보건학석사 학위논문

Analysis on the effect of consultation program to improve medication adherence

투약순응도 향상을 위한 상담프로그램의 효과 분석

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Abstract

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Hypertension and diabetes are the very common chronic diseases with each prevalence of nearly 30% and 10% among South Korean aged over 30 and this is increased along with aging. These diseases are well-known risk factors for severe diseases including cardiovascular disease (CVD) which is a leading cause of death globally, so they needed to manage continually. The purpose of this study is to evaluate the effect of consultation program on medication adherence in hypertension and diabetes patients.

In an effort to improve hypertension and diabetes care, National Health Insurance Service (NHIS) has implemented a consultation program from July 2013 for 3 months. This study examined the effect of this program between before and after conducting intervention using eligibility, medical treatment and health examination data from NHIS. To evaluate the actual effect of the intervention, this study select controls which have similar characteristics with participants using propensity score matching (PSM), and then the change of medication possession ratio were analyzed with Difference-in-Differences (DID) method, comparing with participants and controls.

As results of this study, the effect of consultation program on MPR was confirmed with statistical significance in hypertension and diabetes participants and all types of MPR group. As for IG-MU, the MPR was 2.27% increased after intervention in hypertension participants (p=0.0153) and 7.26% increase in diabetes participants (p=0.0020). As for IG-MO, the MPR was 8.04% decreased after intervention in hypertension participants (p=0.0013) and 9.73% decreased in diabetes participants (p=0.0122). And the

effect of intervention by state of newly diagnosed patients was also found in hypertension participants.

Through this study results, the effect of consultation program change subjects' medication adherence in an appropriate way. Especially, this study shows that the consultation program is more effective in patients who are newly diagnosed as hypertension than pre-existing hypertension patients. This study provides scientific and documented evidences regarding extended enforcement of personalized consultation program to improve medication adherence. And this study suggests that it needs to implement consultation program which is effective and active management service about chronic disease on the national scale.

Key words: Medication adherence, Chronic disease, Intervention program, Propensity score matching, Difference-in-Differences

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Chapter 1. Introduction

1.1 Background

Hypertension and diabetes are the very common chronic diseases with each prevalence of nearly 30% and 10% among South Korean aged over 30 and this is increased along with aging according to Korea National Health and Nutrition Examination Survey 2013 (KNHNES, 2014). This diseases are well-known risk factors for severe diseases including cardiovascular disease (CVD) which is a leading cause of death globally, so they needed to manage continually (Hogan et al., 2003, Collins et al., 1990, Balkrishnan et al., 2003).

According to World Health Organization (WHO), medication adherence is defined as "the extent to which a person's behavior taking medication, following a diet, and/or executing lifestyle changes corresponds with agreed recommendations from health care provider" (Sabaté, 2003). Also medication adherence is very important factor helps in keeping the vital link between the treatment and the therapeutic outcomes in medical care (Parthasarathi and Nyfort-Hansen, 2004). But among patients with chronic diseases, it is easy to get in trouble with medication adherence and approximately 50% of them do not take medication as prescribed (Sabaté, 2003, Lee et al., 2006, Magnabosco et al., 2015). Because they have to take medications for an entire life once they start to take the medications and moreover most patients with hypertension and diabetes tend to be asymptomatic(Donnan et al., 2002, Dowell et al., 2002). And medication adherence is affected by the patient's perception and attitude toward their diseases (Magnabosco et al., 2015).

Medication non-adherence lead to lots of public health problems in patients with chronic diseases (Dartnell et al., 1996, Psaty et al., 1990, Lau and Nau, 2004, Balkrishnan et al., 2003). Above all, taking medication under-dose cause emergency room visit, hospitalization and unscheduled hospital visits following increased morbidity, exacerbation of diseases and development of complications (Brown and Bussell, 2011, Lau and Nau, 2004). Moreover it has demanded that patients who take under-dose pay large medical expenses (Balkrishnan et al., 2003, Osterberg and Blaschke, 2005). Taking or being prescribed excessive medication also lead to socio-economic burden (Elliott et al., 2008). In case of this, it is very hard to have an effect to prevent complications although it spends medical expenses and medicine cost and it makes using national health insurance ineffective consequentially.

Previous studies have shown that the various kinds of interventions by healthcare provider to improve medication adherence were effective in both medication adherence and patient outcomes like their blood pressure or blood glucose level (Morgado et al., 2011, Chabot et al., 2003, Bright et al., 2012, Elliott et al., 2008). And in 2003 report on medication adherence of WHO, it reported that “increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments”(Sabaté, 2003). Through these, the intervention to improve medication adherence is very important to manage chronic diseases in public health aspects. Meanwhile, in an effort to improve hypertension and diabetes care, National Health Insurance Service (NHIS) in South Korea has implemented an intervention by providing chance to

participate the consultation program for medication non-adherence measured by medication possession ratio (MPR) in each person who has hypertension or diabetes from 2013. But it is hard to evaluate the accurate consultation program by comparing the MPR of participants before and after intervention so, it is necessary to fix a control group to evaluate the actual impacts excluded the natural effect by time passes. Moreover this program provides personalized healthcare consultation according to each person's MPR, so it is possible to evaluate the effect of intervention by standards of MPR and to find the vulnerable group. This will encourage to shape this program more segmentalized and detailed for conducting more effective consultation program.

1.2 Objective

The main purpose of this study is to evaluate the effect of the consultation program to improve medication adherence in hypertension and diabetes patients.

Thus, the specific objectives of the study are

Objective 1: Evaluate the effect of the consultation program on medication adherence of patients who are diagnosed with hypertension and diabetes.

Objective 2: Evaluate the effect of the consultation program on medication adherence of patients who are diagnosed with hypertension and diabetes by subgroups (age group, gender and state of newly diagnosed patient).

Chapter 2. Overview of the intervention and literature review

2.1 Overview of the intervention

2.1.1 Consultation program to improve medication adherence

The consultation program in improve medication adherence by NHIS started from 2013 to select appropriate patients according to some criteria in 8 districts which are within the jurisdiction of 6 branch offices of the NHIS during 2012 before providing intervention. The number of participant district group combined 2 districts into 1 branch is 2 on account of low population to cover. The intervention started from July 2013 for 3 months.

This intervention was conducted by administrative staffs in NHIS and pharmacists in each district. At first, the intervention was fully implemented in all eligible patients sending a leaflet. It contains some information about this consultation program including the objective of this intervention and personalized information about each person's disease, how to manage their disease, the reason why they have to take drugs, their state of medication adherence and the importance of medication administration. And also it includes contents of further telephone contacts from NHIS to provide specialized consultation after one week from receiving a leaflet. The second and the third intervention were performed through telephone consultation with standardized questionnaire including 13 to 15 questions about medication administration and lifestyle behavior. The second intervention placed

emphasis on checking participant's medication-taking behavior and lifestyle behavior like smoking, drinking and physical activity state, giving advice and correcting inappropriate behavior to right way. Meanwhile, the main purpose of third intervention is to check how they change their inappropriate behavior to appropriate and also giving advice about effective self-management ways of their disease.

2.1.2 Measurement of medication adherence

There are several methods to measure medication adherence. But there is no 'gold standard' measure for it and this makes assessment of adherence difficult(Hughes, 2004). In this consultation program, medication adherence was calculated by using medication possession ratio (MPR) which is commonly used measurement method and the best available measurement of medication adherence using administrative data(Halpern et al., 2006, Andrade et al., 2006). This is the ratio of total days of medication supplied to total days in a period of time(Halpern et al., 2006). MPR was calculated every 6months as the first half year and the second half year in this study. For example, if a patient with hypertension was prescribed and supplied with hypertension medication for 120 days of the first half year, then the MPR was calculated as 66.3% ((120 days/181 days)*100). When calculating MPR, this study considered the subject's behavioral differences in medical service utilization and types of medications by ingredient to resolve overlapped period between prescriptions. If a patient was prescribed medication at same hospital and same ingredient in each prescription, the overlapped periods were additionally

added to total prescribed days. But in the cases of each prescription were from different hospitals or changed ingredients of medications, overlapped periods of prior prescriptions were excluded in total prescribed days.

On the basis of the previous studies, adherence to medication was defined as an 80%≤MPR(Cramer et al., 2008, Karve et al., 2009, Lee et al., 1996, Mallion et al., 1998), but higher MPR has occurred another problems related to increased medical health costs. So this study defined 80%≤MPR<130% as medication adherence. All study subjects who were non-adherent to mediations were divided into 2 groups according to MPR for the second half year of 2012. The first group is intervention group with under administration of medicine (IG-UAM) with MPR <80% and the second group is the intervention group with over administration of medicine (IG-OAM) with MPR≥130% (Figure 1).

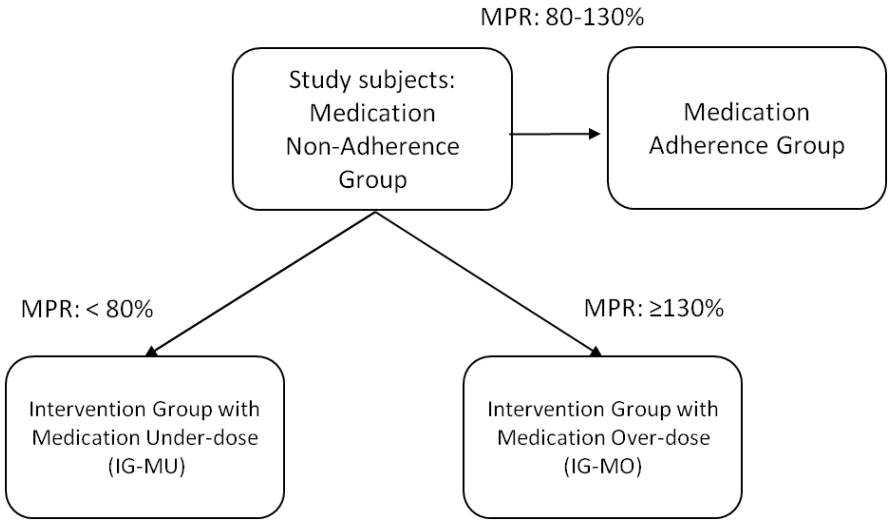

Figure 1. Division into 2 groups according to medication possession ratio (MPR)

2.1.3 Literature review about study method for evaluating the effect of consultation program

The experimental study with randomization is the most proper method to evaluate the outcome of system or policy(Ravallion, 2003). But it is impossible to select the utilization of the system or policy in random. In addition to that, there are an intervention group exposed to the consultation program, no control group was assigned when the intervention was conducted. To deal with this shortcoming, it is appropriate to use propensity score matching (PSM) with difference-in-differences (DID) as quasi-experimental method to evaluate the outcome(Wang et al., 2009).

