.000 0.024	0.005 -0.007 0.018	0.020 0.011 0.029	0.062 0.055 0.070	0.040 0.030 0.049	0.018 0.008 0.028	0.000 -0.011 0.010	0.006 -0.007 0.018	0.048 0.030 0.067
Hajdú-Bihar county / Budapest	-0.012 -0.021	-0.002 -0.012	-0.061 -0.072	-0.018 -0.030	0.020 0.009	0.012 0.004	-0.013 -0.021	-0.004 -0.013	-0.004 -0.013	-0.031 -0.041	-0.022 -0.034 - 0.010	0.008 -0.009

Variables	ATC A	ATC B	ATC C	ATC D	ATC G	ATC H	ATC J	ATC M	ATC N	ATC R	ATC S	ATC V
	-0.002	0.008	-0.050	-0.007	0.032	0.021	-0.006	0.006	0.006	-0.021		0.026
	-0.006	0.003	-0.045	-0.038	-0.007	-0.032	-0.056	-0.036	-0.016	-0.030	-0.052	-0.031
Heves county / Budapest	-0.017	-0.009	-0.058	-0.051	-0.021	-0.042	-0.065	-0.047	-0.027	-0.041	-0.066	-0.051
	0.006	0.015	-0.033	-0.024	0.006	-0.021	-0.048	-0.025	-0.005	-0.019	-0.038	-0.010
	0.059	0.069	0.042	0.010	0.083	0.077	-0.005	0.028	0.054	0.023	0.017	0.024
Jász-Nagykun-Szolnok county / Budapest	0.048	0.057	0.030	-0.003	0.071	0.067	-0.013	0.018	0.043	0.012	0.003	0.004
	0.070	0.080	0.054	0.023	0.096	0.086	0.003	0.039	0.064	0.034	0.030	0.043
	0.085	0.102	0.066	0.035	0.116	0.076	0.019	0.079	0.064	0.077	0.028	0.109
Komárom-Esztergom county / Budapest	0.073	0.090	0.052	0.021	0.102	0.066	0.011	0.068	0.053	0.065	0.014	0.087
	0.097	0.114	0.079	0.049	0.130	0.087	0.028	0.090	0.076	0.089	0.043	0.131
	-0.012	-0.006	-0.021	-0.074	-0.008	-0.028	-0.044	-0.035	-0.031	-0.069	-0.031	0.035
Nógrád county / Budapest	-0.025	-0.020	-0.036	-0.089	-0.024	-0.039	-0.053	-0.047	-0.044	-0.082	-0.047	0.010
	0.001	0.008	-0.006	-0.058	0.008	-0.016	-0.034	-0.022	-0.018	-0.056	-0.014	0.060
	0.004	0.006	-0.011	-0.007	0.008	-0.005	0.015	0.007	0.003	0.002	0.005	0.046
Pest county / Budapest	-0.004	-0.002	-0.020	-0.017	-0.001	-0.012	0.009	0.000	-0.005	-0.005	-0.005	0.031
	0.012	0.014	-0.003	0.002	0.018	0.002	0.021	0.015	0.010	0.010	0.015	0.060
	0.095	0.107	0.058	0.139	0.063	0.073	0.115	0.102	0.076	0.087	0.098	0.082
Somogy county / Budapest	0.083	0.096	0.045	0.126	0.050	0.063	0.107	0.091	0.066	0.075	0.084	0.061
	0.106	0.119	0.071	0.152	0.077	0.083	0.123	0.112	0.087	0.098	0.111	0.103
	0.094	0.123	0.075	0.017	0.107	0.055	0.032	0.075	0.081	0.049	0.021	0.083
Szabolcs-Szatmár-Bereg county / Budapest	0.084	0.113	0.064	0.005	0.095	0.046	0.025	0.066	0.072	0.039	0.008	0.065
	0.104	0.133	0.087	0.029	0.119	0.064	0.040	0.085	0.091	0.059	0.033	0.101
	0.068	0.112	0.044	0.066	0.086	0.041	0.090	0.090	0.053	0.037	0.064	-0.057
Tolna county / Budapest	0.055	0.099	0.030	0.051	0.071	0.030	0.081	0.078	0.041	0.024	0.048	-0.080

Variables	ATC A	ATC B	ATC C	ATC D	ATC G	ATC H	ATC J	ATC M	ATC N	ATC R	ATC S	ATC V
	0.081	0.125	0.059	0.081	0.101	0.053	0.099	0.102	0.066	0.050	0.080	-0.034
	0.102	0.114	0.104	0.034	0.065	0.004	0.035	0.101	0.084	0.084	-0.010	0.057
Vas county / Budapest	0.90	0.102	0.090	0.020	0.051	-0.007	0.026	0.090	0.073	0.072	-0.025	0.034
	0.114	0.127	0.117	0.048	0.079	0.015	0.044	0.112	0.096	0.096	-0.005	0.079
	0.010	0.009	-0.014	0.092	-0.002	0.020	0.049	0.039	0.016	0.016	0.022	0.072
Veszprém county / Budapest	-0.001	-0.003	-0.026	0.079	-0.015	0.010	0.041	0.029	0.005	0.005	0.008	0.051
	0.022	0.020	-0.001	0.105	0.012	0.030	0.058	0.050	0.027	0.027	0.035	0.093
	0.050	0.038	-0.019	0.093	0.029	0.025	0.057	0.060	0.048	0.037	0.060	-0.005
Zala county / Budapest	0.038	0.026	-0.032	0.079	0.015	0.014	0.048	0.048	0.037	0.025	0.046	-0.027
	0.062	0.051	-0.005	0.107	0.043	0.035	0.066	0.071	0.060	0.049	0.075	0.017
P-value for goodness of fit (Pearson Chi- square)	0.059	0.063	0.074	0.081	0.083	0.047	0.032	0.051	0.055	0.058	0.088	0.188

** Box-Cox transformation*

3.3 Evaluation of the SHCP

Demographic characteristics of the intervention area and Hungary.

Table 20 shows the demographic characteristics for the population in the intervention area and Hungary in 2012Q1 (before intervention) and in 2015Q3 (after intervention). In 2012Q1, 33,101 adults aged 18 years and above were in the intervention area. 46.1% were young adults aged 18-44 years old, 33.2% were middle-aged adults (45-64 years old) and 20.7% were elderly adults aged 65 years and above, 47.9% were males, and 5.8% were with exemption certificates in the intervention area. Distribution of age in the intervention area was similar to that of the national distribution before the intervention. However, the chi-square test showed significant differences in this distribution after the intervention. Overrepresentation of males and adults with exemption certificates was noted in the intervention area. The total population of Hungary was 7,886,662 in 2012Q1, and 7,745,112 in 2015Q3.

