보건학박사학위논문

Anticholinergic Use and Incidence of Alzheimer's Disease: Analysis of the National Health Insurance Service (NHIS) Elderly Cohort

항콜린제 사용과 알츠하이머 질환의 발생에 관한 연구: 국민건강보험 노인코호트 분석

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ABSTRACT

Anticholinergic Use and Incidence of Alzheimer's Disease: Analysis of the National Health Insurance Service (NHIS) Elderly Cohort

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Objective:

Anticholinergic agents (anticholinergics) can be used to treat a variety of diseases including allergic diseases, depression, psychosis, and overactive bladder; however they can produce a range of adverse effects such as constipation, urinary retention, agitation, confusion, and cognitive impairment. The elderly people are especially vulnerable to negative anticholinergic effects due to decreased clearance of such drugs and the nature of aging itself. Although many anticholinergics are being

classified as potentially inappropriate medications (PIMs) for the elderly, the prevalence of diseases for which anticholinergics are indicated is much higher in the older people.

Alzheimer's disease (AD), a disease having a very high disease burden on individuals and society, is associated with the use of certain drugs. Drugs with strong anticholinergic properties have negative impact on cognitive function then recommended to be avoided by the elderly, especially those with cognitive impairment or dementia.

Although there are some studies on the use of anticholinergics in the elderly, studies which quantified the exposure of anticholinergic burden to the actual prescription amount in large population were very limited. There are also lack of studies evaluating anticholinergic use in AD patients by thorough investigation of the quantitative exposure. Above all, although the use of inappropriate anticholinergics is known to have a negative impact on cognitive function, there is little research as to whether it increases the risk of AD. The operational definition of anticholinergic exposure varies from study to study making it difficult to compare the results of each study side by side. No studies have compared the difference among the approaches for the estimation of prescription amount of anticholinergics. In addition, there is no detailed study of weak anticholinergic use and their relevance to AD.

The objectives of this study were to (1) calculate the standardized doses of anticholinergics and test their correlation with other approaches for estimating prescription amount, then describe the prescription pattern of anticholinergics in the elderly Koreans by using standardized prescribed doses as an exposure metrics, (2) examine how anticholinergics were prescribed in AD patients by comparison with

non-Alzheimer's group, (3) investigate whether the use of anticholinergic agents increases the risk of AD.

Methods:

(1) The National Health Insurance Service (NHIS) Elderly cohort database was used. The NHIS Elderly cohort data has detailed medical use records and claims data from 2002 to 2013 for about 550,000 people, 10% of all elderly Koreans who have medical insurance or medical aids in 2002. Information on drugs available in Korea was obtained from Health Insurance Review and Assessment Service (HIRA) database.

(2) Using the American Geriatrics Society (AGS) Beers criteria and Anticholinergic Cognitive Burden (ACB) scale, 58 strong anticholinergics and 34 weak anticholinergics were determined. Standardized prescribed doses were calculated for strong, weak and total anticholinergics based on 'the adequate daily dose for the elderly' established by referencing drug approval information, Lexicomp® Online, and Micromedex® DRUGDEX. The relative dose was defined as actual content in prescribed drug in administered units (eg, 1 tablet or 1 capsule) compared to the adequate dose for the elderly. And then the standardized prescribed doses for each anticholinergics were calculated using the generic code, relative dose, dosage unit, daily frequency of administration, and number of prescribed days.

(3) Standardized prescribed doses of anticholinergics in 2012 were then compared with prescribed days and cumulative prescribed days. Although

standardized prescribed doses were adopted as the most proper and reasonable estimation of anticholinergic prescriptions in this study, those three measurement approaches were assumed to be used interchangeably if they were highly correlated. The relationships between the three approaches were examined by correlation analysis and regression analysis for the strong, weak, and total anticholinergics.

(4) Using the standardized prescribed doses of anticholinergics, The prescription patterns of anticholinergic agents including standardized prescribed doses of both strong and weak anticholinergics, number of days on which multiple strong anticholinergics were prescribed were investigated in the elderly ≥70 years old in 2012. The predictors of excessive use of strong anticholinergics were also examined by logistic regression analysis.

(5) The use of anticholinergics in patients with AD were compared with non-AD subjects. AD patients in 2012 was defined as those with Alzheimer' dementia (ICD: F00) or Alzheimer's disease (ICD: G30) diagnoses in 2011 and 2012, respectively, and at least one medical record with an anti-Alzheimer drug prescription at the time of the diagnosis. Annual standardized prescriptions were calculated for all anticholinergics in 2012. Prescription amount of more than 90 doses of strong anticholinergics was defined as excessive use of strong anticholinergics, and logistic regression analysis was conducted to identify how presence of AD predict the excessive use of strong anticholinergics.

(6) The final study was to determine whether the use of inappropriate anticholinergics increases the risk of AD. Among the elderly who had never

been diagnosed with mental and behavioral disability (ICD: F00-F99) and Alzheimer's disease (ICD: G30), including all types of dementia as the primary or secondary diagnosis for three years from 2002 to 2004 years, 342,522 people who were qualified for NHIS in 2005 were selected. In the follow-up study from 1 January 2005 to 31 December 2013, a person with a diagnose of AD (F00 or G30) and a prescription of anti-AD agents at the time of the diagnosis was defined as a patient with AD and the first day of those was defined as the incident date. For measuring the quantitative exposure to strong anticholinergics, the standardized prescribed doses of anticholinergics from 2002 until the end of the follow-up period were summed by individual, and the average doses of prescription per year were calculated by dividing by follow-up period of exposure. Proportional hazard regression model was applied for the analysis. The subjects were stratified according to the follow-up period of exposure and the age at the baseline of exposure. Period of 9-12 years were defined as longer follow-up of exposure, while period of 3-8 years were shorter follow-up of exposure. Subjects were also divided into two strata by age at the baseline of exposure. That is, subjects younger than 65 years of age in 2002, who appeared at age 75 or younger at the time of AD or censoring, were defined as 'the younger elderly', and the others who were ≥ 65 years of age in 2002, were defined as 'the older elderly'. Taken together, two-dimensional strata were constructed using these two time scales, then the incidence rate, and risk of AD according to the strong anticholinergic exposure levels were estimated.

Results:

(1) The standardized prescribed doses and cumulative prescription days showed a high correlation of 83-87%, and the coefficient of determination (R squared, R2) of the regression equation was as high as 0.68-0.76. The correlation between the standardized prescribed doses and prescribed days was about 10% lower than this.

(2) For majority of the subjects (52.8%), strong anticholinergics less than 15 doses were prescribed for one year in 2012, but 9.7% were exposed to very high doses of strong anticholinergics (≥180 dose/year). About 10% of the elderly received two strong anticholinergics on the same days for more than one month of the year. Among the strong anticholinergics, antihistamines and antidepressants were the most prescribed drug classes and chlorpheniramine and amitriptyline were the most prescribed drugs. The prescription amount of these two kind of drugs accounted for 58.7% of the total prescription amount of strong anticholinergics. Several factors associated with excessive use of strong anticholinergics (≥90 dose/year) were confirmed through multivariate logistic regression. The lowest income, polypharmacy, most of diseases such as depression, Parkinson's disease, genitourinary diseases for which strong anticholinergics were indicated were predictors of the excessive use of strong anticholinergics for the older people.

(3) The proportion of people who were exposed to excessive amount of strong anticholinergics (≥ 90 dose) was higher in AD patients comparing to non-AD group (15.63% vs. 28.2%, respectively). When performing multiple

logistic regression analysis to identify whether AD could be a predictor of excessive use of strong anticholinergics (≥ 90 doses/year), the odds for overuse of strong anticholinergics in AD were 36% higher than in non-AD group after adjusting for age, sex, and income. Looking closely at individual drugs and drug classes, the proportions of antihistamines and antidepressants were predominantly high in both AD patients and non-AD groups. Prescription amount of antidepressants, antimuscarinics, antiparkinsonians, and anticonvulsants were higher in patients with AD than in non-AD group. In compared to non-AD group, 12% lower odds for the excessive use of strong anticholinergics were showed in AD group after adjusting for the diseases for which strong anticholinergics were indicated.

(4) In the study to investigate whether anticholinergic use increases the risk of AD, subjects whose anticholinergic exposure were followed up for a longer period of time had increased risk of AD in proportion to their prescription amount of strong anticholinergics. Especially, the HRs in the younger elderly whose exposure were followed up for 9-12 years were highest among the 2 dimensional strata [HR (95% CI)=1.07 (0.99-1.16), HR (95% CI)=1.49 (1.34-1.67), HR (95% CI)=1.78 (1.57-2.03) for 10-49 dose/yr, 50-119 dose/yr, and ≥ 120 dose/yr group respectively, in the younger elderly; in followed-up exposure period of 9-12 years]. In supplementary analyses in which the criteria of anticholinergic exposure were varied to minimize the prodromal effect, the association between use of strong anticholinergics and the risk of AD still kept significant, further supporting that the overuse of anticholinergics could increase the risk of AD.

Conclusions:

(1) The standardized prescribed doses and the cumulative prescribed days were highly correlated that they could be used interchangeably each other. The cumulative prescribed days were more similar estimation to the standardized prescribed doses rather than the prescribed days.