2.1.3.1 Propensity score matching (PSM)

PSM is one of effective and artificial method to find an appropriate control group when there are only case group(Wang et al., 2009). This method constructs control group using matching algorithms to find a similar subjects to the case group as possible along a set of covariates(Khandker et al., 2010) for reducing selection bias(Dehejia and Wahba, 2002, Austin, 2007, Wang et al., 2009). There are two conditions were satisfied before we employ PSM. Those are conditional independence assumption and the range of common support assumption. After these assumptions were fulfilled, the propensity score was estimated to construct control group which has similar characteristics with case group. And then controls were matched to each case on propensity score. Final step is verifying the covariates are balanced across case and control groups in the matched.

2.1.3.2 Difference in Differences (DID) and Difference in Difference in Differences (DDD)

DID is the method of analysis comparing the differences between before and after conducting system in participant group which was affected by system with differences between before and after conducting system in control group which was not affected by system for estimating the actual effect of system. There need to be satisfied pre-condition before this method was employed. It is parallel trend assumption says that if there are no implementation of system, the aspect of transition in accordance with time is same in between participant and control groups.

The equation for the DID is shown below;

$$\mathrm{DD} = \mathrm{E}\left(Y_{t=1}^{p} - Y_{t=0}^{p} \middle| I_{t=1} = 1\right) - \mathrm{E}(Y_{t=1}^{c} - Y_{t=0}^{c} | I_{t=1} = 0)$$

t represent the period, especially *t=0* is a period of before conducting intervention while *t=1* is a period of after conducting intervention. *I* =1 is participant group and *I* =0 represent control group. Y^P and Y^C are measured values of intervention participant group and control group respectively. In other words, change of outcome variable in accordance with consultation program is the amount of difference between the period of before and after intervention in control group subtracted from difference between periods in participant group. But it is hard to consider time varying covariates so using regression-based DID can estimate the effects adjusting it

DDD used same principle with DID but this added one more division criteria to evaluate the effect by new division. In other words, this is the method to estimate the differences between the differences in accordance with implementing intervention in participant and control groups within groups after that, estimate the differences between groups. This statistical method eliminates remaining endogenous relationship in covariates.

But only using DID or DDD has some weakness of selection bias and endogeneity occurred from unobserved heterogeneity. So, there needs to find a solutions to deal with this matter, PSM is the way to overcome this problem(Sari and Osman, 2015).

Chapter 3. Methods

3.1 Data source

This study used secondary data which consisted of eligibility database(included age, gender, residence, 10 brackets of insurance fee and so on), medical treatment database(included diagnosis code which are classified according to International Classification of Disease 10^{th} Revision(ICD-10), data about prescriptions like drug name, dosage, visit date, duration of stay in hospital and so on) and health examination database (included height, weight, blood pressure, results of blood test and so on) of NHIS in South Korea (Song et al., 2014) from 2009 to 2014. Total duration of this study is from January 2009 to December 2014 including the intervention period was from July 2013 to September 2013.

South Korea has a national health insurance system which cover all South Korean, so the NHIS database contains all information for all South Korean who use medical services(Shin et al., 2013). And all people over 40 years old are provided a health examination for every 2 years(Song et al., 2014). Therefore, NHID (National Health Insurance Data) is not limited to specific geographical areas, hospitals or patients(Shin et al., 2013, Song et al., 2014).

NHIS provide data without the individual identifier. Thus resident registration number as identifier number codes of all study subject were changed into anonymous numeric codes representing each individual to

protect private patient information(Shin et al., 2013). The exemption of ethics approval for this study has been obtained from Institutional Review Board of Seoul National University under E1510/002-007.

3.2 Strategy for the selection of study sample

In the case of participants in consultation program to improve medication adherence, there are several criteria when NHIS selected suitable patients who have hypertension or diabetes for this intervention program in 8 districts which are within the jurisdiction of 6 branch offices of the NHIS at 2012. The criteria are like below.

1. The patients who have medical records with diagnosed by hypertension (International Classification of Disease, 10^{th} revision code (ICD-10 code): I10, I11, I12, I13, I15) and diabetes (ICD-10code: E10, E11) for the first half year of 2012.

2. The patients who have prescription records of medication which is classified hypertension and diabetes for the first half year of 2012.

3. The patients who have more than two times of medical service use which are combined medical record and prescription record for more than 14 days or have only one time of medical service use with more than 30 days of prescribed medication for the first half year of 2012.

4. The patients who don’t have rare diseases like cancer, chronic renal failure, dementia, and so on.

5. The patient who are aged above 45 and below 80.

This study considered variables about lifestyle behaviors (state of drinking, smoking and physical activity) as covariates. So subjects who took health examination provided by NHIS before and after consultation program are included. According to these criteria, the total number of participants sample in this study is 10,990(Figure 2.).

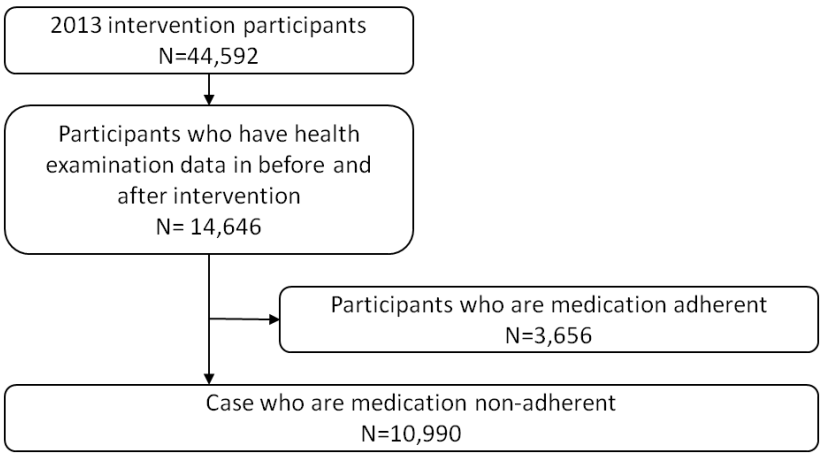

Figure 2. Diagram for selection of participant sample

In order to evaluate the effects of the intervention on the participation of the consultation program, one needs to compare the outcomes between intervention participants and comparable non-participants(Sari and Osman, 2015). But there is only participants group exposed to the intervention, no control group was assigned when the intervention was conducted by NHIS. There needed to define and select the optimal non-participant group as control so, the same criteria were applied when extract that group.

Before we applied these criteria, control districts which have similar character to the intervention conducted districts were selected by 22 indicators for the purpose of having a homogeneity between control districts and case districts in district level for reducing selection bias. That indicators are made up 15 health state indicators and 7 socio-economic state (SES) indicators and the all values are represented state of each district in 2012. The used indicators are recorded in appendix 1 and 2. Using these indicators, Z-score of all districts in South Korea were calculated for standardizing. At first, Z-score of each district and indicator were calculated. Formally the Z_{ij} is defined as;

$$Z_{ij} = \frac{x_{ij} - \mu_{ij}}{\sigma_i} \quad (1)$$

where subscript i stands for 22 health state and SES indicators and j stands for 254 districts respectively. x_{ij} is the raw value of some district and some indicator, μ_i is the mean of the indicator and σ_i is the standard deviation of the indicator. Using calculated all standardized scores of each district and indicator, final Z-score of each district, $Z - score_j$, defined as below;

$$Z - score_j = \sum_{i=1}^{22} Z_{ij} \times \frac{1}{22} \quad (2)$$

where subscript j stands for 254 districts like above equation. And then 2 control districts to 1 intervention district were selected among total districts in accordance with calculated Z-score which have similar score with each intervention district (Control districts 1).

Meanwhile, South Korea is divided into 8 provinces (e.g., Gyeonggi-do),

1 special autonomous province (Jeju-do), 6 metropolitan cities (e.g., Busan), 1 metropolitan autonomous city (Sejong) and 1 special city (Seoul). Each division has their own characteristics, so (1) and (2) were done within each division. As a result, additional 2 control districts to 1 intervention district were selected (Control districts 2) so, total 4 control districts to 1 intervention district were selected finally. Table 1 shows the selected control districts with their Z-score.

Table 1. Intervention districts and selected control districts with Z-score.

Intervention district name	Z-score*	Control districts 1		Z-score*	Control districts 2	
		Districts name	Z-score		Districts name	Z-score
NHIS office branch 1.						
Seoul A	0.0533	Daegu A	0.0410	0.0581	Seoul A1	0.0560
(District 1)		Ulsan A	0.0539		Seoul A2	0.0911
NHIS office branch 2.						
Gyeonggi-do B	-0.1883	Gyeonggi-do B	-0.2048	-0.1818	Gyeonggi-do B1	-0.1986
(District 2)		Seoul B	-0.1780		Gyeonggi-do B2	-0.1779
NHIS office branch 3.						
Chungcheongbuk-do C	-0.6091	Gyeonggi-do C	-0.6846	-0.4779	Chungcheongbuk-do C1	-0.3301
(District 3)		Gangwon-do C	0.8495		Chungcheongbuk-do C2	-0.2469
NHIS office branch 4.						
Jeollabuk-do D	-0.1416	Chungcheongbuk-do D	-0.1591	-0.0962	Jeollabuk-do D1	-0.1439
(District 4)		Jeollabuk-do D	-0.1262		Jeollabuk-do D2	0.0022
Jeollabuk-do E	-0.1031	Gyeongsangbuk-do E	-0.1059	-0.1460	Jeollabuk-do E1	-0.1907
(District 4)		Gyeongsangnam-do E	-0.0793		Jeollabuk-do E2	-0.1439

Intervention district name	Z-score*	Control districts		Z-score*	Control districts	
		Districts name	Z-score		Districts name	Z-score
NHIS office branch 5.						
Gyeongsangbuk-do F (District 5)	-0.0371	Gyeonggi-do F	-0.0545	-0.1572	Gyeongsangbuk-do F1	-0.1617
		Gyeongsangbuk-do F	-0.0105		Gyeongsangbuk-do F2	-0.1399
Gyeongsangbuk-do G (District 5)	0.0254	Chungcheongnam-do G	0.0074	0.1259	Gyeongsangbuk-do G1	0.0635
		Gyeongsangbuk-do G	0.0269		Gyeongsangbuk-do G2	0.1320
NHIS office branch 6.						
Gyeongsangnam-do H (District 6)	0.3416	Seoul H1	0.3373	0.0510	Gyeongsangnam-do H1	0.0329
		Seoul H2	0.3498		Gyeongsangnam-do H2	0.0828

*: Z-score for intervention districts in accordance with calculating method.