By end of the investigated period, 57.9% (18,833) of the adults in the intervention area have participated in the assessment of health status organized in the programme and 95.0% of them were referred to health care professionals working in the GPCs.

Table 20. Demographic characteristics of the population in the intervention area and Hungary

Patient characteristics		**Intervention area % (N)**	**Hungary % (N)**	**P-value***
First-quarter of 2012				
Age groups (years)	18-44	46.1% (15,265)	46.5% (3,667,334)	0.340
	45-64	33.2% (10,973)	33.0% (2,602,749)	
	65 and above	20.7% (6,863)	20.5% (1,616,579)	
Sex	Male	47.9% (15,855)	46.7% (3,679,137)	<0.001
	Female	52.1% (17,246)	53.3% (4,207,525)	
Exemption certificate	Yes	5.8% (1,933)	3.2% (251,027)	<0.001
	No	94.2% (31,168)	96.8% (7,635,635)	
Altogether		100% (33,101)	100% (7,886,662)	-
Third-quarter of 2015				
Age groups (years)	18-44	45.4% (14,690)	44.6% (3,451,254)	<0.001
	45-64	32.5% (10,499)	33.3% (2,578,267)	
	65 and above	22.1% (7,133)	22.2% (1,715,591)	
Sex	Male	47.8% (15,449)	46.7% (3,619,811)	<0.001
	Female	52.2% (16,873)	53.3% (4,125,301)	
Exemption certificate	Yes	5.3% (1,718)	2.5% (194,678)	<0.001
	No	94.7% (30,604)	97.5% (7,550,434)	
Altogether		100% (32,322)	100% (7,745,112)	-

**** Chi-square test***

Dispensed to written ratios by patient sociodemographic characteristics in Hungary

In 2012Q1, overall DWRs were 69.3% (Table 21). However, in 2015Q3 DWR was reduced to 60.8%. No significant differences were noted between males and females before and after the intervention. Across age groups, elderly adults 65 years and above reported better adherence in both periods [71.2% in 2012Q1 and 62.4% in 2015Q3] while middle-aged adults reported the lowest rate [67.2% in 2012Q1 and 58.6% in 2015Q3]. Adherence was significantly higher among patients holding exemption certificates [80.1% in 2012Q1 and 75.8% in 2015Q3] compared to those without exemption certificates [67.9% in 2012Q1 and 59.2% in 2015Q3]. Reduction in DWRs was detected in every socioeconomic stratum and was shown to be significant when checked by the chi-square test ($p<0.001$).

Table 21. Dispensed to written ratios by patient sociodemographic characteristics in Hungary before (2012Q1) and after the intervention (2015Q3)

patient characteristics		**Prescriptions before intervention**			**Prescriptions after intervention**			
		Written	**Dispensed**	**Dispensed ratio (%)**	**Written**	**Dispensed**	**Dispensed ratio (%)**	**P-value***
Age groups (years)	18-44	2,879,000	1,952,263	67.8	2,525,076	1,529,643	60.6	<0.001
	45-64	11,732,996	7,889,604	67.2	10,874,787	6,369,987	58.6	<0.001
	65 and above	15,190,426	10,822,025	71.2	14,899,896	9,304,872	62.4	<0.001
Sex	Male	11,689,243	8,051,849	68.9	11,158,720	6,711,249	60.1	<0.001
	Female	18,113,179	12,612,043	69.6	17,141,039	10,493,253	61.2	<0.001
Exemption certificate	Yes	3,499,275	2,804,373	80.1	2,709,909	2,054,121	75.8	<0.001
	No	26,303,147	17,859,519	67.9	25,589,850	15,150,381	59.2	<0.001
Altogether		29,802,422	20,663,892	69.3	28,299,759	17,204,502	60.8	<0.001

Chi-square test

Dispensed to written ratios by ATC group of drugs in Hungary

The observed DWRs were highest for anti-infective drugs for systemic use (ATC J) [80.1% in 2012Q1 and 76.1% in 2015Q3]. The lowest observed DWRs were reported for various drug groups (ATC V) [57.6% in 2012Q1] and for cardiovascular system agents (ATC C) [55.3% in 2015Q3] as shown in Table 22. Overall, there was a statistically significant reduction in DWRs in every ATC group over time (excluding the ATC V group of drugs) as indicated by the chi-square test ($p<0.001$).

Table 22. Dispensed to written ratios by ATC drug group before (2012Q1) and after the intervention (2015Q3)

ATC group	Prescriptions before intervention			Prescriptions after intervention			
	Written	Dispensed	Dispensed ratio (%)	Written	Dispensed	Dispensed ratio (%)	P-value*
Alimentary tract and metabolism	4,831,608	3,504,498	72.5	4,596,768	3,042,485	66.2	<0.001
Blood and blood forming organs	2,187,096	1,636,426	74.8	1,970,831	1,333,257	67.6	<0.001
Cardiovascular system	15,311,478	10,057,565	65.7	14,642,073	8,094,617	55.3	<0.001
Dermatologicals	289,326	189,229	65.4	300,258	176,043	58.6	<0.001
Genitourinary system and sex hormones	210,643	152,318	72.3	219,692	143,770	65.4	<0.001
Systemic hormonal preparations	323,519	244,649	75.6	354,554	259,049	73.1	<0.001
Antiinfectives for systemic use	1,208,603	968,386	80.1	666,892	507,756	76.1	<0.001
Musculoskeletal system	1,851,092	1,324,670	71.6	2,093,343	1,389,095	66.4	<0.001
Nervous system	1,921,312	1,419,382	73.9	1,845,835	1,255,821	68.0	<0.001
Respiratory system	1,488,397	1,042,395	70.0	1,448,618	901,644	62.2	<0.001
Sensory organs	128,978	95,371	73.9	97,004	63,204	65.2	<0.001
Various	50,370	29,003	57.6	63,891	37,761	59.1	<0.001
Altogether	29,802,422	20,663,892	69.3	28,299,759	17,204,502	60.8	<0.001

Chi-square test

Dispensed to written ratios by patient sociodemographic characteristics in the intervention area

In 2012Q1, number of prescriptions written was 134,470 and number of dispensed prescriptions was 98,213 (Table 23). The observed DWR was 73.0%. Slight differences were observed by gender and age on adherence. A significant difference was observed between clients with exemption certificates and those without exemption certificates. In 2015Q3, after the intervention, The DWR was reduced to 68.7% [133,689 prescriptions were written and 91,881prescriptions were dispensed]. The effects of sex and exemption certificates remained unchanged after the intervention. However, variation in DWR across age groups became very prominent [range was 72.2% - 73.9% before and became 66.5% - 70.8% after the intervention].