(2) The prevalence of inappropriate anticholinergic use was high in the elderly population in Korea, and the amount of prescription was considerably excessive in some people suggesting that efforts to reduce this are needed.

(3) Although strong anticholinergics could negatively affect the course of AD, overuse of strong anticholinergics was more prevalent in the elderly with AD than in the non-AD. There is a need for measures to reduce the use of inappropriate anticholinergics in AD.

(4) Excessive use of strong anticholinergics increased the risk of AD. The risk was more prominent in long-term medication and / or in younger elderly people. Strong anticholinergics may affect not only the progression but also development of AD. Reducing the use of strong anticholinergics may contribute to preventing or delaying incident AD.

Key words: Anticholinergic agents, Alzheimer's disease, National Health Insurance Service (NHIS) Elderly cohort, Older adults, Beers Criteria, Anticholinergic Cognitive Burden (ACB) scale

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LIST OF ABBREVIATIONS

ACB	Anticholinergic Burden
AD	Alzheimer's Disease
AGS	American Geriatric Society
BMI	Body Mass Index
CI	Confidence Interval
CVD	Cardiovascular Diseases
DDD	Defined Daily Dose
DM	Diabetes Mellitus
GUD	Genitourinary Disease
HR	Hazard Ratio
HTN	Hypertension
ICD	International Classification of Diseases
MFDS	Ministry of Food and Drug Safety
MI	Myocardial Infarction
PD	Parkinson’s Disease
PIMs	Potentially Inappropriate Medications
PSM	Propensity Score Method
R2	Coefficient of determination (R squared)
RR	Relative Risk
SBP	Systolic Blood Pressure
VaD	Vascular Dementia
WHO	World Health Organization

CHAPTER 1. INTRODUCTION

1-1. Drug use in older adults

Multimorbidities due to aging inevitably lead to multiple drug use. Elderly people with multiple diseases were reported to reach 55-98% (Nobili, Garattini, and Mannucci 2011, Marengoni et al. 2011). 86.7% of elderly people in Korea are suffering from chronic diseases, and 77.7% are taking at least one oral medicine. Considering the frequent use of non-prescription drugs and herbal medicines, the actual drug use is expected to be even higher in Korea (MFDS 2009).

Since elderly people are different from general adults in terms of pharmacokinetics and pharmacodynamics. Increased gastric pH and changed gastrointestinal motility may cause delays in gastrointestinal emptying, raised bioavailability of drugs with a first-pass effect, and absorption processes may be altered due to decreased absorption area (Klotz 2009). In addition, lipid reduction and changes in blood flow may affect the volume of distribution, and the ability of hepatic metabolism and renal excretion may also be declined (Pretorius et al. 2013). Biochemical and physiological pharmacology and pharmacodynamic aspects are not well understood and it is even difficult to predict the effects of aging (MFDS 2009).

For the elderly, special care needs to be taken to ensure optimal choice of medicines to avoid drug-drug or drug-disease interactions by taking into account both the biological characteristics of the elderly and the underlying diseases and medications. At the same time, the selected ones should be used at an appropriate dosage frequency and dosage.

1-2. Alzheimer' s disease and use of anticholinergic agents

Dementia, characterized by progressive deterioration in cognition, function, and behavior, is one of the most burdensome diseases for both individual and society (Reitz and Mayeux 2014). In Korea, there are about 360,000 elderly with dementia in 2006 and the prevalence rate is 8.2-10.4% of the elderly population over 65 years old (Kim et al. 2014). In the United States, Alzheimer's disease (AD) is one of the four major causes of death, and 5.2 million people have AD in 2016, 11% of elderly people aged ≥ 65 years, and 32% of elderly people aged ≥ 85 have AD (Hebert et al. 2013). The estimated prevalence of late-onset dementia in Japan was 15% from 2009 to 2012 (Asada 2017).

Dementia can be divided into several categories by its etiology. The most common type of dementia is dementia caused by Alzheimer's disease (AD), which accounts for 60-80% of all dementia. Vascular dementia (VaD), also known as 'post stroke dementia' accounts for about 10% of all dementia. Dementia with the Lewy bodies (DLB) characterized by neurons in the aggregation of protein alpha-synuclein, developed in the brain cortex is also another type of dementia. There are also multiple dementias due to more than one cause, the most common type is the combination of vascular dementia and Alzheimer's dementia (Schneider et al. 2007). Vascular dementia (VaD) is decreasing thanks to the prevention of cerebrovascular diseases, but AD is not, thus, efforts are needed to identify and intervene in a variety of factors that affect the development and progression of Alzheimer's disease. The prevalence of vascular dementia was higher than that of Alzheimer's dementia in Asian countries such as Korea and Japan in the past, but the AD / VaD ratio increased

from 1.96 in older adults 1990s to 4.13 in 2010, similar to the global level (Kim et al. 2014). The disease burden of AD is the largest in both the world and Korea.

What causes AD is not clear, but it is thought to be due to multiple factors, rather than a single etiology (Alzheimer's 2015). Aging, Alzheimer's family history, APOE e4 gene are the biggest risk factors for AD. Other risk factors include smoking, middle-aged obesity, middle-aged hypertension, diabetes, low educational level, lack of social and cognitive interactions, and traumatic brain injury. The greatest risk factor among these factors is aging, and most Alzheimer patients are 65 years of age or older, with a prevalence of 15% at 74 and below, but 44% at 75-84 years of age (Hebert et al. 2013, Hebert et al. 2010).

AD can be divided into two stages. The first is mild cognitive impairment (MCI), which shows a decline in cognitive ability that is greater than anticipated at age and education level, but there is no big problem in daily life. The second is Alzheimer 's dementia, characterized by changes in memory, thinking, and behavior that impairs functioning in everyday life. Approximately 15-20% of people over 65 years of age have MCI (Roberts and Knopman 2013). People with MCI-especially memory-related MCIs are more likely to develop AD and other dementia than people without MCI (Kalisch Ellett et al. 2014). In a systematic review of 32 recent studies, 32% of people with MCI were found to develop AD within 5 years (Ward et al. 2013). In Standards and Guidelines for the Diagnosis of Dementia, the MCI has actually been presented as Alzheimer's early stage (called MCI due to AD) or another form of dementia (Albert et al. 2011). However, MCI can develop for reasons other than AD, and MCI does not always lead to dementia. In some cases, the MCI may be reversed to a normal cognitive state or maintained in a stable state. When medications cause cognitive impairment, it can be misdiagnosed as MCI

(Alzheimer's 2015).

Cognitive impairment and dementia are associated with the use of certain drugs. The 2015 American Geriatrics Society (AGS) Beers Criteria presented anticholinergics, benzodiazepines, H2 receptor antagonists, benzodiazepine receptor-agonist hypnotics (eszopiclone, zolpidem, zaleplon), and antidepressants as PIMs for older adults with cognitive impairment or dementia due to the drug-disease or drug-syndrome interactions (Radcliff et al. 2015). Among them, anticholinergics can induce various adverse reactions systemically since muscarinic acetylcholine receptors (M1-M5) are distributed in various organs including the central nervous system, and many drugs with different efficacies and indications have strong anticholinergic properties. Anticholinergics are drugs that inhibit acetylcholine, a neurotransmitter in the central nervous system or peripheral nerves. It is used in a variety of diseases and conditions, such as depression, psychosis, Parkinson's disease, muscle spasms, allergies, nausea/vomiting and gastritis, etc. (Collamati et al. 2016). Many drugs with high anticholinergic activities belong to antihistamines, antiparkinsonians, musculoskeletal relaxants, antidepressants, antipsychotics, antimuscarinics, anticonvulsants, antiepileptics, or antiarrhythmics (Radcliff et al. 2015). Strong anticholinergics can cause various side effects in the whole body. CNS effects include excitement, confusion, delirium, falls, hallucinations, and cognitive dysfunction. Adverse effects on peripheral nerve are such as constipation, dry mouth, dry eye, bradycardia, and urinary retention. Older adults are especially susceptible to the side effects of anticholinergics because not only most of organ functions are decreased, but brain choline uptake is lowered (Cohen et al. 1995). Therefore, many kinds of anticholinergics are classified as inappropriate drugs for the elderly. Moreover strong anticholinergics are not recommended in older adults since they

may accelerate the diseases in patients with cognitive impairment or dementia. Despite this, more frequent use of clinically problematic anticholinergics in the older patients with dementia have been reported by several studies (Roe, Anderson, and Spivack 2002, Giron et al. 2001).

1-3. The need for the study

Korea is one of the fastest aging countries in the world. The proportion of the elderly among the total population is expected to increase rapidly from 13.8% (7.1 million) in 2017 to 24.5% (13 million) in 2030, and enter the later aged society (KOSIS 2016). In addition, the proportion of older adults exposed to polypharmacy is very high. According to a study carried out by the Ministry of Food and Drug Safety (MFDS), the average number of prescriptions for the elderly patients admitted to the general hospital was about 18, and the average number of prescription drugs for older population was 5.8 (MFDS 2004). The prescription of newer anticholinergics, which are frequently indicated for diseases in the elderly, for example new drugs for overactive bladder or psychosis are also on the rise; thus the anticholinergic burden of the elderly may be greater than in the past. On the other hand, the development and launch of new drugs with less anticholinergic adverse effects within the same efficacy group may have reduced the overall anticholinergic burden. As such, it is difficult to easily deduce whether the anticholinergic burden is improving or deteriorating.