After control districts were selected, control sample is extracted by same criteria with participants. Figure 3 shows the description of process used to identify study control sample. The total number of final control sample is made of non-participants of consultation program is 176,883.

Finally, this study distinguished patients who are newly diagnosed as a hypertension or diabetes patient. It is reasonable to separate new patients from pre-existing patient by the reason of new patients' unfamiliarity with managing chronic disease. So it is more easy to be a medication non-adherent for new patients than pre-existing patients. Moreover it is important to study about the effect of consultation program on new patients because if the new patients recognized the importance about taking medicine as a result from this consultation program, they will be good at managing their health by themselves for a long time. And this prevent further complications and unnecessary medical service use and health cost. The new patients is operationally defined as patients who don't have any medical records with diagnosed hypertension and diabetes in 2011 and patients who don't have any prescription records about hypertension and diabetes medication in 2011.

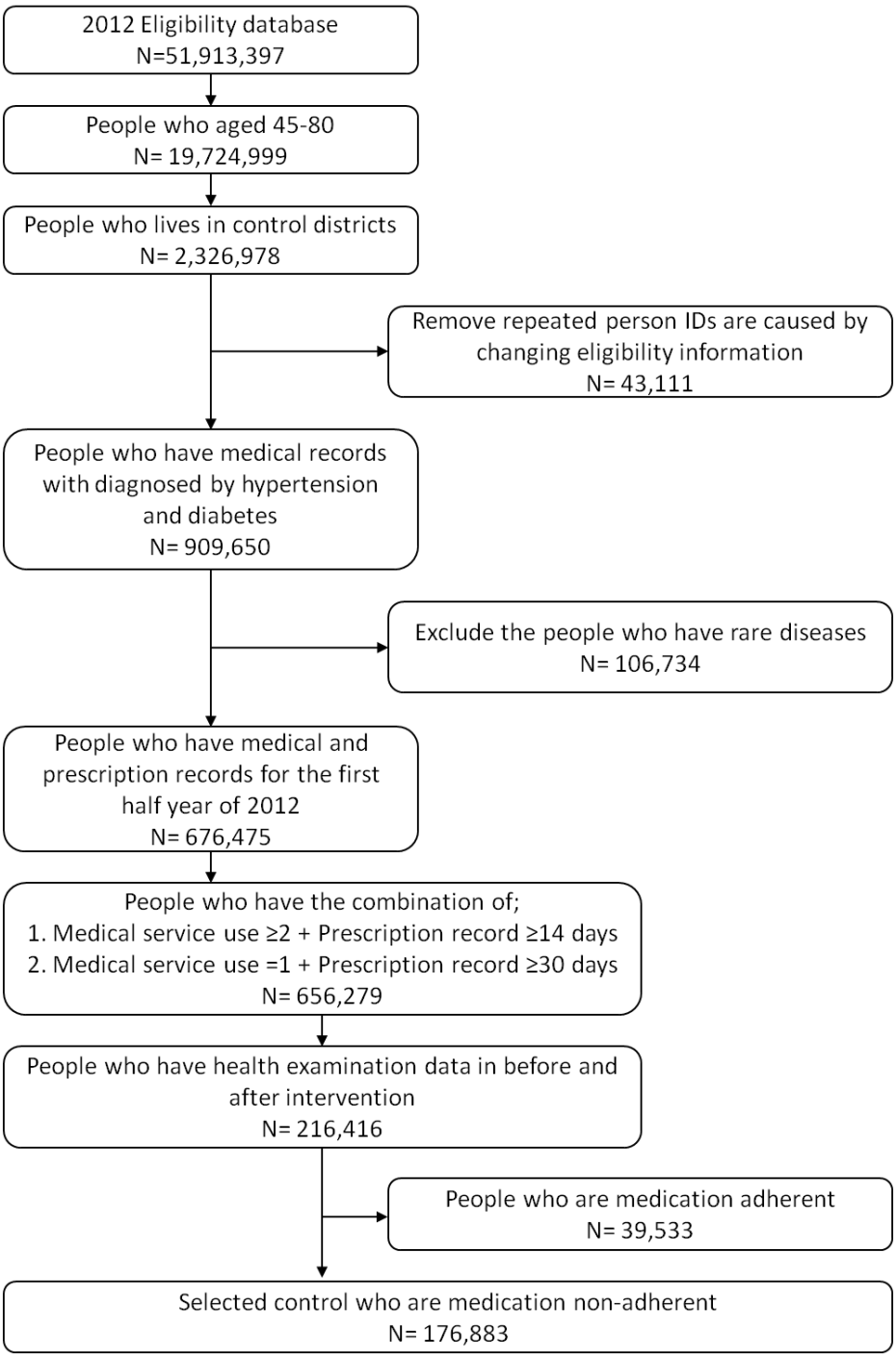

Figure 3. Diagram for selection of control sample

3.3 Analysis strategies

In this study, all eligibility, medical treatment and health examination data of both participant group and control group was extracted from whole NHIS database to examine the effect of this consultation program. After pooling data by each person, this study used quasi-experimental design with PSM, DID and DDD as an analysis method to improve the effect of consultation program.

At first, participants and controls which are used in this study with almost same characters excluding the state of participation are selected using 1:1 PSM method. This study did chi-square test as a test of homogeneity between participant and control group after PSM. A p-value $\leq$ 0.05 was considered statistically significant. After constructing the participant and control group using PSM, regression-based DID approach was used to estimate the effects of this program adjusting some factors affect the study outcome. And then, this study analyzed the effect of consultation program using DDD method to distinguish the systemic differences of effects on the outcomes (Figure 4).

All statistical analyzes were performed using the SAS enterprise guide 7.1 (SAS Institute, Cary, NC, USA).

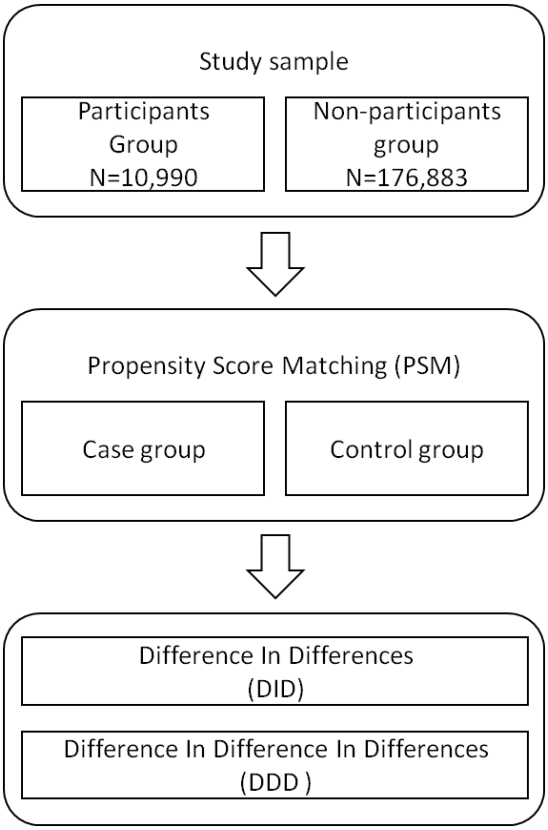

Figure 4. Analysis flow of the consultation program to improve medication adherence

3.3.1 Study variables

3.3.1.1 Variables for PSM

Using PSM, control group which has very similar character with participants is selected to investigate the actual effect of consultation program. There are so many factors affect the relationship between the consultation program and the study outcome. It is impossible to control all factors, but there are many studies to investigate the affecting factors to medication adherence. So this study uses key variables from previous studies. These factors can divide into 2 parts, one of them is demographic and socio-economic part and the other is clinical part. The former contains age, gender, residence area, 5 brackets of insurance fee and so on while the latter contains the state of new patient, body mass index (BMI), blood pressure, blood glucose and so on. Additionally, this study contains variables about lifestyle behavior (state of drinking, smoking and physical activity). The detailed explanation about these variables is presented in Table2.

Table 2. The definition of variables used in PSM.

Variables	Values of variables
Age group	1: 45-59 2: over 60
Gender	1: male 2: female
Residence area	1: Seoul A and control districts (District 1) 2: Gyeonggi-do B and control districts (District 2) 3: Chungcheongbuk-do C and control districts (District 3) 4: Jeollabuk-do D, E and control districts (District 4) 5: Gyeongsangbuk-do F, G and control districts (District 5) 6: Gyeongsangnam-do H and control districts (District 6)
5 brackets of insurance fee	0 to 5 (0: Medical aid beneficiaries)
Disabled	0: Non-disabled 1: Disabled
New patient	0: Pre-existing patients 1: Newly diagnosed patients
BMI	1: Underweight 2: Normal 3: Overweight 4: Obese
Blood pressure	1: Normal 2: Pre-hypertension 3: Grade 1 hypertension 4: Grade 2 hypertension 5: Grade 3 hypertension
Blood glucose level	1: Normal 2: Impaired fasting glucose (IFG) 3: Diabetes

Variables	Values of variables
Blood glucose level	1: Normal 2: Impaired fasting glucose (IFG) 3: Diabetes
Disease group	1: Hypertension 2: Diabetes 3: Hypertension and Diabetes
MPR groups in hypertension	1: Under-dose 2: Over-dose
MPR groups in diabetes	1: Under-dose 2: Over-dose
Drinking	0: No 1: Yes
Smoking	0: No 1: Yes
Physical activity	0: No 1: Yes

BMI, blood pressure and blood glucose level are provided as values in accordance with health examination. These variables are changed into categorical variable in order to using PSM. BMI is divided into 4 groups as underweight, normal, overweight, obese according to WHO BMI classification (WHO, 2004). Blood pressure is divided into 5 groups as normal, pre-hypertension (pre-HTN), grade 1 hypertension (G1 HTN), grade 2 hypertension (G2 HTN), grade 3 hypertension (G3 HTN) (WHO and Group, 2003). Finally, blood glucose level is divided into 3 groups as normal impaired fasting glucose (IFG), diabetes (Mellitus, 2005). The details of classification standards are records in appendix 3.

3.3.1.2 Variables for DID and DDD

Variables used in DID and DDD are presented in Table 3. With regard to evaluate the effect on medication adherence, the dependent variable is MPR representing medication adherence. It was calculated by types of diseases (hypertension and diabetes) and types of MPR groups (IG-MU and IG-MO). And MPR was calculated in every 6 months from July 2011 to December 2014. The period defined as before intervention is from July 2011 to June 2013 and the period defined as after intervention is from July 2013 to December 2014. Meanwhile, calculated MPR in every 6 months included carryover medications from last half year.