Table 23. Dispensed to written ratios by patients sociodemographic characteristics in the intervention area before (2012Q1) and after the intervention (2015Q3)

Patient characteristics		**Prescriptions before intervention**			**Prescriptions after intervention**			**Change of dispensed ratio**
		Written	Dispensed	Dispensed ratio (%)	Written	Dispensed	Dispensed ratio (%)	P-value*
Age groups (years)	18-44	15,808	11,475	72.6	15,670	10,425	66.5	<0.001
	45-64	55,673	40,197	72.2	54,909	36,756	66.9	<0.001
	65 and above	62,989	46,541	73.9	63,110	44,700	70.8	<0.001
Sex	Male	51,818	37,999	73.3	51,349	35,103	68.4	<0.001
	Female	82,652	60,214	72.9	82,340	56,778	69.0	<0.001
Exemption certificate	Yes	24,372	20,656	84.8	22,505	18,617	82.7	0.077
	No	110,098	77,557	70.4	111,184	73,264	65.9	<0.001
Altogether		134,470	98,213	73.0	133,689	91,881	68.7	<0.001

** Chi-square test*

Dispensed to written ratios by ATC drug group in the intervention area

There was a significant variation across ATC drug groups. Before the intervention, the highest DWR was 81.8% reported for systemic hormonal preparations (ATC H) while the lowest was 61.2% and 68.8% reported for various drug group category and cardiovascular system agents, respectively. After the intervention, systemic hormonal preparation remained the highest with 81.2% and cardiovascular agents reported the lowest DWR at 62.0% (Table 24). ATC-specific DWRs wide variability remained unchanged.

Table 24. Dispensed to written ratios by ATC drug group in the intervention area before (2012Q1) and after the intervention (2015Q3)

ATC group	**Prescriptions before intervention**			**Prescriptions after intervention**			**Change of dispensed ratio**
	Written	Dispensed	Dispensed ratio (%)	Written	Dispensed	Dispensed ratio (%)	P-value*
Alimentary tract and metabolism	20,238	15,326	75.7	20,536	15,336	74.7	0.356
Blood and blood forming organs	10,498	8,209	78.2	9,908	7,569	76.4	0.272
Cardiovascular system	64,495	44,383	68.8	65,030	40,319	62.0	0.000
Dermatologicals	1,524	1,141	74.9	1,695	1,189	70.1	0.231
Genitourinary system and sex hormones	835	661	79.2	1,098	834	76.0	0.552
Systemic hormonal preparations	1,662	1,360	81.8	1,796	1,459	81.2	0.886
Antiinfectives for systemic use	6,392	5,212	81.5	3,616	2,906	80.4	0.641
Musculoskeletal system	10,083	7,627	75.6	11,773	8,679	73.7	0.215
Nervous system	9,192	7,133	77.6	9,408	7,302	77.6	0.993
Respiratory system	8,667	6,530	75.3	8,052	5,767	71.6	0.033
Sensory organs	580	445	76.7	535	369	69.0	0.249
Various	304	186	61.2	242	152	62.8	0.851
Altogether	134,470	98,213	73.0	133,689	91,881	68.7	<0.001

**** Chi-square test***

Standardized dispensed to written ratios by ATC drug group in the intervention area

Table 25 below represents variations in SDWRs by the ATC group in the intervention area before and after the intervention and number of additionally dispensed prescriptions which was attributed to the intervention implemented. SDWRs indicated that overall adherence was generally higher in the intervention area than in Hungary for various ATC groups. SDWR for the entire practice was 1.042 in 2012Q1 and increased to 1.108 after the intervention in 2015Q3. When calculated the risk ratio (RR) for SDWRs, this change was shown to be significant [RR= 1.064; 95%CI: 1.054 - 1.073]. An excess number of prescriptions dispensed were 5033.2 in 2015Q3. The most significant impact observed was on both cardiovascular system drugs [RR= 1.062; 95%CI: 1.048-1.077] and alimentary tract and metabolism drugs [RR=1.072; 95%CI: 1.049-1.097] with 2143.5 and 1001.2 excess number of dispensed prescriptions in the intervention area, respectively. In addition, significant positive changes were observed for musculoskeletal drugs [RR=1.041; 95%CI: 1.010-1.074], blood and blood-forming organ drugs [RR=1.077; 95%CI: 1.044-1.111], and drugs of the nervous system [RR= 1.082; 95%CI: 1.047-1.118].

Table 25. Standardized dispensed to written ratios by ATC drug group in the intervention area before (2012Q1) and after the intervention (2015Q3)

ATC groups	**Before intervention**		**After intervention**		**Change of SDWR**	
	SDWR (O/E)*	Excess dispensing	SDWR (O/E)*	Excess dispensing	RR** (95%CI)	Excess dispensing
Alimentary tract and metabolism	1.035 (15,326/14,809.5)	516.5	1.110 (15,336/13,818.3)	1,517.7	1.072 (1.049-1.097)	1,001.2
Blood and blood forming organs	1.042 (8,209/7,878.5)	330.5	1.122 (7,569/6,745.6)	823.4	1.077 (1.044-1.111)	492.9
Cardiovascular system	1.035 (44,383/42,880.5)	1,502.5	1.099 (40,319/36,673)	3,646	1.062 (1.048-1.077)	2,143.5
Dermatologicals	1.134 (1,141/1,006.4)	134.6	1.168 (1,189/1,017.7)	171.3	1.031 (0.950-1.118)	36.7
Genitourinary system and sex hormones	1.087 (661/608)	53	1.154 (834/722.4)	111.6	1.062 (0.959-1.176)	58.6
Systemic hormonal preparations	1.081 (1,360/1,258.1)	101.9	1.108 (1,459/1,316.8)	142.2	1.025 (0.952-1.104)	40.3

Antiinfectives for systemic use	1.011 (5,212/5,157.1)	54.9	1.052 (2,906/2,763.2)	142.8	1.041 (0.994-1.089)	87.9
Musculoskeletal system	1.042 (7,627/7,320.2)	306.8	1.085 (8,679/7,999.9)	679.1	1.041 (1.010-1.074)	372.3
Nervous system	1.045 (7,133/6,828.7)	304.3	1.130 (7,302/6,461.4)	840.6	1.082 (1.047-1.118)	536.4
Respiratory system	1.147 (6,530/5,693.2)	836.8	1.128 (5,767/5,113.5)	653.5	0.983 (0.949-1.019)	-183.4
Sensory organs	1.031 (445/431.6)	13.4	1.048 (369/352.1)	16.9	1.017 (0.886-1.167)	3.6
Various	1.057 (186/176.1)	9.9	1.049 (152/144.9)	7.1	0.993 (0.801-1.230)	-2.9
Altogether	1.042 (98,213/94,275.9)	3,937.1	1.108 (91,881/82,910.7)	8,970.3	1.064 (1.054-1.073)	5,033.2

* (O/E): observed/expected number of the prescriptions dispensed.