Although there are some studies on the use of anticholinergics in the elderly, studies which quantify the exposure of anticholinergic burden to the actual

prescription amount in large population were very limited. In particular, although AD patients are more susceptible to the adverse effects of anticholinergics on cognitive function, few large-scale studies have explored how anticholinergic medications are administered in AD compared to non-AD elderly. There were no long-term follow-up studies that quantified the anticholinergic exposure in a sufficiently large sample. Unlike the use of a validated anticholinergic burden scale that scored an anticholinergic burden according to the potency of anticholinergic properties for each drug (Hilmer et al. 2007, Carnahan et al. 2006, Ancelin et al. 2006, Rudolph et al. 2008), only a small number of studies have measured the exposure through accurate calculating the quantitative use of anticholinergics (Gray et al. 2015).

Although the use of inappropriate anticholinergics is known to have a negative impact on cognitive function (Ruxton, Woodman, and Mangoni 2015, Collamati et al. 2016), there is controversy and little research as to whether it increases the risk of AD. It seems because the long-term measurement of exposure to multiple anticholinergics in large population which is crucial for demonstrating the causal relationship between the exposure and incidence of dementia are very difficult.

1-4. Study Objectives

The purpose of this study were to

(1) Subject 1: calculate the standardized dose of anticholinergics and test their correlation with other approaches for estimating prescription amount, then

describe the prescription pattern of anticholinergics in elderly Koreans by using standardized prescribed doses to estimate the quantities of anticholinergic use.

(2) Subject 2: examine how anticholinergics are prescribed in AD patients by comparison with non-Alzheimer's group and to find factors that predict the prevalence of anticholinergic prescriptions.

(3) Subject 3: investigate whether anticholinergic use increases the risk of AD, and how long a period of anticholinergic exposure is associated with the risk of AD.

The hypotheses for each research subject were as follows.

(1) Subject 1: Standardized prescribed doses would be highly correlated with other approaches for the estimation of prescription amount of anticholinergic agents, such as prescribed days and cumulative prescribed days. In particular, the cumulative prescribed days and the standardized prescribed doses will have a higher correlation. When the anticholinergic use is investigated in older adults, many elderly people will be over-prescribed with both weak and strong anticholinergics.

(2) Subject 2: AD will affect the prevalence of anticholinergic medications. The prescription of strong anticholinergics which are regarded as inappropriate drugs for the elderly will be lower in the AD patients than in non-AD group. However, there will be no significant difference between the two groups in case of weak anticholinergics.

(3) Subject 3: Exposure to strong anticholinergic medications for long periods of time will increase the risk of developing AD. Exposure to weak anticholinergics may also increase the risk of AD, but its effects will be much smaller than in strong anticholinergics.

CHAPTER 2. STUDY MATERIALS

2-1. Data sources

National Health Insurance Service Elderly cohort (2002-2013) database (DB) was used as data source. The NHIS Elderly cohort DB was constructed to provide public health researchers and policy makers with useful information of Korean elderly's medical utilizations. This cohort includes database such as the insurance eligibility DB, medical treatments DB, general health screening from 2002 to 2013 of about 550,000 elderly. They were about 10% of the approximately 5.5 million all elderly Korean aged 60 or older, who were qualified as of 2002. They were recruited by an application of simple random sampling. Especially the medical treatment DB has details on electronic medical treatment bills, diagnoses, and prescription, etc. The general health screening DB comprises information of nationwide health examinations conducted by NHIS, including major health examination results, information on lifestyles and behaviors from questionnaires. In Korea, since 2000, the National Health Insurance has been implemented and all insured persons were enrolled in NHIS (Lee et al. 2016). Details on the DB can be obtained from the National Health Insurance (NHI) Sharing Service website (https://nhiss.nhis.or.kr/bd/ab/bdaba015lv.do). Information of all medicines licensed and distributed in Korea during 2002 to 2013 was obtained from Health Insurance Review and Assessment Service (HIRA), a government-affiliated organization which reviews and assesses healthcare costs and healthcare service quality, as well as supporting the national health insurance policy in determining medical fee schedules and drug prices (HIRA). This information was also double checked with

drug database from Korea Pharmaceutical Information Center (KPIC). KPIC is authoritative public-interest institution providing comprehensive drug information licensed in Korea. It was approved by Ministry of Health and Welfare in 2001. Details on HIRA and KPIC are available at their website https://www.hira.or.kr/dummy.do?pgmid=HIRAJ010000005001 and http://www.health.kr/ respectively.

2-2. Determination of lists of strong and weak anticholinergic agents

Lists of anticholinergic agents were determined using the the 2015 American Geriatrics Society (AGS) Beers Criteria (Radcliff et al. 2015) and the Anticholinergic Cognitive Burden (ACB) Scale developed by Boustani, M. & Campbell et *al*. (Boustani et al. 2008).

The Beers Criteria is the most widely used guideline in research and clinical practice in the field of drug utilization in geriatrics. The Beers Criteria recommends that older adults avoid drugs with strong anticholinergic properties. In particular, patients with cognitive dysfunction or dementia are more at risk for disease-drug interactions and therefore require more attention to using potent anticholinergic agents. The list of drugs with strong anticholinergic properties in Beers Criteria was drafted by the composite of published scales for anticholinergic agents. It specified 52 strong anticholinergic agents in nine categories, such as antihistamines, antidepressants, antiparkinsonians and urinary antimuscarinics etc. (Radcliff et al. 2015).

Anticholinergic properties of medicines are generally quantified by the combination of the following methods, that is, serum radioreceptor anticholinergic activity assay (SAA) (Mulsant et al. 2003), *in vitro* measurement of affinity to muscarinic receptors (Rudd et al. 2005), or experts opinion (Rudolph et al. 2008). Several investigators have published list of anticholinergic agents along with designation of anticholinergic burden scores which could be utilized in assessing the anticholinergic burden of drugs with anticholinergic properties. Most of them graded anticholinergics into 2-4 levels according to their anticholinergic potency (Jamsen et al. 2017, Carnahan et al. 2006, Ancelin et al. 2006, Rudolph et al. 2008). Among these, ACB scale, developed by Boustani, M. & Campbell et al., provides a list of drugs with anticholinergic effects related to negative impact on cognitive ability. ACB scale was developed on a four-point (0-3) scale based on published data and expert opinion. In ACB scale, drugs which were found to be anticholinergic *in vitro*, but not clinically meaningful were given ACB score 1. ACB scores 2 and 3 were given to drugs that were proved to affect cognitive function clinically. Then they were separated into score 2 and 3 according to their blood brain barrier permeability and development of delirium (Boustani et al. 2008).

In this study, 58 strong anticholinergics and 34 weak anticholinergics were specified based on AGS Beers Criteria and ACB scale. The strong anticholinergics selected in this study are those listed on the Beers Criteria, and/or all drugs corresponding to the ACB scores of 2 and 3. Weak anticholinergics are drugs of ACB score 1. Strong anticholinergics are medicines that have high risk of adverse effects in the elderly thus are inappropriate for use in older adults. The ‘strong anticholinergic agent’ was used synonymously with the ‘inappropriate anticholinergic agent for the elderly’ in this study. The list of strong anticholinergics

in the Beers Criteria was very similar to the list of drugs with ACB score of 3 since most of the drugs were on both the lists. Most of drugs with ACB score of 2 have not been available and have not prescribed in Korea except for carbamazepine, oxcarbamazepine and amantadine, thus list of strong anticholinergics defined in this study was very similar to the list of strong anticholinergics from Beers Criteria. Weak anticholinergic agents were defined as drugs with ACB score of 1. Drugs with an ACB score of 1 but listed on the Beers Criteria, such as brompheniramine, were classified as strong anticholinergics by applying more stringent criteria. When both strong anticholinergics and weak anticholinergics were included, it was named as 'total anticholinergic agents'.

The primarily interested exposure index was strong anticholinergics. However main analyzes were performed for the exposure to the weak anticholinergics as well since mild anticholinergics were reported to be a major contributor to the anticholinergic load in dementia (Mate et al. 2015), and few studies have been explored on multiple and long-term medications of weak anticholinergics. The list of strong anticholinergics and weak anticholinergics are presented in Table 2-1 and Table 2-2, respectively.