The independent variables are state of participation and period of before and after intervention. Age group, gender and state of new patient are used in DDD model to investigate the effect by these subgroups. The interaction term for state of participation and period of before and after intervention is estimated in DID model. In the case of DDD model, the interaction term for state of participation, period of before and after intervention and subgroup is estimated.

The control variables contain residence area, state of disabled, 5 brackets of insurance fee, value of BMI, blood pressure, value of blood glucose, state of drinking, state of smoking and sate of physical activity.

Table 3. The definition of variables used in DID and DDD.

Variables			Values of variables
Dependent variable	Medication Possession Ratio		Continuous variable
Independent variable	State of participation	Participants group Control group	Participants =1 Control =0
	Period of before and after intervention	Before intervention (2011.6~2013.6) After intervention (2013.7~2014.12)	Before =0 After =1
	Age group*		45-59 = 1 Over 60 = 2
	Gender*		Male = 1 Female = 2
	State of new patient*		Pre-existing patient = 0 Newly diagnosed patient = 1

	Variables	Values of variables
Control variable	Residence area	District 1 to District 6
	State of disabled	Non-disabled = 0 Disabled =1
	5 brackets of insurance fee	0 to 5 (0: Medical aid beneficiaries)
	BMI	Continuous variable
	Systolic blood pressure	Continuous variable
	Diastolic blood pressure	Continuous variable
	Blood glucose	Continuous variable
	State of drinking	No = 0 Yes =1
	State of smoking	No = 0 Yes =1
	State of physical activity	No = 0 Yes =1

*: Variables used in DDD model as independent variables.

3.3.2 Application of the model

The purpose of this study is to evaluate the effect of consultation program to improve medication adherence using DID and DDD with PSM. This intervention was implemented to specific subjects for specific period, so the effect is investigated by estimating the interaction term of state of participation and period. And the effects by subgroups are investigated by estimating the interaction term of state of participation, period and subgroups.

The model of this study is as follows:

1. Analysis Ⅰ: the effect on medication adherence

- Model Ⅰ: DID model

$$Y_{(i,t)} = \beta_0 + \beta_1(Participation) + \beta_2(Period) + \beta_3(Participation * Period) + \beta_4(Other\ covariates) + \varepsilon$$

i: subject, t: year, Y: MPR by disease group and MPR group

2. Analysis Ⅱ: the effect on medication adherence by subgroups

- Model Ⅱ: DDD model

$$Y_{(i,t)} = \beta_0 + \beta_1(Participation) + \beta_2(Period) + \beta_3(Subgroups) + \beta_4(Participation * Period) + \beta_5(Period * Subgroups) + \beta_6(Participation * Subgroups) + \beta_7(Participation * Period * Subgroups) + \beta_8(Other\ covariates) + \epsilon$$

i: subject, t: year, Y: MPR by disease group and MPR group

Subgroups: gender, age group and state of newly diagnosed patients

Chapter 4. Results

4.1 Descriptive statistics of the study variables

This study used logit model with participation of consultation program as a binary variable to estimate propensity score. The control group was selected by 1:1 Nearest Matching algorithm which is one of the PSM method. Participants are matched to controls on 8 digits of the propensity score

Before PSM, study subjects consisted of 10,990 of participants and 176,883 of controls. After selected controls having similar propensity score with participants, whole study subjects consist of 8,646 of participants and control group respectively. Figure 5 shows the distribution of propensity score in participant and control group

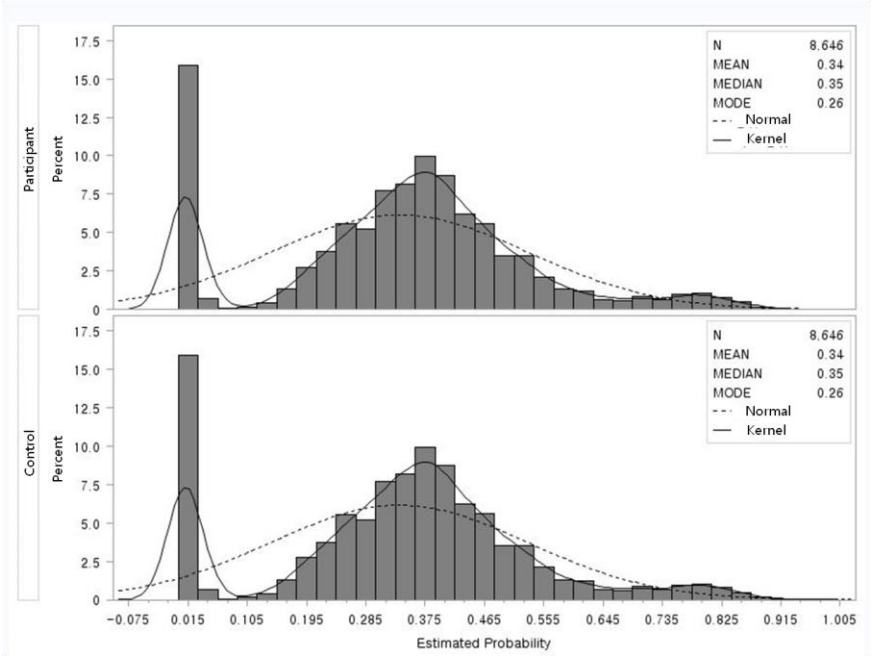

Figure 5. Distribution of propensity score in each group

Table 4 shows the distribution about demographic and socio-economic characters of study subjects before and after PSM and also shows the results of homogeneity test.

First of all, about the results of homogeneity test before PSM, there are heterogeneity between participant group and control group about all covariate except two variables; disease (p-value: 0.6694) and physical activity (p-value: 0.0687). But after PSM, there are no differences between participant group and control group in all covariates. It means that the characters of two groups are very similar in all observable covariates except the state of participation in consultation program.

With regard to the distribution of age group, gender, residence area, disabled and 5 brackets of insurance fee as a demographic and socio-economic characters, the distribution of all variables are same in participant group and control group. As for age group, 48.29% of participants and controls are in age group 45-59 years of age on the baseline period and 51.71% of both two groups are in age group over 60. Among study subjects, there are more male subjects than female subjects with the proportion of 53.38% as male and 46.62% as female. About the distribution of residence area, more than 70% of study subjects live in District 1 (26.07%), District 2 (21.72%) and District 3 (25.32%). 7.01% of participants and controls are disabled. Finally, there are more subjects who were charged higher national health insurance fee than subjects who are included in lower brackets of all in both participants and control groups.

Table 5 shows the distribution about clinical characters of study subjects before and after PSM and also shows homogeneity between participant group and control group.

As for clinical characters, the distribution of participant and control groups is same except 2 variables; blood pressure and drinking. 11.83% of participants and controls are newly diagnosed patients at 2012. With regard to the results of BMI, 55.82% of study subjects are in the range of underweight with the highest proportion of each participant and control groups. The second-highest proportion of study subjects is overweight with 40.08%. As for blood pressure, distribution of participant and control groups are little different but approximately half of the study subjects are in the range of pre-hypertension state. Among the study subjects who are diagnosed hypertension as results of blood pressure examination, the case of G1 HTN took the largest proportion of the others with 22% of participant group and 22.3% of control group. Approximately 49% of participants and controls are in normal range of blood glucose level, while, 17.5% of participants and 17.05% of controls are diagnosed diabetes as results of blood test. There are 78.09% of both two groups have HTN and 11.22% have diabetes. And the subjects who have both HTN and diabetes take 10.69%. Among participants and controls who have HTN, 83.01% are included IG-MU and 16.99% are in IG-MO. And about subjects who have diabetes, 68.32% are in IG-MU while, 31.58% are in IG-MO. There are more subjects who are non-drinking (participant group: 76.87%, control group: 77.24%), non-smoking (participant group: 84.48%, control group: 84.48%) and who don't physical activity (participant group:

66.37%, control group: 66.72%).

Table 4. Comparison the homogeneity of demographic and socio-economic characters between participant and control group in initial study sample dataset and matched study sample dataset.

Variables		Initial study sample					Matched study sample				
		Participant group		Control group		p-value	Participant group		Control group		p-value
		N	(%)	N	(%)		N	(%)	N	(%)	
Total number of study sample		10990	(100)	176883	(100)		8646	(100)	8646	(100)	
Age group	45-59	5608	(51.03)	74791	(42.28)	<.0001*	4175	(48.29)	4175	(48.29)	1.0000
	over 60	5382	(48.97)	102092	(57.72)		4471	(51.71)	4471	(51.71)	
Gender	Male	6047	(55.02)	89454	(50.57)	<.0001*	4615	(53.38)	4615	(53.38)	1.0000
	Female	4943	(44.98)	87429	(49.43)		4031	(46.62)	4031	(46.62)	
Residence area	District 1	2868	(26.1)	36497	(20.63)	<.0001*	2254	(26.07)	2254	(26.07)	1.0000
	District 2	2594	(23.6)	25878	(14.63)		1878	(21.72)	1878	(21.72)	
	District 3	680	(6.19)	13326	(7.53)		498	(5.76)	498	(5.76)	
	District 4	1032	(9.39)	33488	(18.93)		858	(9.92)	858	(9.92)	
	District 5	1243	(11.31)	22322	(12.62)		969	(11.21)	969	(11.21)	
	District 6	2573	(23.41)	45372	(25.65)		2189	(25.32)	2189	(25.32)	

Variables		Initial study sample					Matched study sample				
		Participant group		Control group		p-value	Participant group		Control group		p-value
		N	(%)	N	(%)		N	(%)	N	(%)	
Disabled	Non-disabled	9997	(90.96)	157758	(89.19)	<.0001*	8040	(92.99)	8040	(92.99)	1.0000
	Disabled	993	(9.04)	19125	(10.81)		606	(7.01)	606	(7.01)	
5 brackets of insurance fee	0	84	(0.77)	3339	(1.89)	<.0001*	44	(0.51)	44	(0.51)	1.0000
	1	2102	(19.19)	30363	(17.22)		1584	(18.32)	1584	(18.32)	
	2	1741	(15.89)	25501	(14.46)		1317	(15.23)	1317	(15.23)	
	3	1810	(16.52)	27347	(15.51)		1399	(16.18)	1399	(16.18)	
	4	2171	(19.82)	35561	(20.17)		1761	(20.37)	1761	(20.37)	
	5	3047	(27.81)	54187	(30.74)		2541	(29.39)	2541	(29.39)	

*p<0.05

Table 5. Comparison the homogeneity of clinical characters and lifestyle behavior state between participant and control group in initial study sample dataset and matched study sample dataset.