** $RR=SDWR_{after}/SDWR_{before.}$

4 Discussion

4.1 Prevalence and determinants of primary nonadherence in Hungary

We conducted data analyses on all adults' GMPs operating in Hungary for the calendar years 2012 -2015. The main purpose was to assess primary nonadherence to prescribed regimens and to determine some of the associated factors and their impact on adherence. We used the key indicator of patient care "percentage of drugs actually dispensed" recommended by the WHO to estimate the DWRs of drugs (117). This is the first study in Hungary conducted at the national level which deals with nonadherence to all prescribed medications. Overall, 64.1% of the prescribed medications by GPs were dispensed. Adherence varied across ATC groups with cardiovascular system drugs reported as the lowest at 59.4% and anti-infective agents for systemic use as the highest at 79.1%.

The registered level of nonadherence in Hungary was 35.9%. This prevalence is higher than those reported by other studies. For instance, a study conducted in Canada to assess the incidence of primary nonadherence between 2006 and 2009 found that out of 37,506 prescriptions written, 31.3% were not filled (35). In addition, a study analyzed 195,930 electronic prescriptions in Massachusetts reported that 22.5% of the total prescriptions were not dispensed (24). Moreover, another study conducted in Woonsocket (USA) on 423,616 electronic prescriptions of new medications revealed that 24.0% of the written prescriptions were not filled (95). A study conducted to assess primary nonadherence in Scotland revealed that 14.5% of the patient did not dispense the given prescriptions from the beginning of their treatment course (86). Furthermore, a study analyzed 91,704 electronic prescriptions in Sweden found that primary nonadherence was 2.4% (123).

Impact of patients' demographic characteristics on primary nonadherence

In the Hungarian context, our investigations showed that gender is not a significant determinant of nonadherence. While the results showed some slight variations across age groups, the middle-aged adults' category was shown to be at higher risk of nonadherence. However, possession of an exemption certificate was a major positive determinant of adherence, reflecting the impact of the socioeconomic status of the patients, and the effectiveness of the exemption certificating system. The elderly reported better adherence than younger population probably since elderly people are more aware of their health needs, having one or more chronic conditions, and perceive medications as more beneficial and necessary (7, 66).

Impact of the place of residence on primary nonadherence

This study detected a relationship between place of residence and levels of nonadherence. Living in urban areas was found to have a negative impact on adherence. There is an increasing interest in determining and analyzing effects of place of residence and geographic distribution on adherence to medications (124). Some studies have detected a slight positive association between better adherence and living in urban areas and have attributed this to ease of access to health services and better economic conditions of urban residents (10, 125). In contrast, this study reported lower levels of adherence among urban compared to rural residents. This finding is supported by findings of a study conducted in South Korea to compare adherence to antidiabetic drugs in rural and urban areas and reported higher levels of nonadherence in urban areas (126). Low levels of adherence in urban areas are believed to be attributed to people's socioeconomic, cultural, attitudes and beliefs affecting their behavior and decision concerning their health and use of prescribed regimens (127, 128). Other studies explained this trend by the fact that urban residents have a "busy lifestyle" and working schedule that either cause them to forget taking medications or affect their ability to properly adhere to their regimens (34, 129). In Hungary, this may also be attributed to the poor patient-physician relationship. Given that this forms a major barrier against the adherence of adults in Hungary, further investigations are required to address details behind our findings.

Impact of patient education level on primary nonadherence

Our study indicated that education is an important predictor of levels of adherence. The effect of education on adherence is complex (130) and both knowledge and education largely affect individuals' attitudes and behavior (131). It is expected that higher levels of education will lead to better adherence to regimens. This positive impact was reported in some studies (125, 132), and was attributed to the fact that highly educated people perceive medications as more beneficial and less harmful to health (74). However, our study found a negative association between education and levels of adherence. Our finding is consistent with findings reported by the self-reported "European Social Survey, Round 2" that indicated higher adherence levels among people with lower education levels (19). It is believed that highly educated people hold themselves accountable for their own health and thus more likely to decide whether or not to dispense drugs or to continue medications (133). Furthermore, researches in health psychology demonstrated that educated people display a "high self-esteem" and hence have a tendency to resist given messages or commands and be more critical towards instructions given by health care professionals (134). We believe that this result could reflect

poor communication between patients and their health care providers that outweigh knowing the benefits of the medications leading eventually to nonadherence. However, further investigations are required to address this issue.

Impact of vacancy of the GP position on primary nonadherence

This study indicated that vacancy of the GP position has a negative impact on adherence to medications. (In this setting, vacancy of the GP position means health care service is provided by a temporary contracted GP available at specific times and place.) Changing the prescribing GPs was associated with lower ratios of adherence, a finding which corresponds to findings of a study of Park and colleagues conducted to assess adherence to antihypertensive agents in South Korea at the national level (10). Researches on the field of patient-physician relationship indicated that possibilities of occurrence of nonadherence are likely to be reduced when patients come to know their providers and get familiar with them (135). This is probably attributed to the impact of continuity of care on patient satisfaction and trusts in their physicians that enhances adherence to prescribed regimens and eventually improves the desired therapeutic outcomes (136, 137). In addition, this finding sheds the light on the workforce crisis in PHC in Hungary leading to increased vacant GMPs and its impact on disease prognosis resulting from low adherence (138).

Impact of the geographic location of the county on primary nonadherence

Our study revealed geographic inequalities in adherence to medications. This finding is similar to findings of other studies conducted to assess impact of geographic variation on adherence to chronic regimens in the USA and Italy and likewise reported a significant impact of region and geography on adherence (139, 140). In fact, few studies have focused on effect of geographic dimension on adherence. Our study revealed that county of Fejer has shown a consistent negative association with medication adherence when compared with other counties like Komarom and Somogy which showed positive association over the whole period of time investigated. Indeed, the county in the Hungarian context is an indicator of spatially structured variables other than education level, urbanization, vacancy of the GMP, and socioeconomic situation. This finding can be attributed to variation in the availability of health care services and resources, certain lifestyle and culture, access to health care and health literacy that are well known to impact adherence as documented in the literature (141). Further investigations are required to determine specific context-related factors leading this pattern of nonadherence. Our result demonstrated that effect of geographic location on

adherence was smaller (b ranges between -0.132 [-0.142;-0.121] for Fejér county and 0.103 [0.091; 0.115] for Vas county) than impact of education level [b=-0.440, 95%CI: -0.468;-0.413] and GP vacancy [b= -0.193, 95%CI: -0.204;-0.182] and not greater than impact of the urban environment [b= -0.099, 95%CI: -0.103;-0.094].