Table 2-1. The list of strong anticholinergic agents

Antihistamines	**Antipsychotics**
Brompheniramine	Chlorpromazine
Carbinoxamine	Clozapine
Chlorpheniramine	Loxapine

Clemastine

Cyproheptadine

Dexbrompheniramine

Dexchlorpheniramine

Dimenhydrinate

Diphenhydramine

Doxylamine

Hydroxyzine

Meclizine

Triprolidine

Antiparkinsonian agents

Benztropine

Trihexyphenidyl

Amantadine

Skeletal muscle relaxants

Cyclobenzaprine

Orphenadrine

Antidepressants

Amitriptyline

Amoxapine

Clomipramine

Desipramine

Doxepin

Imipramine

Molindone

Olanzapine

Perphenazine

Pimozide

Quetiapine

Thioridazine

Trifluoperazine

Antimuscarinics

Darifenacin

Fesoterodine

Flavoxate

Oxybutynin

Solifenacin

Tolterodine

Trospium

Antispasmodics

Atropine

Belladonna alkaloids

Clidinium chlordiazepoxide

Dicyclomine

Homatropine

Hyoscyamine

Propantheline

Scopolamine

Nortriptyline	**Antiemetics**
Paroxetine	Prochlorperazine
Protriptyline	Promethazine
Trimipramine	**Anticonvulsants**
Antiarrhythmic	Carbamazepine
Disopyramide	Oxcarbazepine

Table 2-2. The list of weak anticholinergic agents

Alimemazine	Fentanyl
Alverine	Furosemide
Alprazolam	Fluvoxamine
Atenolol	Haloperidol
Bupropion hydrochloride	Hydralazine
Captopril	Isosorbide
Chlorthalidone	Loperamide
Cimetidine hydrochloride	Metoprolol
Clorazepate	Morphine
Codeine	Nifedipine
Colchicine	Prednisone
Coumadin	Quinidine
Diazepam	Ranitidine
Digoxin	Risperidone
Dipyridamole	Theophylline

Disopyramide phosphate	Trazodone
Hydrocortisone	Triamterene

All data were processed and analyzed using SAS 9.4 (SAS Institute, Inc., Cary, NC). The study has been approved by the Bioethics Committee of Seoul National University Institutional Review Board and the approval number is E1705 / 001-003.

CHAPTER 3. MEASUREMENT OF STANDARDIZED PRESCRIBED DOSES AND USE OF ANTICHOLINERGIC AGENTS

3-1. Background

Although a considerable number of studies have demonstrated that the strong anticholinergic medications were associated with wide range of negative clinical outcomes (Pfistermeister et al. 2017, Egberts et al. 2017, Fox et al. 2014), studies which quantified the exposure to anticholinergics up to the actual prescription amount in large population were very limited. Many studies have analyzed anticholinergic agents as part of the all PIMs (Johnell 2015, Montastruc et al. 2013, Parsons et al. 2012), and studies on the use of one or several specific anticholinergic agent (Bali et al. 2015, Miskovic 2015) seemed to be more common. There are some studies on the measurement metrics of drug use, but they are mainly focused on the use of other drug classes such as antibiotics (Haug and Reikvam 2013, Polk et al. 2007). Moreover, those were largely studies comparing defined daily dose (DDD) assigned by World Health Organization (WHO 2018) with other measurement approaches such as recommended daily dose, days of therapy (Bestehorn, Steib-Bauert, and Kern 2009, Sinnott et al. 2016, Nielsen et al. 2017). However, since DDD is the assumed maintenance dose per day for a drug in adults (WHO 2018), it is not quite reasonable to apply it directly to older people. There were no studies investigating whether such exposure indicators are appropriate for assessing the anticholinergic exposure. In some studies, the anticholinergic exposure was only

assessed based on whether or not the subjects were using at a particular point of time (Jessen et al. 2010). In a study of PIMs in 1,700,000 veterans aged 65 years and older, relatively detailed anticholinergic prescription patterns were presented in the results by using the pharmacy claim data. In 2004, 23.9% and in 2009, 10% of the elderly were reported to use at least one PIM, and diphenhydramine, promethazine, hydroxyzine and nitrofurantoin were the most dispensed drugs. However, those results were calculated from the proportion of persons who were once exposed (Dosa et al. 2013).

Although there was a domestic study to investigate the prescription patterns of anticholinergics in patients with dementia, how the anticholinergic burden scale was used was not specified, and the quantitative evaluation for the exposure was not performed (Lee and Lee 2013). In a 6-year, longitudinal study of Campbell et al. (2010) in 1,652 African-Americans aged over 70 years, the number of definite use of anticholinergics at baseline was associated with the risk of cognitive impairment (OR 1.46 , 95% CI 1.07-1.99). However anticholinergic exposure was assessed as drugs in the subjects' home. Medication adherence and dose of medication were not considered during the follow-up period (Campbell et al. 2010). In a French study of 1,700 elderly people aged 70 years or older who assessed the association between exposure to anticholinergics and cognitive performance, 13.7% of the subjects were reported to be exposed to anticholinergics at any one time but the actual frequency or amount of anticholinergics was not considered (Lechevallier- Michel et al. 2005). As such, studies which quantified the exposure of anticholinergics to the level of actual prescription amount in large population were very limited.

This study has two purposes. First, the standardized prescribed doses of anticholinergics were calculated then compared with prescribed days and cumulative

prescribed days. Although standardized prescribed doses were adopted as the most proper and reasonable estimation of anticholinergic prescriptions in this study, those three measurement approaches were assumed to be used interchangeably if they were highly correlated. The relationships between the three approaches were examined by correlation analysis and regression analysis for the strong, weak, and total anticholinergics. Second, this study could be contribute to establish strategies for inducing appropriate anticholinergic medications in older adults by investigating the pattern of prescription of anticholinergic agents in elderly Koreans by using standardized prescribed dose and identifying predictors of the excessive use.

3-2. Methods

Among the 405,614 subjects aged ≥ 70 years in the NHIS Elderly cohort DB in 2012, 388,629 people, excluding 16,985 people who died in 2012, were included. Quantification of exposure to anticholinergics were estimated by means of three methods. First, the prescribed days were calculated as the sum of the number of days at which subjects were exposed to at least one anticholinergics out of a total 366 days in 2012. Second, the cumulative prescribed days was calculated by summing all prescription days for each anticholinergic agent. For example, if a subject have been prescribed three kind of anticholinergic agents for two days, the prescribed days will be two days, while the cumulative prescribed days will be six days. Both the prescribed days and the cumulative prescribed days are the exposure metrics that do not take into account administered doses. Finally standardized prescribed doses were calculated. For this, the adequate daily dose for the elderly for each anticholinergic agent was set based on the drug approval information, Lexicomp® Online, and

Micromedex® DRUGDEX, then the standardized prescribed doses for each anticholinergics were calculated using the generic name code, dosage unit, daily frequency of administration, and number of prescribed days. For the adequate daily dose for the elderly, recommended doses for the elderly were used whenever available and if not available, the lower limit of effective dose was set as the adequate daily dose for the elderly. Appendix 1 presents adequate daily dose for the elderly for each anticholinergic agent. The formula for obtaining the standardized prescribed doses was as follows.

- Relative dose = actual content in prescribed drug / adequate daily dose for the elderly
- Standardized prescribed doses (doses) = relative dose x number of unit of administration x daily frequency of administration x number of prescribed days

The prescription amounts in 2012 measured by these three different measurement metrics were calculated by summing these doses by individual. The relations between the three exposure measurement metrics, namely standardized prescribed doses, prescribed days, cumulative prescribed days, were examined by correlation analysis and regression analysis for the strong, weak, and total anticholinergics. Strong anticholinergics were divided into four categories based on the frequency and distribution of prescription amount. Basic demographic characteristics including sex, age, and level of income; weak anticholinergic use;

polypharmacy; cumulative prescribed days of non-anticholinergics that can impair cognitive functions were examined.

Number of days on which multiple strong anticholinergics were prescribed during 2012 was investigated. Major diagnoses for which strong anticholinergics prescribed highly were also ranked. Prescription patterns of anticholinergics were provided by frequency, proportion, mean ± standard deviation (mean ± SD), and percentiles. The relationship of prescription amount of strong anticholinergics with basic demographic variables such as age, sex, level of income, and other medications were investigated by using multivariate logistic regression.

Prescription amount of $\geq$ 90 dose per year of strong anticholinergics was defined as excessive use of strong anticholinergics, and logistic regression analysis was conducted to identify the predictors of those excessive use. To examine comorbidities which could predict the excessive use of strong anticholinergics, records of ICD diagnostic codes in 2012 year were utilized. In detail, subjects who have been diagnosed with the following diseases as primary or secondary diagnoses at least three times during 2012 were considered as having the corresponding morbidities; common or major diseases in the elderly: hypertension, diabetes mellitus, myocardial infarction, or cardiovascular diseases etc.; diseases for which strong anticholinergic agents were mainly indicated: Parkinson's disease, epilepsy, neuralgia, dizziness including by vestibular abnormalities, sleep disorder, genitourinary diseases and skin diseases etc.. Then, the diseases stated above were all included as covariates and multivariate analysis were conducted to identify the factors which predict excessive use of strong anticholinergics. For comparison, univariate analysis was also carried out.

3-3. Results

There was a total of 388,629 subjects in the 2012 NHIS elderly cohort. Females comprised 61.5% of the subjects. Among the age groups divided into 5-year-olds, subjects aged 70 to 74 accounted for the majority (43.6%) and more than 10% were above 85 years (10.4%). More than 70% of the subjects were exposed at least once to strong and weak anticholinergics. When polypharmacy was defined as five or more average daily prescribed drugs, 36.2% of the subjects were polypharmacy (Table 3-1).