Variables		Initial study sample					Matched study sample				
		Participant group		Control group		p-value	Participant group		Control group		p-value
		N	(%)	N	(%)		N	(%)	N	(%)	
Newly diagnosed	No	9109	(82.88)	170091	(96.16)	<.0001*	7623	(88.17)	7623	(88.17)	1.0000
	Yes	1881	(17.12)	6792	(3.84)		1023	(11.83)	1023	(11.83)	
BMI	Underweight	5972	(54.34)	89576	(50.64)	<.0001*	4826	(55.82)	4826	(55.82)	1.0000
	Normal	146	(1.33)	1719	(0.97)		34	(0.39)	34	(0.39)	
	Overweight	4323	(39.34)	74842	(42.31)		3465	(40.08)	3465	(40.08)	
	Obese	549	(5.00)	10746	(6.08)		321	(3.71)	321	(3.71)	
Blood Pressure	Normal	2139	(19.46)	31529	(17.82)	<.0001*	1686	(19.50)	1638	(18.95)	0.2385
	Pre-HTN	5496	(50.01)	92489	(52.29)		4354	(50.36)	4436	(51.31)	
	G1 HTN	2419	(22.01)	41091	(23.23)		1902	(22.00)	1928	(22.30)	
	G2 HTN	748	(6.81)	9920	(5.61)		568	(6.57)	504	(5.83)	
	G3 HTN	188	(1.71)	1854	(1.05)		136	(1.57)	140	(1.62)	
Blood glucose level	Normal	5091	(46.32)	80533	(45.53)	0.0005*	4214	(48.74)	4227	(48.89)	0.7245
	IFG	3679	(33.48)	62292	(35.22)		2919	(33.76)	2945	(34.06)	
	Diabetes	2220	(20.20)	34058	(19.25)		1513	(17.50)	1474	(17.05)	

Variables		Initial study sample					Matched study sample				
		Participant group		Control group		p-value	Participant group		Control group		p-value
		N	(%)	N	(%)		N	(%)	N	(%)	
Disease	HTN	8035	(73.11)	129811	(73.39)	0.6694	6752	(78.09)	6752	(78.09)	1.0000
	DM	1364	(12.41)	22008	(12.44)		970	(11.22)	970	(11.22)	
	HTN & DM	1591	(14.48)	25064	(14.17)		924	(10.69)	924	(10.69)	
MPR groups in hypertension	IG-MU	8295	(86.17)	11775	(7.60)	<.0001*	6372	(83.01)	6372	(83.01)	1.0000
	IG-MO	1331	(13.83)	143100	(92.40)		1304	(16.99)	1304	(16.99)	
MPR groups in diabetes	IG-MU	2335	(79.02)	2943	(6.25)	<.0001*	1294	(68.32)	1294	(68.32)	1.0000
	IG-MO	620	(20.98)	44129	(93.75)		600	(31.68)	600	(31.68)	
Drinking	No	8316	(75.67)	137244	(77.59)	<.0001*	6646	(76.87)	6678	(77.24)	0.5628
	Yes	2674	(24.33)	39639	(22.41)		2000	(23.13)	1968	(22.76)	
Smoking	No	8976	(81.67)	150870	(85.29)	<.0001*	7304	(84.48)	7304	(84.48)	1.0000
	Yes	2014	(18.33)	26013	(14.71)		1342	(15.52)	1342	(15.52)	
Physical activity	No	7252	(65.99)	115212	(65.13)	0.0687	5738	(66.37)	5769	(66.72)	0.6173
	Yes	3738	(34.01)	61671	(34.87)		2908	(33.63)	2877	(33.28)	

*p<0.05

4.2 Evaluation of effect on medication adherence of th e consultation program

4.2.1 Evaluation of effect in hypertension patients

Table 6 shows the results of DID analysis about the effect on medication adherence in hypertension patients by types of MPR groups.

As for subjects who are in IG-MU, MPR of participants decreased of 10.46% from 64.49% to 54.02% while, MPR of controls decreased of 12.74% from 78.54% to 65.80%. The value of DID is 2.27% with the statistical significance (p=0.0153). It means that the consultation program improved MPR of participants who have hypertension with taking their medication under-dose.

Among subjects who are in IG-MO, MPR of participants decreased of 3.15% from 128.42% to 125.27% while, MPR of controls is 4.89% increased from 114.09% to 118.98%. The value of DID is -8.04% with the statistical significance (p=0.0013). Therefore the consultation program is effective intervention in reducing MPR of participants who have hypertension with taking over-dose medication.

Table 6. The result of DID about MPR(%) in hypertension patients by types of intervention.

		Before intervention (2011.07~2013.06)	After intervention (2013.07~2014.12)	Difference between time points
IG-MU (N=12,744)	Participant group	64.49	54.02	-10.46
	Control group	78.54	65.80	-12.74
	Difference between groups	-14.06(<.0001)*	-11.78(<.0001)*	
	DID			**2.27(0.0153)***
IG-MO (N=2,608)	Participant group	128.42	125.27	-3.15
	Control group	114.09	118.98	4.89
	Difference between groups	14.33(<.0001)*	6.29(0.0009)*	
	DID			**-8.04(0.0013)***

*p<0.05

Table 7 represents the results of DDD about the effect on medication adherence in hypertension subjects who take hypertension medication with under-dose by subdivisions (gender, age group and state of newly diagnosed patients). The effects of consultation program by subdivisions are not statistically significant in all divisions.

As for gender, MPR of female participants is 2.61% increased after participate in consultation program according to the results of DID in female group (p=0.0478). But in the case of male group, MPR of male participants is 2.61% increased but the effect is not statistically significant. And also value of DDD is not statistically significant. Through this, it can be concluded that gender doesn't affect the effect of consultation program systemically in this study. But the intervention is more effective in female group than male group.

As for age group, MPR of participants who are in age group with 45-59 years of age is 0.97% increased than control group as a result of DID while, MPR of participants who are in age group with over 60 years of age is 3.66% increased with statistical significance. So this intervention is more effective in older age group than younger age group. But the value of DDD is not statistically significant. Therefore, age group also doesn't affect the effect of consultation program.

As for the change of MPR by states of newly diagnosed patients, MPR of newly diagnosed participants are 6.21% increased than control group (p=0.0177). And the MPR of pre-existing participant increase of 1.83% but this is not statistically significant. And also value of DDD is not statistically significant. Through this, it can be concluded that state of newly diagnosed

patients doesn’t affect the effect of consultation program systemically but, this program is more effective in newly diagnosed patient group than pre-existing patient group.

Table 7. The result of DDD about MPR(%) in hypertension patients who are taking medication under-dose.

			Before intervention (2011.07~2013.06)	After intervention (2013.07~2014.12)	Difference between time points
Gender	Male (N=6,308)	Participant group	67.22	62.63	-4.59
		Control group	80.05	73.50	-6.56
		Difference between groups	-12.84(<.0001)*	-10.87(<.0001)*	
		DID			**1.97(0.1409)**
	Female (N=6,436)	Participant group	60.94	56.48	-4.46
		Control group	76.21	69.13	-7.07
		Difference between groups	-15.27(<.0001)*	-12.66(<.0001)*	
		DID			**2.61(0.0478)***
		DDD = -0.64 (0.7326)			

			Before intervention (2011.07~2013.06)	After intervention (2013.07~2014.12)	Difference between time points
Age group	45-59 (N=5,962)	Participant group	57.1641	54.2674	-2.90
		Control group	68.5246	64.6606	-3.86
		Difference between groups	-11.36(<.0001)*	-10.39(<.0001)*	
		DID			**0.97(0.5044)**
	over 60 (N=6,782)	Participant group	71.12	65.61	-5.50
		Control group	87.48	78.31	-9.17
		Difference between groups	-16.36(<.0001)*	-12.70(<.0001)*	
		DID			**3.67(0.0031)***
		DDD = -2.70 (0.1564)			
New/ Existing	Newly diagnosed (N=1,690)	Participant group	35.92	49.85	13.93
		Control group	59.38	67.10	7.72
		Difference between groups	-23.47(<.0001)*	-17.25(<.0001)*	
		DID			**6.21(0.0177)***
	Pre-Existing (N=11,054)	Participant group	81.87	74.70	-7.18
		Control group	94.64	85.64	-9.00
		Difference between groups	-12.77(<.0001)*	-10.95(<.0001)*	
		DID			**1.83(0.0693)**
		DDD = 4.39 (0.1179)			

Table 8 represents the results of DDD about the effect on medication adherence in hypertension subjects who take hypertension medication with over-dose by subdivisions (gender, age group and state of newly diagnosed patients). The effects of consultation program by subdivisions are not statistically significant in all divisions.

With regard to gender, MPR of male participants decreased of 10.22% after intervention (p=0.00212). MPR of female participants decreased of 4.38% but it is not statistically significant. MPR of male participants are higher than female participants in both before and after intervention. And the value of DDD is not statistically significant. According to these results, this consultation program reduced their MPR more in male group than female group but state of gender doesn't affect the effect of consultation program.

As for age group, MPR decreased of 10.56% in age group with 45-59 years of age (p=0.0079) while, MPR decreased of 9.09% in age group with over 60 years of age. These results represent that this intervention is more effective in younger age group.

As for state of newly diagnosed patients, MPR decrease of 18.06% in participants who are newly diagnosed patients as a result of DID in this subgroup. But this is not statistically significant. Meanwhile, MPR of participants who are pre-existing patients decreased of 7.73% with statistical significance (p=0.0025). The value of DDD is also not statistically significant.

Table 8. The result of DDD about MPR(%) in hypertension patients who are taking medication over-dose.