Impact of GMP list size on primary nonadherence.

This study demonstrated an association between GMP list size and adherence. GMPs serving more patients and clients have relatively lower rates of adherence. Given that the PHC team usually includes one GP and one practice nurse in Hungary (108), in larger localities serving more people, less time and care will be given to patients thus negatively affecting their adherence. Spending less time with the health care provider is likely to affect both physician decision and patient satisfaction (7). The optimum time is necessary to understand patient complaints, take his history, understand his situation and describe the best possible regimen (142). In addition, it is necessary for the patient to have sufficient time with the GP for proper patient-physician interaction, mutual understanding, comprehension of instructions, and having a good attitude towards doctors and their prescribed regimens as has been documented in the literature (143).

The SHCP

We estimated effectiveness of the SHCP (a multifaceted intervention) in improving adherence to the prescribed medications. In fact, enhancement of adherence was a secondary impact of the newly implemented programme activities conducted to improve overall health outcomes through health promotion, disease prevention, health restoration and rehabilitation of chronically ill individuals in an integrated manner.

The overall impact of the SHCP

The overall increase in sex, age, and exemption certificate- standardized adherence for the prescribed regimens was 6.4%. This improvement is somewhat modest but similar to what was reported in other review studies that revealed a mild improvement in adherence even when the most effective interventions were implemented (144). A meta-analysis of 61 interventions conducted between 1966 and 2000 indicated an increase between 4 to 11% in adherence (84). Yet, a review study in 2005 by Haynes and colleagues concluded that half of the interventions failed to improve health outcomes and even the most effective multifactorial interventions failed to achieve a considerable improvement in adherence (145). Thus, designing and operating the GPC model intervention with the extended activities conducted

in an integrated manner in the programme seems beneficial and likely to foster the adherence further.

Impact of the SHCP on ATC drug groups

The most significant impact of the programme was noted on cardiovascular system drugs and alimentary tract and metabolism drugs (including oral antidiabetic drugs) were 42.6% and 19.9% of the excess dispensed prescription in the Programme were reported, respectively. This finding reflects that patients with diseases of high prevalence were more responsive to the intervention, and receiving more intensive health care services make patients more committed towards adherence to their regimens. In addition, significant enhancement with smaller practical impact was noted for nervous system drugs, blood, and blood-forming organ drugs, and musculoskeletal drugs with 10.7%, 9.8%, and 7.4% excess dispensing were reported, respectively.

Impact of the improved patient-provider relationship on adherence

Patient-provider relationship is an important predictor of adherence (146, 147). Improved communication and counseling among the patients and their health care provider has a positive impact on adherence as has been demonstrated in many studies (148-151). Collaborative communication entails shared mutual understanding, cooperation, and coordination. Furthermore, the providers listen carefully to patients, deliver clear and understandable information about medications, conditions of their patients, and explain concerns and expectations of treatment in addition to interaction with patients in such a way that creates trust in their relationship (150). This is more likely to affect patients' beliefs about his medications and conditions and enhance adherence (60, 152, 153). Interestingly, a meta-analysis of studies conducted between 1949 and 2008 to assess impact of patient-physician communication on drug adherence found that poor communication between health care provider and patient increases risk of nonadherence by 19% (154).

Seasonal variation in adherence in Hungary

Significant differences were noted in DWRs for the national reference data of Hungary between 2012Q1 [which covers the period from January to March] and 2015Q3 [which covers the period from July to September]. This national change was not investigated in our study but kept controlled for through the study design which involved a before-after data analysis. However, seasonal effects on health insurance and reduced number of holders of exemption certificates are expected to be the reason behind this change.

Health promotion activities conducted in the SHCP

Health promotion is a core concept in public health and refers to "enabling people to increase control over and to improve their health" through acting on various health determinants and fostering equity (155). Health promotion is a comprehensive approach that involves different actors in various sectors to improve circumstances essential for health (156) by enhancing community participation, empowerment, equity, and partnership (157). The intervention implemented in the SHCP focused on patient education (especially augmenting health literacy, patient knowledge, skills, and attitude), patients' motivation, enhancing patient-provider communication and interaction to enhance trust and beliefs in health care providers and the given medications, lifestyle changes, and integration of primary health care services.

Patient education

Patient educational interventions are essential to improve adherence to medications. Several studies found a strong association between patient education and adherence (90, 158-160). Such interventions entail education and motivation of patients to make them more informed and empowered (7, 161, 162). Educational interventions need to be built on precise information on health literacy (160), drug utilization (94), and lifestyle practices (34). A meta-analysis of 79 clinical trials conducted between 1995 and 2011 estimated a 5% increase in adherence in interventions that involved cognitive educational elements (163). The main reasons for such improvement include increasing knowledge of patients on importance of the given therapy, better communication between patients and their physicians in addition to increasing understanding of patients to their diseases and conditions (158).

Health literacy

Health education to improve health literacy, knowledge, and life skills enhances individual and community health (60, 155) and is a key factor in improving adherence (42, 91). Health literacy indicates that the client or patient is able to communicate, read, understand, access and use information related to therapy so as to make an informed health decision (58). It also involves that health care providers are able to communicate and convey their messages in a clear and understandable way (58, 160). Unfortunately, results from the International Adult Literacy Survey (IALS) indicated that Hungary has ranked at the lower end of the scale of international literacy (164). Low levels of health literacy are associated with low levels of adherence (57, 71) since it is largely associated with misunderstanding of therapy-related instructions such as labels, dosage, and duration (98). In fact, a systematic review of health

literacy reported that low levels of health literacy results in 3 – 5% increase in the total health care cost annually (165).

Patient motivation

Patient motivation and empowerment have been viewed as key factors in enhancing adherence to regimens. This association was reported in many studies that showed positive outcomes for patient motivations on adherence (153, 166-168). The reason behind this improvement could be due to the fact that involving patients in the treatment process or their motivation to participate in the decision of their treatment strategy increases personal confidence in their abilities, autonomy and facilitate changing their attitude and health behavior including adherence (160, 169). However, a proper description of clients' conditions by health care providers is a prerequisite for motivation and behavioral change (101).

Lifestyle counseling

Knowledge of patients' lifestyle is essential to improve adherence (34). Indeed, adherence to therapeutic agents requires some sort of lifestyle changes to incorporate the recommended regimen into daily activities (47, 168). Healthy lifestyle changes have been shown to be effective in enhancing adherence and therapeutic outcomes (42, 93, 170). In this study, lifestyle counseling as part of various activities performed was carried out by various health care providers each according to their knowledge, specialization, and competences. The aim of this counseling was to increase health literacy (by providing information to patients to increase their awareness and knowledge about their conditions and the given therapy) in order to motivate, support and empower them to improve adherence and use of health care services (115).