Table 3-1. Basic characteristics of the study subjects (NHIS – Elderly cohort, 2012)

		Numbers of subjects (%) (n=388629)
Sex	Male	149494 (38.5)
	Female	239135 (61.5)
Age	70-74	169442 (43.6)
	75-79	115053 (29.6)
	80-84	63577 (16.4)
	≥ 85	40557 (10.4)
Income	0 (Medical aid)	34354 (8.8)
	4/10 quartile	93097 (24.0)
	8/10 quartile	111605 (28.7)

	Numbers of subjects (%) (n=388629)
10/10 quartile	149573 (38.5)
Subjects with at least one prescription of strong anticholinergics	282991 (72.8)
Subjects with at least one prescription of weak anticholinergics	287064 (73.9)
Number of average prescribed daily dose	4.4±3.5
Polypharmacy*	140734 (36.2)

*polypharmacy: number of average daily prescribed drugs ≥ 5

Prescribed days of strong anticholinergics in 2012 were 40.5 days on average in all subjects. The cumulative prescribed days and standardized prescribed doses were 60.2 days and 65.6 doses respectively, which were 50% higher than the value of the prescribed days. The standard deviation was very large, that is, large variation of individual prescription amount existed. In all three exposure measurement metrics, the higher the age group, the higher the amount of prescription, except for the oldest group (Table 3-2).

Table 3-2. Measurement of annual prescription amount of anticholinergic agents in 2012 by three exposure measurement methods (n=388629)

Age group	Strong anticholinergics	Weak anticholinergics	Total anticholinergics
overall	40.5±78.8	86.3±118.9	106.3±123.7
70-74	36.5±73.4	80.0±114.8	98.3±119.7
75-79	43.3±81.0	91.3±120.9	112.4±125.4

	Age group	Strong anticholinergics	Weak anticholinergics	Total anticholinergics
Prescribed days	80-84	47.2±86.5	96.4±124.2	119.0±128.6
	≥ 85	39.0±80.6	83.1±119.5	102.3±125.1
Cumulative exposed days	overall	60.2±131.2	131.7±217.4	191.9±280.4
	70-74	54.5±122.4	119.6±205.4	174.3±265.2
	75-79	64.8±136.7	140.3±223.8	205.0±289.1
	80-84	69.7±143.3	150.3±233.8	220.0±301.6
	≥ 85	56.3±129.3	127.7±218.3	184.1±277.8
Standardized prescribed doses	overall	65.6±163.0	106.6±214.1	172.5±290.1
	70-74	61.0±157.2	99.0±207.1	160.2±281.9
	75-79	70.2±168.9	113.6±221.0	184.1±299.2
	80-84	73.8±170.8	119.5±226.7	193.5±303.8
	≥ 85	59.0±155.4	98.6±200.0	157.9±272.0

The relationships between the three methods of exposure measurement, namely standardized prescribed doses, prescribed days, cumulative prescribed days, were examined by both correlation analysis and regression analysis for the strong, weak, and all anticholinergics. As a result, the standardized prescribed doses and cumulative prescription days showed a high correlation of 83-87%, and the coefficient of determination (R squared, R2) of the regression equation was as high as 0.68-0.76. The correlation between the standardized prescribed doses and prescribed days was about 10% lower than this (Table 3-3).

Table 3-3. Correlation and regression analysis between prescribed days, cumulative prescribed days, and standardized prescribed doses

		Correlation Coefficient	Regression R2*	Regression p-value
Strong anticholinergics	Standardized prescribed doses vs. Prescribed days	0.77	0.60	<0.0001
	Standardized prescribed doses vs. Cumulative prescribed days	0.87	0.76	<0.0001
Weak anticholinergics	Standardized prescribed doses vs. Prescribed days	0.73	0.53	<0.0001
	Standardized prescribed doses vs. Cumulative prescribed days	0.83	0.68	<0.0001
Total anticholinergics	Standardized prescribed doses vs. Prescribed days	0.72	0.52	<0.0001
	Standardized prescribed doses vs. Cumulative prescribed days	0.86	0.74	<0.0001

*R2: The coefficient of determination (R squared)

More than half of the subjects (52.8%) had less than 15 annual doses of strong anticholinergics; thus, belonging to the lowest group. However, 17.0% of the elderly were prescribed more than 90 doses, and a relatively high proportion (9.7%) of the subjects were exposed to very high amounts of anticholinergics (≥ 180

doses/year). People who were prescribed high amount of strong anticholinergics were also using more weak anticholinergics and 'other non-anticholinergics that could impair cognitive functions'. Multiple medications were more severe in those in the higher level of strong anticholinergic exposure. The elderly of the lowest income level with Medical aid had noticeably higher percentages of exposure to very high doses of anticholinergics than those with higher income and recipients of National health insurance program (Table 3-4).

Table 3-4. The basic characteristics of subjects by level of prescribed doses of strong anticholinergics (n = 388629)

	Standardized prescribed doses of strong anticholinergic agents (dose/year)			
	0-14	**15-89**	**90-179**	**≥180**
N (%)	205125 (52.8)	117677 (30.3)	28317 (7.3)	37510 (9.7)
Age	76.8±5.9	76.2±5.2	76.8±5.4	77.0±5.4
Sex (%)	82425 (55.1)	42637 (28.5)	9958 (6.7)	14474 (9.7)
Income (%)				
0 (Medical aid)	15154 (44.1)	10484 (30.5)	3227 (9.4)	5489 (16.0)
4/10 quartile	49734 (53.4)	27890 (30.1)	6874 (7.4)	8509 (9.1)
8/10 quartile	60294 (54.0)	33733 (30.2)	7864 (7.1)	9714 (8.7)
10/10 quartile	79943 (53.5)	45480 (30.4)	10352 (6.9)	13798 (9.2)

	Standardized prescribed doses of strong anticholinergic agents (dose/year)			
	0-14	**15-89**	**90-179**	**≥180**
Total prescribed dose of weak anticholinergics	72.4±172.8	104.1±189.6	152.1±223.3	201.6±280.2
Number of average prescribed daily dose for all prescribed drugs	3.4±2.9	4.5±3.1	6.1±3.4	8.2±4.0
Other non-anticholinergics that can impair cognitive functions*	1.4±4.4	2.8±6.2	4.6±8.5	6.1±11.0

*Prescription amount of other non-anticholinergics that could impair cognitive functions was measured by cumulative prescribed days.

The average prescribed annual dose of strong anticholinergics was 65.6 doses; the prescription amount was higher for weak anticholinergics (106.6 doses) than for strong anticholinergics. Both strong and weak anticholinergics had big individual variation in dose of prescription, which led to a very high standard deviation. The median was much lower than the mean, and the dose for the third quartile was very high suggesting that only some elderly, not most, received very high dose of anticholinergics. Exposure to anticholinergics increased with age, except for the oldest age group (Table 3-5).

Table 3-5. Standardized prescribed doses of both strong and weak anticholinergic agents by age group

		Age group				
		70-74	**75-79**	**80-84**	**≥ 85**	**total**
Strong anticholinergics	Mean ± SD	60.9±157.1	70.2±168.4	73.8±170.8	59.0±155.4	65.6±162.7
	Median	12.0	14.0	13.0	6.0	12.0
	75th percentile	46.0	57.0	61.0	41.0	51.0
Weak anticholinergics	Mean ± SD	92.4±190.5	106.6±204.6	113.2±212.3	94.7±191.0	106.6±214.1
	Median	16.0	20.0	21.0	10.0	17.0
	75th percentile	92.0	121.0	135.0	101.0	109.0

The number of days on which multiple strong anticholinergics were prescribed were counted. 9.7% of the subjects were prescribed two strong anticholinergics on the same day for more than 30 days per year, and 26.1% had experiences of being prescribed three strong anticholinergics on the same day (Table 3-6).

Table 3-6. Number of days on which multiple strong anticholinergics were prescribed

Number of days on which multiple strong anticholinergics were prescribed	None	1-29 days	30-89 days	≥ 90 days
≥ 2 drugs in a day	198146 (51.0%)	152723 (39.3%)	22055 (5.7%)	15705 (4.0%)
≥ 3 drugs in a day	287225 (73.9%)	92053 (23.7%)	6380 (1.6%)	2971 (0.8%)

When the standardized prescribed doses of strong anticholinergics were measured for each drug class, antihistamines were prescribed the most, followed by antidepressants and antimuscarinics; these drug classes accounted for 88.49% of all prescriptions of strong anticholinergics. When the mean exposed dose among people who were prescribed these drugs at least once was calculated, the amount of prescription of drugs used for chronic diseases, such as antiparkinsonians, antidepressants, and urinary antimuscarinics, was much higher than that of antihistamines. When the prescription amount was measured after the elderly were split into 5 groups by age, tendency to reduce the anticholinergic use due to aging was not found both ‘in all subjects’ and ‘in those who were prescribed the corresponding drug at least once’ except for the antiparkinson's drugs. In general, the amount of prescription increased according to age until the age of 85 years, and slightly decreased after reaching to the oldest old (Table 3-7, Figure 3-1).

Table 3-7. Average annual prescription amount of strong anticholinergics by drug class in 2012

Rank	Drug class	Average annual prescription amount*	Proportion (%)	Cumulative proportion (%)
1	Antihistamines	32.93	49.94	49.94
2	Antidepressants	18.57	28.16	78.10
3	Antimuscarinics	6.85	10.39	88.49
4	Antiparkinsonians	2.42	3.67	92.16
6	Anticonvulsants	1.85	2.81	94.97
5	Antispasmodics	1.52	2.31	97.28
8	Skeletal muscle relaxants	0.92	1.40	98.67
7	Antipsychotics	0.88	1.33	100.00

*Average annual prescription amount of strong anticholinergics; calculated by standardized prescribed doses

There were no prescriptions of strong anticholinergics classified as antiarrhythmics and antiemetics.