			Before intervention (2011.07~2013.06)	After intervention (2013.07~2014.12)	Difference between time points
Gender	Male (N=1,646)	Participant group	136.80	122.59	-14.21
		Control group	118.19	114.20	-3.99
		Difference between groups	18.61(<.0001)*	8.39(0.0005)*	
		DID			**-10.22(0.0012)***
	Female (N=962)	Participant group	118.24	105.60	-12.64
		Control group	111.11	102.85	-8.26
		Difference between groups	7.13(0.0082)*	2.75(0.3769)	
		DID			**-4.38(0.2888)**
DDD = -5.85 (0.2598)					

*p<0.05

			Before intervention (2011.07~2013.06)	After intervention (2013.07~2014.12)	Difference between time points
Age group	45-59 (N=1,164)	Participant group	108.64	96.58	-12.06
		Control group	106.80	105.30	-1.50
		Difference between groups	1.84(0.4563)	-8.72(0.0052)*	
		DID			**-10.56(0.0079)***
	over 60 (N=1,444)	Participant group	146.29	130.29	-16.00
		Control group	122.10	115.19	-6.91
		Difference between groups	24.19(<.0001)*	15.10(<.0001)*	
		DID			**-9.09(0.0049)***
		DDD = -1.46 (0.7756)			
New/ Existing	Newly diagnosed (N=106)	Participant group	119.88	116.47	-3.41
		Control group	80.72	95.37	14.65
		Difference between groups	39.16(<.0001)*	21.10(0.0241)*	
		DID			**-18.06(0.1503)**
	Pre-Existing (N=2,502)	Participant group	141.78	127.69	-14.09
		Control group	128.38	122.02	-6.36
		Difference between groups	13.40(<.0001)*	5.67(0.0035)*	
		DID			**-7.73(0.0025)***
		DDD= -10.32(0.4203)			

4.2.2 Evaluation of effect in diabetes patients

Table 9 shows the results of DID analysis about the effect on medication adherence in diabetes patient by types of MPR groups.

With regard to subjects who are in IG-MU, MPR of participants decreased of 5% from 71.10% to 66.10% while, MPR of controls decreased of 12.26% from 85.93% to 73.66%. The value of DID is 7.26% with the statistical significance (p=0.0020). Therefore, the consultation program is effective in increasing MPR of participants who have diabetes with taking under-dose medication.

Meanwhile, in the case of subjects who are in IG-MO, MPR of participants is 2.7% decreased from 135.52% to 132.82% while, MPR of controls increased of 7.03% from 125.97% to 133%. So, the value of DID is -9.73% (p=0.0122). Therefore, consultation program reduce MPR of participants who have diabetes with taking their medication over-dose.

Table 9. The result of DID about MPR(%) in diabetes patients by types of intervention.

		Before intervention (2011.07~2013.06)	After intervention (2013.07~2014.12)	Difference between time points
IG-MU (N=2,588)	Participant group	71.10	66.10	-5.00
	Control group	85.93	73.66	-12.26
	Difference between groups	-14.83(<.0001)*	-7.57(<.0001)*	
	DID			**7.26(0.0020)***
IG-MO (N=1,200)	Participant group	135.52	132.82	-2.7
	Control group	125.97	133	7.03
	Difference between groups	9.55(0.0002)*	-0.18(0.9531)	
	DID			**-9.73(0.0122)***

*p<0.05

Table 10 represents the results of DDD about the effect on medication adherence in diabetes subjects who take diabetes medication with under-dose by subdivisions (gender, age group and state of newly diagnosed patients). The effects of consultation program by subdivisions are not statistically significant in all divisions.

As for gender, MPR is increased of 7.83% in male participant group than male control group after intervention with statistical significance (p=0.0093) while, MPR is increased of 6.51% in female participant group with statistical non significance. And it is possible to conclude that the effect of consultation program as per gender doesn't exist in this study according to the result of DDD.

As for age group, MPR increase of 8.36% in participant who are in age group of 45-59 after intervention while, MPR is 6.33% increase in participant who are in age group of over 60. The amount of change is larger in younger age group than older age group. But the estimated value of DDD is not statistically significant so, there is no differences in effect of consultation program as per age group.

Finally, in the case of state of newly diagnosed patients, MPR is increased of 8.64% in participants who are newly diagnosed after intervention. And MPR of participants who are pre-existing patients is 7.30% increased with statistical significance (p=0.0031). But there are no differences in effect of consultation program as per state of newly diagnosed patients with non-significance of estimated DDD.

Table 10. The result of DDD about MPR(%) in diabetes patients who are taking medication under-dose.

			Before intervention (2011.07~2013.06)	After intervention (2013.07~2014.12)	Difference between time points
Gender	Male (N=1,598)	Participant group	69.40	73.27	3.87
		Control group	83.16	79.19	-3.97
		Difference between groups	-13.76(<.0001)*	-5.92(0.0093)*	
		DID			**7.83(0.0093)***
	Female (N=990)	Participant group	69.44	68.53	-0.91
		Control group	86.04	78.62	-7.42
		Difference between groups	-16.60(<.0001)*	-10.09(0.0004)*	
		DID			**6.51(0.0865)**
DDD = 1.32 (0.7852)					

			Before intervention (2011.07~2013.06)	After intervention (2013.07~2014.12)	Difference between time points
Age group	45-59 (N=1,344)	Participant group	56.76	63.63	6.87
		Control group	71.77	70.28	-1.49
		Difference between groups	-15.01(<.0001)*	-6.66(0.0130)*	
		DID			**8.36(0.0152)***
	over 60 (N=1,244)	Participant group	82.50	80.16	-2.34
		Control group	97.17	88.50	-8.67
		Difference between groups	-14.67(<.0001)*	-8.33(0.0005)*	
		DID			**6.33(0.0519)**
		DDD = 2.03 (0.6690)			
New/ Existing	Newly diagnosed (N=240)	Participant group	38.30	56.53	18.23
		Control group	63.04	72.63	9.59
		Difference between groups	-24.74(<.0001)*	-16.10(0.0061)*	
		DID			**8.64(0.2779)**
	Pre-Existing (N=2,348)	Participant group	89.47	89.98	0.51
		Control group	103.46	96.67	-6.79
		Difference between groups	-13.99(<.0001)*	-6.69(0.0004)*	
		DID			**7.30(0.0031)***
		DDD = 1.34 (0.8722)			

Table 11 represents the results of DDD about the effect on medication adherence in diabetes subjects who take diabetes medication with over-dose by subdivisions (gender, age group and state of newly diagnosed patients). The effects of consultation program by subdivisions are not statistically significant in all divisions.

As for gender, MPR of male participants is 8.84% decrease compared with controls after intervention while, MPR of female participants is 11.64% decreased. But these estimated values of DID by gender are not statistically significant. Also the estimated value of DDD is not statistically significant.

In the case of age group, MPR of older age group decreased of 12.05% compared with controls after intervention with statistical significance ($p=0.0176$). But the effect of consultation program on MPR in younger age group is no statistically significant.

And as for state of newly diagnosed patients, MPR decreased of 42.20% in participants who are newly diagnosed after intervention. And MPR of participants who are pre-existing patients is 9.06% decreased with statistical significance ($p=0.0216$). But there are no differences in effect of consultation program as per state of newly diagnosed patients with non-significance of estimated DDD.

Table 11. The result of DDD about MPR(%) in diabetes patients who are taking medication over-dose.

			Before intervention (2011.07~2013.06)	After intervention (2013.07~2014.12)	Difference between time points
Gender	Male (N=792)	Participant group	145.15	132.39	-12.76
		Control group	130.83	126.91	-3.92
		Difference between groups	14.32(<.0001)*	5.48(0.1336)	
		DID			**-8.84(0.0658)**
	Female (N=408)	Participant group	126.04	113.41	-12.63
		Control group	125.32	124.33	-0.99
		Difference between groups	0.72(0.8699)	-10.92(0.0303)*	
		DID			**-11.64(0.0805)**
DDD = 2.79 (0.7339)					

			Before intervention (2011.07~2013.06)	After intervention (2013.07~2014.12)	Difference between time points
Age group	45-59 (N=554)	Participant group	117.35	107.94	-9.41
		Control group	118.10	118.59	0.49
		Difference between groups	-0.75(0.8437)	-10.65(0.0274)*	
		DID			**-9.90(0.1059)**
	over 60 (N=646)	Participant group	155.47	139.22	-16.25
		Control group	137.26	133.06	-4.20
		Difference between groups	18.21(<.0001)*	6.16(0.0991)*	
		DID			**-12.05(0.0176)***
		DDD = 2.14 (0.7878)			
New/ Existing	Newly diagnosed (N=30)	Participant group	95.55	90.68	-4.87
		Control group	115.26	152.59	37.33
		Difference between groups	-19.71(0.2395)	-61.91(0.0012)*	
		DID			**-42.20(0.0974)**
	Pre-Existing (N=1,170)	Participant group	154.95	142.04	-12.91
		Control group	144.60	140.75	-3.85
		Difference between groups	10.35(<.0001)*	1.29(0.6651)	
		DID			**-9.06(0.0216)***
		DDD = -33.13 (0.1983)			

4.3 Evaluation of effect on medication adherence of th e consultation program in specific group.

Figure 6 shows the trend of MPR by disease and types of intervention from the second half year of 2011(2011_2) to the second half year of 2014(2014_2). Participants and controls are divided into IG-MU and IG-MO in accordance with calculated MPR in the second half year of 2012. According to figure 6, it is possible to predict there are some participants who have large difference between MPR of the second half year of 2012 and the first half year of 2013 as a period of before intervention. So, this study extracted participants who are in same MPR group due to calculate MPR in both the second half year of 2012 and the first half year of 2013 among participants who are selected by PSM. And then, controls who are matched that participants with propensity score were extracted. Figure 7 shows the MPR trend with newly extracted study subjects. MPR trends of participants in hypertension and diabetes have more consistency than before.

DID and DDD analysis were done with newly extracted study subjects and the results are represented in Table 12. Other results are represented in Appendix 4-9. The results of DID are same with previous analysis. The MPRs of participants who are in hypertension and diabetes IG-MU are decreased due to the consultation program, while the MPRs of participants who are in IG-MO are decreased. On the other hands, there are no effects by subgroups in previous analysis, but there are some effects by state of newly diagnosed patients with newly extracted study subjects.

As for hypertension subjects who are in IG-MU, MPR is 13.81%

increase in participants group with newly diagnosed patients then control group ($p < .0001$). And MPR in participants group with pre-existing patient increase of 3.35%, but this is not statistically significant. The effect of consultation program is not clarified in the pre-existing hypertension patients but according to estimate value of DDD, the effect of consultation program can be changed by state of newly diagnosed patients. Therefore, MPR of newly diagnosed participants increase of 10.46% then MPR of pre-existing participants in IG-MU ($p=0.0058$). Like this, as for hypertension subjects who are in IG- MO, MPR of newly diagnosed participant decrease of 62.81% then MPR of pre-existing participants ($p=0.0332$).