Integration of health care services

Integration of health care services is a key issue in enhancing health care outcomes (171, 172), patient safety (173) and making informed health decisions (14). Since nonadherence has a multifactorial etiology that covers individual, social and health care system-related dimensions, integrated work of health care providers remains essential to improve health outcomes (53). In fact, integration of primary health care data, electronic health connectivity among various health care providers within the same cluster and among individual GMP at the national level were prominent features of the SHCP. In the GPC model, the GPC used high quality and information technology, enhanced the partnership between GP team

members and clients, empowered clients, and increased their health literacy and quality of care (115).

4.2 Study implications

High nonadherence to prescribed medications detected in this study contributes substantially to poor disease prognosis. Although this dimension has not been investigated and estimated in our research, a low rate of adherence at 59.4% for cardiovascular system drugs the leading cause of death and the major determinant of life expectancy across European countries, the impact is expected to be great. However, further detailed investigations and relevant interventions are required.

On the other hand, a high number of unfilled prescriptions result in considerable loss of time, work, capacities, and wastage of health care resources. Thus, the detected nonadherence can be assumed as an indicator of poor patient-physician cooperation. Indeed, the wide variation in adherence noted across various GMPs shows that GPs have variable effectiveness in dealing with and managing their clients. In addition, evidence on the weak role of GPs in managing diseases of clients in urban areas and highly educated adult patients is observed. As a result, the monitoring system in PHC for primary medication adherence needs to be established to identify and manage the poorly performing GMPs.

In the SHCP, no training was given to health care professionals on how to educate patients, affect their psychology, and support them and their families to enhance medication adherence. Despite the fact that the programme did not entail specific activities to enhance adherence to medications, the programme confirmed that good patient-physician cooperation marked by massive care of patients through the extension of primary care activities to include preventive services improved adherence.

Although interventions targeting adherence remains the first choice in enhancing adherence to medications (174), our investigations propose that systemic use of indicators such as DWRs should be an important part of any PHC development, reorientation, or reform programme as improvement in adherence could be a secondary effect of any intervention programme that affects patient-physician cooperation (175). Thus DWRs-like measures can be used as an indicator for enhanced patient-physician cooperation in any intervention.

At this point, we would like to emphasize that health care professionals have no adequate information about nonadherence and its prevalence among patients (176, 177). In addition, health care professionals are willing to get feedback on this vital issue so as to know if their

practice needs to be modified (178). Furthermore, due to the established information technology (IT) infrastructures, indicators for routine monitoring are available with no burden of extra costs and can support general medical practice and monitoring activities.

4.3 Strengths and limitations

Our study has got several strengths. Health insurance in Hungary, given solely by the NHIF, is compulsory and overlay more than 96% of the population. The cost of the dispensed prescriptions is shared between patients and the NHIF by health insurance plan (108). Therefore, its data on written and filled prescriptions are credible and can be used to estimate adherence to medications at the national level. In addition, the statistical power was strong and assured by the applied study design.

The SHCP involved a before-after analysis design. Thus, possible confounders -such as socioeconomic status of the clients, therapeutic tools available, and disease severity and disability among the clients- which were not investigated in the statistical analysis could be deemed constant. Potential factors that may have influenced DWRs and variation throughout the country (without being identified and quantified) were controlled for by the study design which used the national reference data. Otherwise, the impact of GPCs on medication adherence could not be predicted and estimated.

Given that more than half of the population in the intervention area had participated in the organized health status assessment and the extra health care services carried out in the GPCs by the end of the programme, about half of the targeted population had achieved some improvement in the specific-DWRs of the intervention area. However, evaluation of the programme through DWRs alone is an underestimation of the effectiveness of the interventions.

Our study has got some limitations. Although estimation of drugs dispensing is an objective process and deemed the most credible method for assessing primary adherence in a well-equipped and integrated health care system, other aspects of adherence such as actual ingestion of the medications and proper utilization of drugs in line with the given guidelines cannot be addressed. In fact, this study approach gives a notion about the initial decision of the patient to keep on prescribed medications.

Furthermore, some important factors which affect adherence and that could better explain the situation such as polypharmacy, comorbidity, side effects of medication, access to health care services, patient beliefs and attitude towards health care providers and medications were not

investigated, thus incarcerating the convincing power of the detected association by our model. Hence, further studies with more explanatory factors are needed to foster the relevance of our findings. Finally, more studies are required on patient individual characteristics to emphasize our results.

In the SHCP, we could not establish the link between the use of the extra services offered by the GPCs, drug consumption, and related data on written and dispensed medications at the individual client level. Studying and evaluating the programme through its impact on adherence is an underestimation of the real impact of the GPCs model. Nevertheless, this assessment does not menace our inferences on the effectiveness of the programme. Besides, the mechanism by which the programme enhanced adherence was not investigated since increasing adherence was not among the objectives of the programme. Thus, additional investigations are required to identify the advantageous changes induced.

5 Conclusions and recommendations

About one-third of the prescribed prescriptions written by GPs working in PHC was not filled in Hungary indicating an overall alarming high rate of nonadherence. The study also demonstrated a wide variability of adherence across various GMPs. This variation can be attributed to GMPs' structural characteristics, patients' socioeconomic status, and more importantly the magnitude and shape of patient-physician cooperation and communication style.

Regarding the SHCP, we found evidence that the extension of PHC services to include integrated and preventive services with proper protocol and necessary capacities enhanced medication adherence. This improvement was remarkable among adult patients with cardiovascular diseases and alimentary tract and metabolic disorders. The improvement of 6.4% reported in the programme without any specific activity for increasing adherence goes in line with published multifaceted intervention studies (range 4%-11%) devoted totally to enhance adherence using multifaceted interventions.

The multidimensional nature of adherence makes improvement in this field challenging. However, some agents can still be modified. Those factors include reducing cost of the medications, provision of services, and providing social support. Improving health literacy of patients to increase knowledge and skills on disease and importance of medications would enhance adherence. Another important aspect to target is the patient-physician relationship. Good patient-physician communication increases satisfaction of the clients and can positively alter their beliefs and attitude towards medications. Good communication skills include active and sufficient listening to clients and their concerns, careful examination of the clients, providing simple and straightforward instructions, showing empathy, value, and respect to patients and their feelings, and involving patients in decision making and health care process to ensure their commitment. This skilled communication along with physician quality that demonstrates good knowledge and competence can be very useful in altering people's behavior and attitude. Hence, it can be a useful tool to manage educated patients and urban residents who showed low adherence in Hungary.