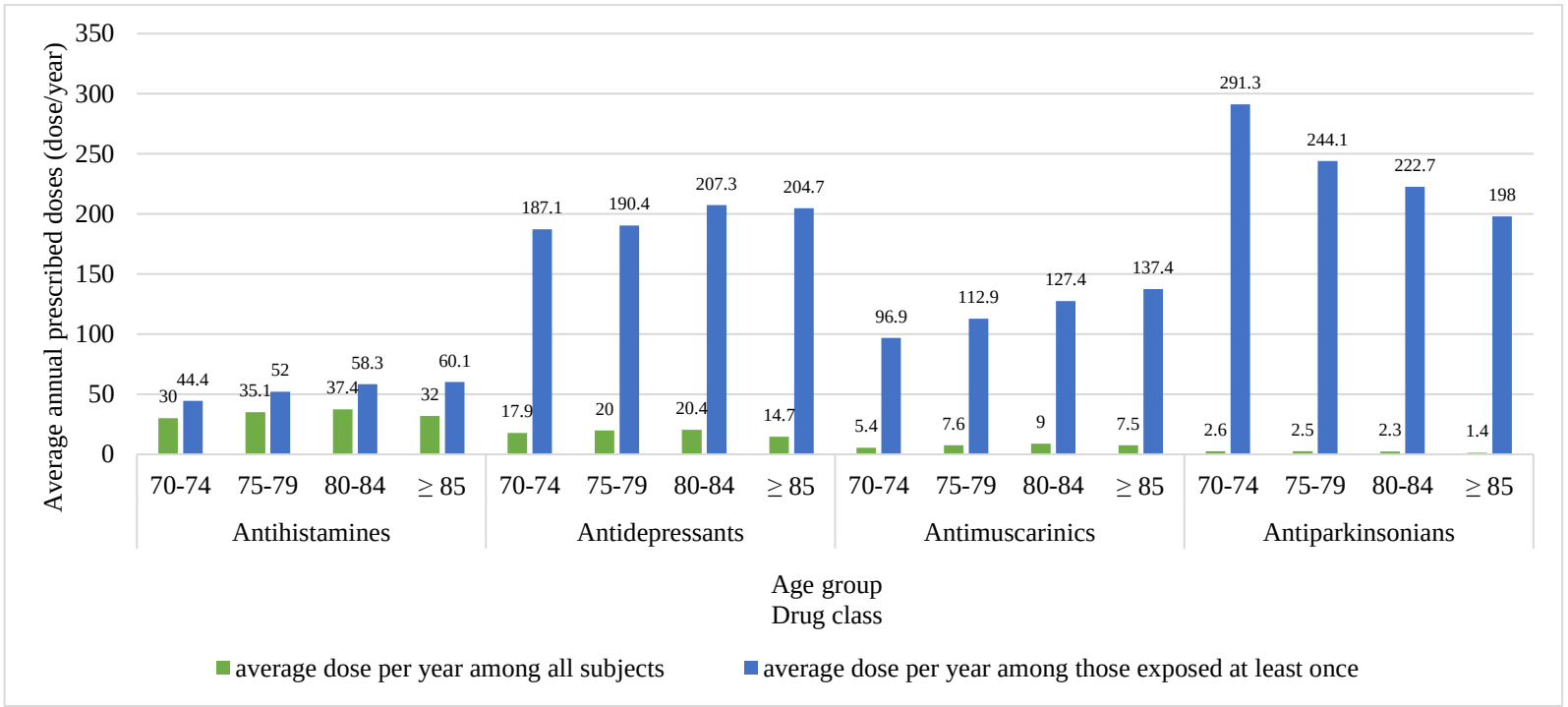


Figure 3-1. Average annual prescribed doses of frequently used strong anticholinergics by drug class and age group

Both the strong and the weak anticholinergics were ranked according to their sum of annual standardized prescribed doses. Among strong anticholinergics, the prescription amount of chlorpheniramine was highest (36.8%), followed by amitriptyline (21.9%). These drugs accounted for 58.7% of the total dose of prescription of strong anticholinergics. Among weak anticholinergics, the prescription amount of diazepam was the highest (17.9%), followed by ranitidine (17.3%) and furosemide (13.9%) (Table 3-8).

Table 3-8. Rank and proportion of strong and weak anticholinergic agents by sum of annual standardized prescribed doses in 2012

Rank	Strong anticholinergics	Proportion (%)	Cumulative proportion (%)	Weak anticholinergics	Proportion (%)	Cumulative proportion (%)
1	Chlorpheniramine	36.8	36.8	Diazepam	17.9	17.9
2	Amitriptyline	21.9	58.7	Ranitidine	17.3	35.3
3	Dimenhydrinate	7.3	66.0	Furosemide	13.9	49.2
4	Hydroxyzine	5.7	71.7	Atenolol	10.0	59.2
5	Tolterodine	3.7	75.4	Isosorbide	9.4	68.6
6	Paroxetine	3.0	78.4	Cimetidine	8.3	76.9
7	Solifenacin	2.9	81.3	Nifedipine	6.2	83.1
8	Carbamazepine	2.5	83.8	Alprazolam	3.7	86.8
9	Amantadine	2.0	85.8	Digoxin	3.1	89.9
10	Fesoterodine	1.9	87.7	Alverine	2.6	92.5

When the diagnoses for which six strong anticholinergics with high prescription amount were identified, chlorpheniramine was prescribed mostly for relatively mild diseases, for example, common cold, rhinitis or allergic contact dermatitis. Amitriptyline was prescribed for various diseases, such as anxiety and neuropathic pain, in addition to depression (Table 3-9).

Table 3-9. Major diagnoses for which strong anticholinergics with high prescription amount were prescribed

Rank	Chlor-pheniramine	Amitriptyline	Dimenhydrinate	Hydroxyzine	Toltero-dine	Paroxetine
1	Gastritis and duodenitis	Depressive episode	Disorders of vestibular function	Allergic contact dermatitis	Neuromuscular dysfunction of bladder	Depressive episode
2	Acute bronchitis	anxiety disorders	Dizziness and giddiness	Urticaria	Hyperplasia of prostate	Other anxiety disorders
3	Vasomotor and allergic rhinitis	Sleep disorders	Other anxiety disorders	Pruritus	Other disorders of urinary system	Nonorganic sleep disorders
4	Acute nasopharyngitis[common cold]	Dorsalgia	Other peripheral vascular diseases	Irritant contact dermatitis	Cystitis	Recurrent depressive disorder
5	Acute upper respiratory infections	Spinal stenosis	Nausea and vomiting	Other dermatitis	Unspecified urinary incontinence	Sleep disorders

Rank	Chlor-pheniramine	Amitriptyline	Dimenhydrinate	Hydroxyzine	Toltero-dine	Paroxetine
6	Allergic contact dermatitis	Other soft tissue disorders	Other disorders of ear	Seborrheic dermatitis	Other disorders of bladder	Persistent mood [affective] disorders
7	Other soft tissue disorders	Post zoster neuralgia	Headache	Dermatophytosis	Polyuria	Somatoic disorders

The diagnoses were based on ICD 3 digits. The unrelated indications such as hypertension and diabetes were excluded.

Several factors associated with excessive prescription amount (≥ 90 dose/year) of strong anticholinergics were confirmed through multivariate logistic regression analysis. The elderly in the lowest income group were more likely to be exposed to the excessive amount of strong anticholinergics when compared to the highest income group. Polypharmacy, other non-anticholinergics that could impair cognitive functions, and weak anticholinergics positively predicted excessive use of strong anticholinergics (Table 3-10).

Table 3-10. Predictors of excessive use of strong anticholinergic agents (≥ 90 dose/year)

Covariate		Excessive use of strong anticholinergics * Odds ratio (95% CI)
Age	70-74	reference
	75-79	1.11 (1.09-1.13)
	80-84	1.19 (1.16-1.22)
	≥ 85	1.10 (1.07-1.14)
Sex	Female	0.97 (0.95-0.99)
Income	10/10 quartile	reference
	8/10 quartile	1.03 (1.00-1.05)
	4/10 quartile	1.07 (1.04-1.10)
	0 (Medical aid)	1.38 (1.33-1.42)
weak anticholinergics	0-29	reference
	30-179	2.11 (2.07-2.16)
	≥ 180	2.04 (1.99-2.09)
Polypharmacy*		3.82 (3.74-3.90)
Cumulative prescribed days of other non-anticholinergics that could impair cognitive functions	0-9	reference
	≥ 10	2.03 (1.98-2.09)

*Excessive use of strong anticholinergics (≥ 90 dose/year): calculated by annual standardized prescribed doses.

†polypharmacy: number of average prescribed daily dose ≥5

Finally both univariate and multivariate analyzes were conducted to determine which diseases predict excessive use of strong anticholinergics. As expected, most of these diseases for which strong anticholinergics were mostly indicated were the predictors of the excessive use of them. In particular, the elderly with Parkinson's disease, respiratory disease, depression, dizziness (including by vestibular abnormalities), or genitourinary diseases strongly predicted excessive use of strong anticholinergics in multivariate logistic regression analysis. Other chronic diseases which were considered as main morbidities in the older adults such as hypertension, diabetes mellitus, cardiovascular diseases were shown to be positively related to the excessive use of strong anticholinergics in univariate analysis. However the relevance has become very weak or rather reversed after adjusted for the covariates. Polypharmacy was a very strong predictor of the excessive use of strong anticholinergics (Table 3-11).