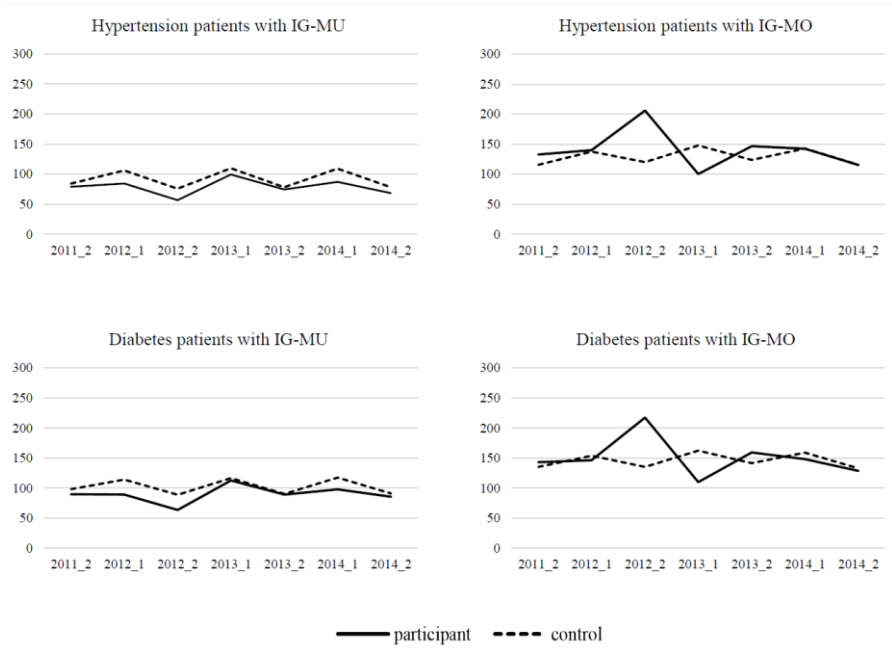

Figure 6. MPR trends by disease and types of intervention

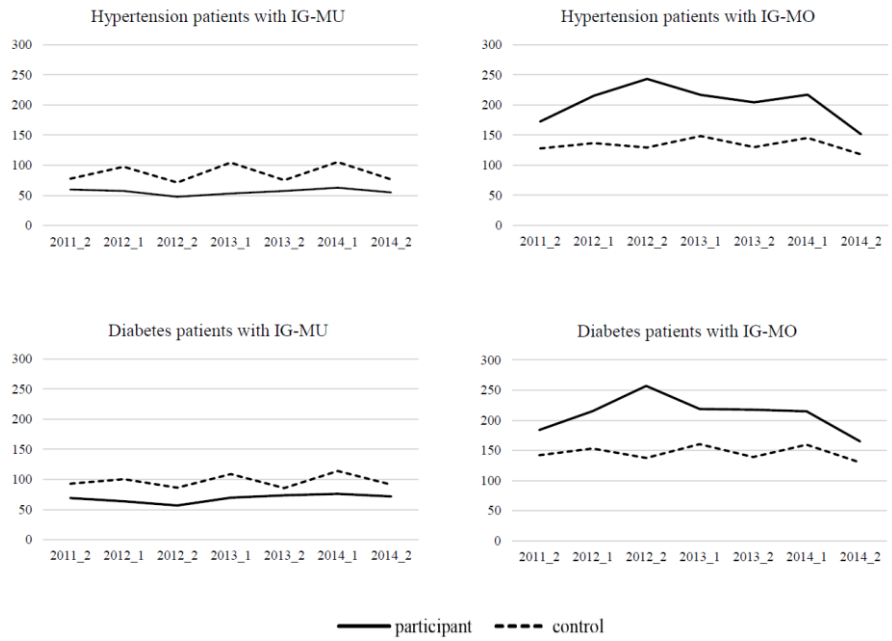

Figure 7. MPR trends by disease and types of intervention after extract specific group

Table 12. The result of DDD about MPR(%) by diseases, type of MPR group and state of newly diagnosed patient..

			Before intervention (2011.07~2013.06)	After intervention (2013.07~2014.12)	Difference between time points
HTN IG-MU	Newly diagnosed	Participant group	23.24	45.64	22.40
		Control group	57.58	66.18	8.59
		Difference between groups	-34.34(<.0001)*	-20.53(0.0093)*	
		DID			**13.81(<.0001)***
	Pre-Existing	Participant group	59.25	55.47	-3.78
		Control group	91.63	84.50	-7.13
		Difference between groups	-32.39(<.0001)*	-29.03(<.0001)*	
		DID			**3.35(0.0708)**
		DDD = 10.46 (0.0058)*			
HTN IG-MO	Newly diagnosed	Participant group	195.62	148.63	-46.99
		Control group	66.03	98.59	32.57
		Difference between groups	129.59(<.0001)*	50.04(0.0229)*	
		DID			**-79.56(0.0062)***
	Pre-Existing	Participant group	203.05	179.63	-23.42
		Control group	128.75	122.08	-6.67
		Difference between groups	74.30(<.0001)*	57.55(0.0005)*	
		DID			**-16.75(0.0010)***
		DDD = -62.81 (0.0332)*			

			Before intervention (2011.07~2013.06)	After intervention (2013.07~2014.12)	Difference between time points
DM IG-MU	Newly diagnosed	Participant group	28.19	53.48	25.28
		Control group	74.15	80.47	6.32
		Difference between groups	-45.95(<.0001)*	-27.00(0.0061)*	
		DID			**18.96(0.1026)**
	Pre-Existing	Participant group	71.76	78.04	6.27
		Control group	101.05	98.77	-2.28
		Difference between groups	-29.29(<.0001)*	-20.74(0.0004)*	
		DID			**8.55(0.0781)***
		DDD = 10.41 (0.4084)			
DM IG-MO	Newly diagnosed	Participant group	236.15	241.65	5.50
		Control group	24.29	78.43	54.13
		Difference between groups	211.86(0.0011)*	163.22(0.1205)	
		DID			**-48.63(0.6940)**
	Pre-Existing	Participant group	215.76	191.27	-24.49
		Control group	143.70	138.66	-5.04
		Difference between groups	72.06(<.0001)*	52.61(0.0004)*	
		DID			**-19.45(0.0077)***
		DDD = -29.19 (0.8137)			

*p<0.05

Chapter 5. Discussion and Conclusion

These days, many people have chronic diseases like hypertension and diabetes which are very common chronic diseases globally. So, it is very important to manage chronic diseases for healthy life. Because of this diseases tend to be asymptomatic unless complications arise(Donnan et al., 2002), it is easy to get in trouble with managing their chronic disease appropriately. Taking medication is widely known as one of factors which affect administration of disease directly(Parthasarathi and Nyfort-Hansen, 2004). And patients who have chronic disease have to take medication for an entire life after diagnosed so, it is important to manage medication adherence.

NHIS implemented consultation program to improve medication adherence with 3 times interventions for 3 months in 2013. Among People who have hypertension and diabetes are defines using medical and prescription record in NHIS database, the consultation program provided intervention for only people who are medication non-adherent. Moreover, this program is on the way to expand the range of districts where this intervention enforced year after year. So, it is necessary to evaluate how this consultation program achieved its goals and who is affected by this in a positive way. Therefore, the purpose of this study is to evaluate the effect of consultation program on medication adherence of study subjects by types of MPR group and subgroups.

As results of this study, the effect of consultation program on MPR was confirmed with statistical significance in hypertension and diabetes participants and all types of MPR group. As for IG-MU, the MPR was 2.27% increased after intervention in hypertension participants (p=0.0153) and 7.26% increase in diabetes participants (p=0.0020). As for IG-MO, the MPR was 8.04% decreased after intervention in hypertension participants (p=0.0013) and 9.73% decreased in diabetes participants (p=0.0122). But the results of analysis about the effect of consultation program by subgroups were not statistically significant. There are some medication non-adherent participants whose MPR of the second half year of 2012 is different from MPR of the first half year of 2013. These participants are eliminated for the purpose of evaluating more accurate effect of consultation program. After that, the effect of intervention by state of newly diagnosed patients was found in hypertension participants. The MPR of participants who are newly diagnosed as hypertension in 2012 was increase of 10.46% than MPR of participants who are pre-existing patient in IG-MU (p=0.0058). And the MPR of participants who are newly diagnosed as hypertension in 2012 was 62.81% decrease than the MPR of participants who are pre-existing patient in IG-MO (p=0.0332).

The above results are come from each participant's medication-taking behavior. Medication adherence is one of health care habit so, it is not easy to change in a short time. But as for the newly diagnosed patients, the habit of taking medication doesn't fully develop. However, as for the pre-existing patients who are medication non-adherent, they may make a habit about

taking medication inappropriate way for a long-time, so the amount of difference in MPR may be lower than newly diagnosed patient. Moreover, the intervention program consisted of 1 time of providing leaflet and 2 times of telephone consultation for 3 months. This is not sufficient to correct their medication adherence even though the effect in pre-existing patient group was confirmed. And the barriers to good medication-taking behavior clearly tend to occur early in the therapeutic course (Burnier, 2006). So, it is important to provide consultation program to newly diagnosed patients. And if this consultation program focuses on newly diagnosed patients, it will be one of the way to improve effectiveness of this intervention than to provide consultation program to pre-existing patient. As for pre-existing patient, this consultation program is too short to improve their medication adherence, so it needs to develop a long-term consultation program.

This study has strengths in some parts. First, this study use z-score matching with 22 indicators about health state and socio-economic state in district level and propensity score matching with various covariates. Therefore this study investigated using study sample which was reduced or eliminated possible selection bias. So, the effect measured in this study represents the actual effect of this program. Second, this study use MPR as a measurement method of medication adherence considered the subject's behavioral differences in medical service utilization and types of medications by ingredient to resolve overlapped period between prescriptions. Third, this study has subgroups so it is possible to find which subgroup took more benefits to correct their medication adherence in a good and healthy way.

Some limitations of this study deserve a mention. First, the study have short period of after intervention. In the case of behavior, it has been made for a long time, so it is hard to change their habit in a short period. And previous study reported that the initial effect started to decrease after the intervention period (Otsuki et al., 2009). However, this consultation program has conducted since 2013, so this study only can investigate short-term effect of the consultation program. Therefore further study will be needed to long-term effect of this consultation program on medication adherence. Second, the consultation providers of this program consisted of administrative staffs in NHIS and pharmacists in each district so, there are some differences in effect of intervention by provider. But the information about it wasn't obvious. So there need to record some information about consultants.

Finally, the effect of consultation program on MPR was confirmed in hypertension and diabetes participants who have problem in medication adherence. According to the results, this study provides a scientific and documented evidence regarding extended enforcement of personalized consultation program to improve medication adherence. And this study suggest that it needs to implement consultation program which is effective and active management service about chronic disease on the national scale.