Our findings propose that DWRs retrieved from electronic health records can be used in routine monitoring of the operation of PHC and can support substantial interventions. This finding endorses recommendations of the WHO in using the percentage of drugs actually dispensed in regular monitoring as a key indicator of patient care. Furthermore, measuring

DWRs could be a useful indicator of the effectiveness of client- health care professionals' relationships in PHC. Proper training of health care professionals on good communication should be conducted regularly to increase their awareness of the importance of this element in patient overall satisfaction and adherence. Use of information technology and electronic health records is essential for integration, control, and monitoring operation of GMPs and is necessary to offer optimum services. DWR indicator needs to be adopted and added to other indicators-based financing systems of GMPs running in Hungary. Future studies should investigate other important determinants of adherence such as comorbidity, polypharmacy, patient satisfaction, patient beliefs and perceptions of medications, and impact of the internet and the mass media.

6 New findings

Prevalence of primary nonadherence to prescribed medications in Hungary is high

More than one-third of the written prescriptions (35.9%) for the adult population in Hungary were not dispensed. Given that adherence is a key factor in achieving therapeutic goals and improving overall health status and quality of life, this high burden of nonadherence is crucial and suggested to be a major contributory factor behind the poor health status and the high amenable mortality of the Hungarian population when compared to other Western European countries.

Prevalence of nonadherence varies by ATC group of drugs

The primary nonadherence differed by the ATC class of drugs. The best practice was reported for anti-infective drugs for systemic use (79.1% of the prescriptions were dispensed) while the worst practice was reported for medication used for the treatment of cardiovascular diseases (59.4% were dispensed). This is important not only in detecting differences in GMPs' performance but also in identifying priorities where interventions are substantial.

Determinants of primary nonadherence among adults in Hungary are uncovered

We have detected and uncovered the major determinants of the high nonadherence to medications among adults. We found significant negative association between primary adherence and relative education of patients [b=-0.440, 95%CI: -0.468;-0.413], vacancy of the GMPs [b= -0.193, 95%CI: -0.204;-0.182], and living in urban areas [b= -0.099, 95%CI: -0.103;-0.094]. On the other hand, a better adherence was noted for GMPs running in a relatively smaller list sizes [$b_{X\text{-}800}$= 0.052, 95%CI: 0.041; 0.063, $b_{801\text{-}1200}$= 0.031, 95%CI: 0.025; 0.037, $b_{1201\text{-}1600}$= 0.017, 95%CI: 0.013; 0.022] compared to those running in larger list sizes [$b_{2001\text{-}X}$= -0.014, 95%CI: -0.019;-0.009].

Levels of adherence vary by geographical location of the county

We have found variations in adherence ratios by the county's geography. Geographical location is an indicator of spatially important health-related variables like the variation in the availability of health services and resources, certain lifestyle and culture, access to health care and health literacy that are well known to impact adherence as documented in the literature. Thus, it could reflect health inequity across the country.

The SHCP improved primary adherence in the intervention area

Extending PHC services to encompass preventive and rehabilitation services achieved significant improvement in adherence to prescribed medications. The magnitude of this improvement was 6.4% [RR= 1.064; 95%CI: 1.054 - 1.073] and corresponds to 5,033 excess number of dispensed prescriptions. This improvement suggests that proper and intensive care of the clients improved their adherence without even conducting specific activities focused on adherence itself.

Remarkable effects were noted on cardiovascular and alimentary tract and metabolism drugs

The major impact of the SHCP was noted on both cardiovascular system drugs [RR= 1.062; 95%CI: 1.048-1.077] and alimentary tract and metabolism drugs [RR=1.072; 95%CI: 1.049-1.097] with 42.6% and 19.9% an excess number of dispensed prescriptions achieved, respectively. This finding reflects that patients with diseases of high prevalence were more responsive to the intervention, and receiving more intensive health care services make patients more committed towards their regimens.

Percentage of drugs actually dispensed is a useful indicator of monitoring PHC

The indicator percentage of drugs actually dispensed can be used in routine monitoring of PHC operation and support the substantial interventions to improve overall health care services in PHC. This finding endorses recommendations of the WHO on the importance of the indicator on the health care process.

Percentage of drugs actually dispensed is a useful indicator of the patient-physician relationship

We noted that measuring dispensed to written ratios could be a useful indicator of the effectiveness of client- health care professionals' relationship and collaboration in PHC.

7 Summary

Background: Adherence is defined as taking medications as described or prescribed by health care professionals. Adherence is an important notion that reflects the degree to which patients conform or follow instructions and recommendations of health care providers throughout the prescribed treatment course. It involves a retrospective memory for remembering the way the medicines to be used and a prospective memory concerning the time at which the medications to be taken. The adherence process entails three main elements: initiation of therapy; implementation of the therapy as prescribed; and persistence on the given therapy for the desired period of time.

Primary nonadherence refers to a situation when people do not dispense the new prescriptions written by their health care providers from the beginning of the treatment course. Although primary adherence to medications is crucial for any successful treatment strategy in both acute and chronic health conditions, less attention has been given to this issue until recently. In fact, little is known about frequency, causes, and consequences of primary nonadherence. In addition, the published literature shows variable impact of risk factors on adherence. Primary nonadherence has not been investigated previously in Hungary at the national level.

Objectives: The aim of this study was to (1) estimate primary nonadherence to GMP prescribed medications among adults in Hungary using the WHO key indicator of patient care "percentage of drugs actually dispensed" as a basic concept to quantify the dispensed medications at the period between 2012 and 2015; (2) to determine effects of GMP structure and patient characteristics on adherence; (3) to describe variation of adherence across GMPs; and (4) to test whether operating GPC model for the purpose of organizing and improving effectiveness of PHC implemented in the "Public Health Focused Model Programme for Organising Primary Care Services Backed by a Virtual Care Service Centre" increases the percentage of drugs actually dispensed.

Methods: National data on all GMPs were obtained from the National Health Insurance Fund and the Hungarian Central Statistical Office for the period 2012 -2015. The data were aggregated for all running GMPs around the country for all ATC group of drugs. Ratios of dispensed to written (DWRs) prescriptions written by GPs for adults aged 18 years and above were used to determine levels of primary adherence to prescribed medications at the national level. Standardized DWRs (SDWRs) were calculated using the indirect standardization method for age, sex, and eligibility for an exemption certificate. Generalized linear regression

modeling was used to identify the major determinants of the SDWRs while controlling for the time. Characteristics of GMPs including patient education obtained from the GMPs, vacancy of the GMPs, type of settlement as urban or rural, county list size according to the number of adults receiving health care, and geographical location of the county were the investigated determinants in the regression model. The data analyses were completed using SPSS version 20.

To evaluate impact of the SHCP, SDWRs were calculated in the first quarter of 2012 (2012Q1 representing before intervention status) and in the third quarter of 2015 (2015Q3 representing post-intervention status). Risk ratios (RR) were estimated by taking after to before ratios for SDWRs along with their corresponding 95% confidence intervals (95%CI).