Table 3-11. The diseases which predicted the excessive use of strong anticholinergic agents (≥ 90 dose/year)

		Univariate Analysis	**Multivariate Analysis**
		Odds ratio (95% Confidence interval)	
Age			
	70-74	Reference	Reference
	75-79	1.23 (1.21-1.26)	1.08 (1.06-1.11)
	80-84	1.35 (1.32-1.39)	1.16 (1.13-1.19)
	≥ 85	1.06 (1.03-1.09)	1.16 (1.12-1.20)

	Univariate Analysis	Multivariate Analysis
	Odds ratio (95% Confidence interval)	
Sex, female	1.07 (1.05-1.09)	1.15 (1.13-1.17)
Income		
10/10 percentile	Reference	Reference
8/10 percentile	0.97 (0.95-0.99)	1.06 (1.03-1.08)
4/10 percentile	1.03 (1.01-1.05)	1.11 (1.08-1.14)
0 (Medical aids)	1.77 (1.72-1.82)	1.29 (1.25-1.33)
Hypertension	1.52 (1.49-1.54)	0.87 (0.85-0.88)
Cardiovascular disease	2.15 (2.10-2.19)	1.07 (1.04-1.09)
Myocardial infarction	1.37 (1.31-1.43)	0.77 (0.73-0.80)
Diabetes mellitus	1.47 (1.45-1.50)	0.84 (0.82-0.86)
Depression	4.61 (4.53-4.70)	2.58 (2.51-2.66)
Anxiety	3.75 (3.67-3.84)	0.81 (0.78-0.84)
Genitourinary disease	3.15 (3.09-3.21)	2.12 (2.08-2.18)
Dizziness*	3.62 (3.55-3.70)	2.10 (2.05-2.15)
Sleep disorder	3.28 (3.20-3.36)	1.35 (1.32-1.39)
Neuralgia	2.09 (2.05-2.13)	1.20 (1.17-1.22)
Respiratory disease	2.81(2.76-2.86)	2.06 (2.02-2.11)
Dermatological disease	2.80 (2.75-2.86)	1.99 (1.94-2.03)
Parkinson's disease	4.57 (4.36-4.79)	2.54 (2.41-2.68)
Psychosis	3.67 (3.43-3.93)	1.27 (1.17-1.37)
polypharmacy	5.55 (5.45-5.65)	3.32 (3.24-3.39)

*Dizziness including by vestibular abnormalities

3-4. Discussion

In this study, standardized prescribed doses were calculated to quantify the exposure to anticholinergics up to the actual prescription amount. Very detailed and exact prescription records including dosage unit, daily frequency of administration, and number of prescribed days made it possible. As far as I know, this is the first study to examine the relationships between quantitative measurement metrics of exposure to anticholinergics. Although standardized prescribed doses have the disadvantage that the value can vary depending on how the elderly dosage is set up by each researcher, It would be desirable to quantify and evaluate drug use at the level of doses of medication, if possible. However, most of studies do not use data containing information of prescription or medication as described above. In fact, the prescribed days or cumulative prescribed days are more easy to obtain. This study showed that the standardized prescribed doses and the cumulative prescribed days were highly correlated; then they could be used interchangeably each other. In addition, the cumulative prescribed days were identified to be closer estimation to the standardized prescribed doses rather than the prescribed days. This comparative assessment of the quantitative measurement methods may be a practical reference when deciding which approach to apply in studies of anticholinergic use.

We found that 72.8% of the subjects were exposed to strong anticholinergics at least once. In a study investigating the burden of anticholinergic use among 3,013 older adults, the prevalence of exposure to drugs belonging to ACB 2 or 3, which were very similar to strong anticholinergics defined in our study, was 23% (Boustani et al. 2008). Moreover, in a study conducted in New Zealand comparing anticholinergic exposure according to burden scales of various

anticholinergics, the prevalence of anticholinergic use was 22.8–55.9% depending on the scale applied (Salahudeen, Hilmer, and Nishtala 2015). The reason for the high prevalence of anticholinergic use in this study compared with the existing studies is not clear, but first of all, in Korea, universal coverage health insurance system was implemented for all citizens, thus medical accessibility is very high compared to other countries; this could have led people to seek doctor's care even for mild diseases. Second, since this study used the NHIS claim data to calculate the prescribed doses for the entire period of 2012, It seems to have been able to count drug use almost without omission.

The mean prescribed doses of strong anticholinergics was very high with a very big individual deviation (65.6 ± 162.7) and the median was very low (12.0) compared to this. Besides, the proportion of elderly people who were prescribed very high doses of strong anticholinergic agents ($\geq$ 180 doses/year) was about 10%, suggesting that overuse of inappropriate anticholinergics may be serious for some elderly people, rather than for the majority of them. Although not provided in the results, approximately 4.2% of the elderly subjects were prescribed very high doses of strong anticholinergics above 365 doses. Then the risks of severe and irreversible side effects, as well as mild and reversible adverse effects, arising from the use of anticholinergics can not be ignored in those people. In particular, the ACB scale used in this study is a tool that aims to identify the negative effects of anticholinergics on cognition. Accordingly, the influences on cognitive function in elderly exposed to very high doses of strong anticholinergics should be investigated in further detail.

The subjects who got prescription of $\geq$ 90 doses/year of strong anticholinergics also had high doses of weak anticholinergics, other non-anticholinergics with negative effects on cognition, and polypharmacy; this effect

still held true even after adjusting for demographic variables, such as age, sex, and income. Moreover, approximately 10% of the subjects were prescribed two or more strong anticholinergics on the same day for more than 1 month of the year. People with high prescriptions of strong anticholinergics are expected to have high risks of adverse effects arising from drug-drug interactions and drug-disease interactions.

When prescription patterns were assessed in each age group, the dose of prescription of strong anticholinergics increased until 80-84 years of age and then decreased in the oldest age group (above 85) overall. More attention to minimize the use of strong anticholinergic drugs should be given to younger elderly people.

In terms of drug classes, the older people were exposed most often to antihistamines. When the average annual prescribed doses among the elderly who were prescribed with anticholinergics at least once was calculated, the dose of prescription was much higher in antiparkinsonians, antidepressants, and antipsychotics which were normally used to treat chronic diseases, than in antihistamines mainly indicated for common cold or allergic diseases. This suggests that exposure to inappropriate anticholinergics could be much more serious in the old people with multiple chronic diseases.

Chlorpheniramine and amitriptyline were prescribed the most, accounting for more than half of the total prescription amount of strong anticholinergics. Since chlorpheniramine is present in many combined non-prescription drugs, the volume of exposure was thought to be higher than the measured amount if self-medications taken into account. In a follow-up study conducted in France, the proportion of chlorpheniramine prescription among strong anticholinergics was much lower (Lechevallier- Michel et al. 2005). It seems that, as stated above, the universally available Korean NHI system would have led to a high medical accessibility, thus

resulting in increased prescriptions of chlorpheniramine, which is mainly used in mild diseases, such as common cold and allergies. As a result, this would have led to the increased total anticholinergic use (Mate et al. 2015). When frequently prescribed anticholinergics were classified into five groups based on their anticholinergic potencies, amitriptyline belonged to the group of the strongest anticholinergic activity (Carrière et al. 2009); In other words, amitriptyline has especially high risk of anticholinergic side effects among strong anticholinergic agents in the elderly. It is necessary to find out the reasons for such excessive prescription size and the ways to reduce it. As such, since the anticholinergic burden in Korean elderly is mainly due to the several specific agents, efforts should be made preferentially to decrease prescriptions of those medicines. Antihistamines can be replaced with second generation antihistamines, and amitriptyline and paroxetine can be substituted for new antidepressants with less anticholinergic activities; since cost differs by each drug, the pharmacoeconomic utility of such replacement should be reviewed as well (Chew et al. 2008).

In a study which investigated anticholinergic exposure in the PAQUID cohort through interviews, the authors reported that antipsychotics were the most commonly used anticholinergics (Lechevallier- Michel et al. 2005) which results were very different from those in this study. It may be due to the tendency to be reluctant to receive psychiatric treatment for fear of social stigma in Korea. In addition, oxybutynin, which was reported to be the most commonly prescribed drug in a study, was used very little in Korea. The reason why the proportion of each drug in prescription of strong anticholinergics differs in the studies could be because of differences in prescription patterns observed among countries. It could be also due to different study designs. For example, some studies evaluated anticholinergic

exposure by means of participant interviews (Fox et al. 2011) or evaluation of recently used drugs (Lechevallier- Michel et al. 2005). Moreover, only a very limited number of studies conducted sufficient quantitative evaluation (Carnahan et al. 2006).

After adjusting for covariates, the ORs for excessive exposure to strong anticholinergics became higher, particularly in the Medical aid beneficiary group. Adding on large disease burden arising from low economic status, low co-payment rate in Medical aid possibly led to excessive medical utilization (Pauly 2004). Moreover, when compared to Medical insurance recipients, Medical aid recipients was reported to have used advanced general hospitals less, while using general hospitals and clinics more often as outpatients (이용재 2017). Therefore, studies should investigate whether the prescription behaviors of inappropriate anticholinergics differ by type of medical institutions.