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Appendix

Appendix 1. Health state indicators used calculating Z-score

	health state indicators
1	Prevalence of diagnosed hypertension in over 30 years old
2	Prevalence of diagnosed diabetes in over 30 years old
3	Averaged BMI
4	Walking rate
5	Vigorous physical activity rate
6	High-risk drinking rate
7	Hypertension medication treatment rate in over 30 years old
8	Hypertension treatment rate in over 30 years old
9	Diabetes treatment rate in over 30 years old
10	Self-reported hypertension control rate
11	Self-reported diabetes control rate
12	Yearly drinking rate
13	Drinking rate
14	Smoking rate
15	Health institute use rate

Appendix 2. Socio-economic state indicators used calculating Z-score

	Socio-economic state (SES) indicators
1	Mortality rate
2	Averaged amount of local tax collection
3	Gross regional domestic product (GRDP) per capita
4	Activity rate
5	Accession rate
6	Unemployment rate
7	Aging population rate

Appendix 3. Classification standards of BMI, blood pressure and blood glucose level.

BMI	
Underweight	<18.5kg/m^2
Normal	18.5-24.9kg/m2
Overweight	25-29.9kg/m2
Obese	≥30kg/m2
Blood pressure	
Normal	SBP:<120mmHg and DBP:<80mmHg
Pre-HTN	SBP: 120-139mmHg or DBP: 80-89mmHg
G1 HTN	SBP: 140-159mmHg or DBP: 100-109mmHg
G2 HTN	SBP: 160-179mmHg or DBP: 100-109mmHg
G3 HTN	SBP: ≥180mmHg or DBP: ≥110mmHg
Blood glucose level	
Normal	<100mg/dl
IFG	100-125mg/dl
Diabetes	≥126mg/dl

Appendix 4. The result of DID about MPR(%) in hypertension patients by types of intervention with newly extracted study subjects.

		Before intervention (2011.07~2013.06)	After intervention (2013.07~2014.12)	Difference between time points
IG-MU	Participant group	43.57	43.38	-0.19
	Control group	76.38	70.32	-6.05
	Difference between groups	-32.81(<.0001)*	-26.95(<.0001)*	
	DID			**5.86(0.0003)**
IG-MO	Participant group	187.31	167.65	-19.66
	Control group	111.41	110.30	-1.11
	Difference between groups	75.90(<.0001)*	57.35(<.0001)*	
	DID			**-18.55(0.0002)**

Appendix 5. The result of DDD about MPR(%) in newly extracted study subjects who are taking HTN medication under-dose.

			Before intervention (2011.07~2013.06)	After intervention (2013.07~2014.12)	Difference between time points
Gender	Male	Participant group	49.43	51.59	2.15
		Control group	79.81	76.48	-3.34
		Difference between groups	-30.38(<.0001)*	-24.89(<.0001)*	
		DID			**5.49(0.0194)***
	Female	Participant group	38.80	41.60	2.79
		Control group	73.81	70.34	-3.47
		Difference between groups	-35.01(<.0001)*	-28.74(<.0001)*	
		DID			**6.26(0.0052)***
		DDD = -0.7737 (0.8116)			
Age group	45-59	Participant group	38.59	44.52	5.93
		Control group	67.46	66.38	-1.08
		Difference between groups	-28.87(<.0001)*	-21.86(<.0001)*	
		DID			**7.01(0.0041)***
	Over 60	Participant group	49.69	49.85	0.16
		Control group	86.10	80.41	-5.69
		Difference between groups	-36.41(<.0001)*	-30.56(<.0001)*	
		DID			**5.85(0.0071)***
		DDD = 1.1583 (0.7232)			

Appendix 6. The result of DDD about MPR(%) in newly extracted study subjects who are taking HTN medication over-dose.

			Before intervention (2011.07~2013.06)	After intervention (2013.07~2014.12)	Difference between time points
Gender	Male	Participant group	194.23	171.14	-23.09
		Control group	114.42	110.05	-4.37
		Difference between groups	79.81(<.0001)*	61.09(<.0001)*	
		DID			**-18.72(0.0018)***
	Female	Participant group	180.30	153.88	-26.42
		Control group	113.17	105.08	-8.09
		Difference between groups	67.13(<.0001)*	48.80(<.0001)*	
		DID			**-18.33(0.0432)***
		DDD = -0.3863 (0.9716)			
Age group	45-59	Participant group	171.28	164.58	-6.70
		Control group	105.02	106.35	1.33
		Difference between groups	66.26(<.0001)*	58.23(<.0001)*	
		DID			**-8.03(0.4894)**
	Over 60	Participant group	199.03	170.76	-28.27
		Control group	120.39	113.50	-6.89
		Difference between groups	78.64(<.0001)*	57.26(<.0001)*	
		DID			**-21.38(0.0001)***
		DDD = 13.3352 (0.3009)			

Appendix 7. The result of DID about MPR(%) in diabetes patients by types of intervention with newly extracted study subjects.

		Before intervention (2011.07~2013.06)	After intervention (2013.07~2014.12)	Difference between time points
IG-MU	Participant group	54.76	59.75	4.99
	Control group	86.27	81.21	-5.06
	Difference between groups	-31.51(<.0001)*	-21.46(<.0001)*	
	DID			**10.05 (0.0245)***
IG-MO	Participant group	208.67	189.27	-19.40
	Control group	135.87	135.87	0.00
	Difference between groups	72.80(<.0001)*	53.40(<.0001)*	
	DID			**-19.40 (0.0077)***

Appendix 8. The result of DDD about MPR(%) in newly extracted study subjects who are taking DM medication under-dose.

			Before intervention (2011.07~2013.06)	After intervention (2013.07~2014.12)	Difference between time points
Gender	Male	Participant group	58.98	72.06	13.08
		Control group	93.83	93.83	-0.01
		Difference between groups	-34.86(<.0001)*	-21.77(<.0001)*	
		DID			**13.09(0.0196)***
	Female	Participant group	54.25	56.16	1.91
		Control group	80.06	77.40	-2.66
		Difference between groups	-25.81(<.0001)*	-21.24(0.0002)*	
		DID			**4.57(0.5395)**
		DDD = 8.52 (0.3612)			
Age group	45-59	Participant group	37.02	53.75	16.73
		Control group	75.87	80.30	4.43
		Difference between groups	-38.85(<.0001)*	-26.55(<.0001)*	
		DID			**12.30(0.0458)***
	Over 60	Participant group	76.52	75.93	-0.58
		Control group	98.73	92.68	-6.05
		Difference between groups	-22.21(<.0001)*	-16.74(0.0005)*	
		DID			**5.47(0.4020)**
		DDD = 6.83 (0.4464)			

Appendix 9. The result of DDD about MPR(%) in newly extracted study subjects who are taking DM medication over-dose.

			Before intervention (2011.07~2013.06)	After intervention (2013.07~2014.12)	Difference between time points
Gender	Male	Participant group	210.24	187.84	-22.4
		Control group	129.22	125.00	-4.22
		Difference between groups	81.02(<.0001)*	62.84(<.0001)*	
		DID			**-18.18(0.0367)***
	Female	Participant group	191.48	163.09	-28.39
		Control group	137.01	132.01	-5.00
		Difference between groups	54.47(<.0001)*	31.08(0.0021)*	
		DID			**-23.39(0.0785)**
		DDD = 5.1993 (0.7436)			
Age group	45-59	Participant group	185.29	178.05	-7.24
		Control group	120.91	120.18	-0.73
		Difference between groups	64.38(<.0001)*	57.87(<.0001)*	
		DID			**-6.51(0.6577)**
	Over 60	Participant group	217.19	186.94	-30.25
		Control group	141.05	135.30	-5.75
		Difference between groups	76.14(<.0001)*	51.64(<.0001)*	
		DID			**-24.50(0.0037)***
		DDD = 17.9819 (0.2895)			

국문초록

투약순응도 향상을 위한 상담프로그램의 효과분석

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고혈압과 당뇨는 널리 알려진 주요 만성질환으로 30세 이상에서 그 유병률이 각각 30%, 10%인 것으로 나타났으며 연령이 증가할수록 유병률이 증가하는 것으로 나타났다. 또한 이는 심각한 질환의 원인이 되므로 지속적인 관리가 요구된다. 본 연구의 목적은 투약순응도 향상을 위한 상담 프로그램이 고혈압 및 당뇨 환자에 있어 투약순응도 변화에 미친 영향을 평가하는 것이다.

2013년 7월부터 3개월에 걸쳐 시행된 국민건강보험공단의 적정투약관리 프로그램을 대상으로 건강보험 및 건강 검진 자료를 활용하여 프로그램 시행 전후로 프로그램의 효과를 분석하였다. 실제 프로그램의 효과를 평가하기 위해 성향점수매칭법(PSM)을 활용하여 프로그램 참여자와 유사한 성향을 가진 대조군을 선정하였고, 에 대하여 각각 이중차이분석(DID)을 실시하였다.

분석 결과, 고혈압과 당뇨 환자의 MPR에 따른 과소투약군(IG-MU)과 과다투약군(IG-MO) 모두에 있어 프로그램의 시행이 통계적으로 유의한 효과를 가지고 있음을 확인했다. 과소투약군의

경우 MPR이 프로그램 시행 후 증가하는 것을 알 수 있었으며 (고혈압: 2.27% 증가(p=0.0153), 당뇨: 7.26% 증가(p=0.0020)), 과다투약군의 경우 MPR이 프로그램 시행 후 감소하는 것으로 확인되었다 (고혈압: 8.04% 감소(p=0.0013), 당뇨: 9.73% 감소(p=0.0122)). 또한 세부 그룹에 따른 상담프로그램의 효과의 경우, 성별과 연령에 따른 프로그램의 효과 차이는 유의한 결과값을 갖지 못하였으나 신규환자 여부에 따른 프로그램의 효과 차이는 고혈압 대상자들에 있어 신규환자에서의 효과가 기존환자에서의 효과보다 더 큰 것으로 나타났다 (과소투약군: 10.46% (p=0.0058), 과다투약군: −62.81% (p=0.0332)).

본 연구의 결과를 바탕으로 투약순응도 향상을 위한 상담 프로그램의 효과를 확인하였으며, 신규환자에게 있어 프로그램이 더 효과적임을 알 수 있었다. 따라서 본 연구는 개인 수준의 맞춤형 상담 프로그램의 확대실시의 근거로 활용될 것으로 기대하며, 효과적이고 적극적인 만성질환 관리 서비스 제공의 필요성을 제언할 수 있다.

주요어 : 투약순응도, 만성질환, 중재프로그램, 성향점수매칭, 이중차이분석

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