Results: Out of 438,614,000 written prescriptions between 2012 and 2015, 281,315,386 prescriptions were dispensed. Overall, 64.1% of the written prescriptions were dispensed. Based on the generalized linear regression coefficient (b), there was an inverse association between SDWRs and relative education of patients [b=-0.440, 95%CI: -0.468;-0.413], vacancy of the GMPs [b= -0.193, 95%CI: -0.204;-0.182], and living in urban areas [b= -0.099, 95%CI: -0.103;-0.094]. A better SDWRs was noted for GMPs running in a relatively smaller localities [$b_{X\text{-}800}$= 0.052, 95%CI: 0.041; 0.063, $b_{801\text{-}1200}$= 0.031, 95%CI: 0.025; 0.037, $b_{1201\text{-}1600}$= 0.017, 95%CI: 0.013; 0.022] compared to those running in larger localities [$b_{2001\text{-}X}$= -0.014, 95%CI: -0.019;-0.009]. In addition, geographical location of the county was an important determinant.

In the intervention area where the SHCP was implemented, SDWRs indicated that overall adherence was generally higher in the intervention area than in Hungary for various ATC groups. SDWR for the entire practice was 1.042 in 2012Q1 and increased to 1.108 after the intervention in 2015Q3. When the RR was calculated for SDWRs, this change was shown to be significant [RR= 1.064; 95%CI: 1.054 - 1.073] indicating an overall improvement of 6.4% in adherence. The excess number of prescriptions dispensed was 5,033 in 2015Q3. The most significant impact observed was on both cardiovascular system drugs [RR= 1.062; 95%CI: 1.048-1.077] and alimentary tract and metabolism drugs [RR=1.072; 95%CI: 1.049-1.097] with 2,143 and 1,001 excess number of dispensed prescriptions, respectively. In addition, significant positive changes were observed for musculoskeletal drugs [RR=1.041; 95%CI: 1.010-1.074], blood and blood-forming organ drugs [RR=1.077; 95%CI: 1.044-1.111], and drugs of the nervous system [RR= 1.082; 95%CI: 1.047-1.118].

Study implications: Nonadherence contributes substantially to poor disease diagnosis. This impact was not investigated in our analysis but expected to be great since only 59.4% of cardiovascular system drugs are actually dispensed although cardiovascular diseases are the leading causes of death and the major determinants of Life expectancy in the European region. In addition, nonadherence results in considerable loss of time, work, capacities and resources of the Hungarian health care system. It may reflect poor patient-physician relationship. Also, the observed variations in adherence among various GMPs reflect various capacities of the GPs in managing and dealing with their customers. Moreover, the study provided evidence on the weak role of GPs in managing clients in urban areas and those with high levels of education. The intensive care given to patients in the SHCP was fruitful in enhancing adherence although increasing adherence was not among objectives of the programme. This probably confirms that improved patient-physician relationship is a cornerstone not only in enhancing adherence but also the overall health status of the population. Use of the WHO indicator percentage of drugs actually dispensed is a good tool for monitoring performance of GMPs and assessment of effectiveness of intervention programmes.

Conclusions: About one-third of the prescriptions written by GPs working in PHC were not filled in Hungary indicating an overall alarming high rate of nonadherence. The study also demonstrated a wide variability of adherence across various GMPs. This variation can be attributed to GMPs' structural characteristics including patients' socioeconomic status, vacancy of GMPs, list size of the county, locality type, and geographic location of the counties and more importantly magnitude of patient-physician cooperation and communication style.

The SHCP provided evidence that extension of PHC services to include integrated and preventive services with proper protocol necessary capacities enhanced medication adherence. This improvement was remarkable among adult patients with cardiovascular diseases and alimentary tract and metabolic disorders. The improvement of 6.4% reported in the programme without any specific activity for increasing adherence goes in line with published studies (range 4%-11%) devoted totally to enhance adherence using multifaceted interventions.

In addition, our findings proposed that DWRs can be used in routine monitoring of the operation of PHC and support substantial interventions. This finding endorses recommendations of the WHO in using the percentage of drugs actually dispensed in regular

monitoring as a key indicator of patient care. Furthermore, measuring DWRs could be a useful indicator of the effectiveness of client- health care professionals' relationships in PHC.

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9 Keywords

Adherence to medications, primary nonadherence, prescribed drugs, dispensing ratio, education levels, vacancy of GP, geographic inequality, urbanization, List size of GMPs, patient-physician cooperation, assessment of health status.

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12 Appendix

List of publications and manuscripts

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Subject: PhD Publikációs Lista

Candidate: Nouh Harsha
Neptun ID: C6NIJL
Doctoral School: Doctoral School of Health Sciences

List of publications related to the dissertation

1. **Harsha, N.**, Kőrösi, L., Pálinkás, A., Bíró, K., Boruzs, K., Ádány, R., Sándor, J., Czifra, Á.: Determinants of Primary Nonadherence to Medications Prescribed by General Practitioners Among Adults in Hungary: cross-Sectional Evaluation of Health Insurance Data. *Front. Pharmacol. 10*, 1-9, 2019.
   DOI: http://dx.doi.org/10.3389/fphar.2019.01280
   IF: 3.845 (2018)
2. **Harsha, N.**, Papp, M., Kőrösi, L., Czifra, Á., Ádány, R., Sándor, J.: Enhancing Primary Adherence to Prescribed Medications through an Organized Health Status Assessment-Based Extension of Primary Healthcare Services.
   Int. J. Environ. Res. Public Health. 16 (20), 1-13, 2019.
   DOI: http://dx.doi.org/10.3390/ijerph16203797
   IF: 2.468 (2018)

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List of other publications

3. **Harsha, N.**, Ziq, L., Giacaman, R.: Disability among Palestinian elderly in the occupied Palestinian territory (oPt): prevalence and associated factors.
   BMC Public Health. 19 (1), 1-9, 2019.
   DOI: http://dx.doi.org/10.1186/s12889-019-6758-5
   IF: 2.567 (2018)
4. Kovács, N., Pálinkás, A., Sipos, V., Nagy, A., **Harsha, N.**, Kőrösi, L., Papp, M., Ádány, R., Varga, O., Sándor, J.: Factors associated with practice-level performance indicators in primary health care in Hungary: a nationwide cross-sectional study.
   Int. J. Environ. Res. Public Health. 16 (17), 1-15, 2019.
   DOI: https://doi.org/10.3390/ijerph16173153
   IF: 2.468 (2018)
5. **Harsha, N.**, Ziq, L., Ghandour, R., Giacaman, R.: Well-being and associated factors among adults in the occupied Palestinian territory (oPt).
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