It is natural that people who were affected by morbidities for which strong anticholinergic agents were indicated were at high risk for overuse of anticholinergic agents. However, in this study, almost all of these diseases were included as covariates in the analysis, and the risk of excessive use of those agents was presented comparatively as odds ratios. This provides specific guidance on which patients should be monitored more closely for inappropriate use of anticholinergics.

This study is significant in that, first, it made an accurate calculation of prescribed doses using the NHIS Elderly cohort DB, thus measuring the actual exposure to anticholinergics almost without omission during the entire period of 2012. Second, the findings obtained from the very large-scale sample of the Korean elderly enabled to grasp the actual situation in the entire population. Third, this study evaluated not only overall anticholinergic use, but also contribution of each drug

(class) to the anticholinergic burden. Predictive diseases of excessive anticholinergic use were also elucidated thus providing specific guidance in setting up strategies to induce appropriate drug utilization for the elderly people.

This study has limitations in the following aspects. First, measurement bias could not be ruled out since the adequate daily dose for the elderly could be determined differently by experts. However, as in this study, if the basis in determining the doses and the values set for each drug were provided, it will not be a problem. Second, it was difficult to filter the records with errors in the prescription input stage. Extreme values due to these input errors may have affected the distribution of anticholinergic dosage. However, such errors, if present, would have exerted only minimal influences thanks to the very large sample size.

Although many studies have shown that the inappropriate anticholinergic use was prevalent in older adults, we confirmed that such inappropriate use was more serious in 10–15% of the elderly. Therefore, detailed evaluation of negative clinical influences should be conducted in those elderly group to which too much amount of strong anticholinergics were used. Moreover, the prescription amount of weak anticholinergics, which were known to have no clinically negative anticholinergic effects, were almost twice as large as those of strong anticholinergics; therefore, the influences should be also investigated in the elderly exposed to high doses of weak anticholinergics, along with strong anticholinergics.

CHAPTER 4. USE OF STRONG ANTICHOLINERGIC AGENTS IN ALZHEIMER'S DISEASE

4-1. Background

The elderly people with cognitive impairment or dementia especially should avoid the use of strong anticholinergic agents as possible due to their negative impact on cognitive function. In recent literature review studies, frequent use of anticholinergics with high potency were reported in older people with cognitive dysfunction or dementia (Johnell 2015). On the other hand, in a study evaluating PIMs for veterans, relatively low rate of the use in dementia comparing to non-dementia elderly was reported, but patients disease conditions were not considered sufficiently in clinical practice (Dosa et al. 2013). In a study of the use of inappropriate anticholinergics in 394 patients with dementia which used the US 2009-2010 medical expenditure panel surveillance data, one in four subjects were found to have been using inappropriate drugs. The most commonly prescribed drugs were oxybutynin, solifenacin, paroxetine, and tolterodine, and there was a high risk of inadequate anticholinergic use in self-reported anxiety, mood disorders, and fair / poor general health status (Kachru et al. 2015). In another study that evaluated the use of inappropriate drugs, including anticholinergics in 684 Alzheimer's patients, only polypharmacy and women affected PIMs, and PIMs were not associated with severity of dementia. They found that one of the two mild-moderate Alzheimer's patients was exposed to PIM, suggesting that the characteristics of the disease, the pharmacokinetic and pharmacodynamic properties of the AD patients have not been

considered enough in prescription. However, the PIMs appeared to have not been sufficiently assessed since it has been evaluated as user vs. non-user dichotomously (Montastruc et al. 2013). As such, although the studies evaluating the use of anticholinergics in AD exist, majority of them dealt with anticholinergic exposure as a part of PIMs and the results were mixed, requiring in-depth analysis in large elderly population.

4-2. Methods

Among the 388,629 subjects of the study in Chapter Ⅲ, AD prevalent subjects and the non-AD prevalent control group in 2012 were defined. The operational definition of AD patients in 2012 was that Alzheimer's Dementia (ICD; F00) or Alzheimer's disease (ICD; G30) was diagnosed in both 2011 and 2012, and one or more anti-Alzheimer' agents were prescribed at the time of each diagnosis. The non-AD control group was defined as the elderly who has been without Alzheimer's Dementia (ICD; F00), Alzheimer's disease (ICD; G30), vascular dementia, and MCI for two years in 2011 and 2012, and has never received anti-Alzheimer's agents. Anti-Alzheimer's agents were limited to drugs that are ascertained to have efficacy in Alzheimer's disease, that is, donepezil, rivastigmine. galantamine, and memantine.

Exposure to anticholinergics was measured by calculating standardized prescribed doses as suggested in Chapter Ⅲ. Multiple logistic regression analysis was performed to determine whether Alzheimer 's disease was associated with excessive use of strong anticholinergic agents. Excessive use of strong anticholinergics was defined as 'more than 90 doses per year in 2012, i.e., strong anticholinergic prescriptions for more than 3 months in a year with the adequate daily

dose for the elderly. Sex, age, income, polypharmacy, cumulative prescribed days of other non-anticholinergics that could impair cognitive functions, and the prescribed doses of weak anticholinergics were included as covariates in the analysis.

For the elderly who have taken the general health screening examination in 2011 or 2012 year, additional information on their major health examination results and lifestyle such as history of stroke, cardiac disease, hypertension, diabetes mellitus, dyslipidemia, other diseases including cancer, smoking status, alcohol intake, level of exercise were available (Lee et al. 2016), thus the analysis was conducted after adjusting for these all covariates additionally.

Another analysis was conducted to examine if the presence of AD would induce the restraint of anticholinergic prescription. In detail, subjects who have been diagnosed with the following diseases as primary or secondary diagnoses at least three times during 2012 were considered as having the corresponding morbidities; common or major diseases in the elderly: hypertension, diabetes mellitus, myocardial infarction, or cardiovascular diseases etc.; diseases for which strong anticholinergic agents were mainly indicated: Parkinson's disease, epilepsy, neuralgia, dizziness including by vestibular abnormalities, sleep disorder, genitourinary diseases and skin diseases etc.. Then, the diseases stated above and AD were all included as covariate, and multivariate analyzes were conducted. The results of the analysis was also used to identify comorbidities which could predict the excessive use of strong anticholinergics in the AD patients. For comparison, univariate analysis was also carried out.

4-3. Results

A total of 329,043 people over 70 years of age were included in the study, of whom 9,547 (2.9%) were AD patients. The proportion of patients over 80 years in the AD group was significantly higher (56.3% vs. 23.4% in AD group and non-AD group, respectively), with a higher proportion of AD patients in Medical aid (15.9% vs. 7.9% in AD group and non-AD group, respectively). The percentage of the subjects who were exposed to excessive amount of strong anticholinergics (≥ 90 dose/year) was higher in AD patients (22.5% vs. 16.3% in AD group and non-AD group, respectively). Weak anticholinergics, the average number of prescriptions per day, the number of annual diagnoses, and cumulative prescribed days of other non-anticholinergics that could impair cognitive functions were all higher in AD group than in non-AD group (Table 4-1).

Table 4-1. Characteristics of Alzheimer's disease group and non-Alzheimer's disease group (n=329043)

		Non-Alzheimer's disease (%) n=319496 (97.1)	Alzheimer's disease (%) n=9547 (2.9)
Sex	Male	127073 (39.8)	2250 (23.6)
	Female	192423 (60.2)	7297 (76.4)
Age	Mean±SD	76.2±5.3	80.8±6.0
	70-74	149111 (46.7)	1587 (16.6)
	75-79	95540 (29.9)	2587 (27.1)
	80-84	48262 (15.1)	2770 (29.0)
	≥ 85	26583 (8.3)	2603 (27.3)
Income	0 (Medical aid)	25075 (7.9)	1517 (15.9)
	4/10 percentile	76445 (23.9)	2009 (21.0)
	8/10 percentile	93084 (29.1)	2366 (24.8)
	10/10 percentile	124892 (39.1)	3655 (38.3)
Prescribed doses of strong anticholinergics	Mean±SD	63.1±155.8	90.2±202.9
	Median	13.0	6.0
	0-14	164396 (51.5)	5563 (58.3)
	15-89	102862 (32.2)	1842 (19.3)
	90-179	23413 (7.3)	635 (6.7)
	≥ 180	28823 (9.0)	1507 (15.8)
Prescribed doses of weak anticholinergics	Mean±SD	101.5±199.1	107.0±203.7
	Median	18.0	16.0

	Non-Alzheimer's disease (%)	**Alzheimer's disease (%)**
	n=319496 (97.1)	n=9547 (2.9)
Polypharmacy	112749 (35.3)	4693 (49.2)
Number of diagnoses (ICD, digits)	19.3±11.5	18.7±12.4
Other non-anticholinergics that could impair cognitive functions*	2.3±6.0	4.6±8.8

*Cumulative prescribed days of other non-anticholinergics that could impair cognitive functions (unit: days)

Of the 110,520 people who took the general health screening examinations in 2011 or 2012 year, 1,535 subjects (1.4%) were Alzheimer's patients. Those who received the examinations were generally younger comparing to the member of all subjects, and the number of people receiving Medical aid was much fewer (0.6% in the recipients of general health screening examinations vs. 15.9% in all subjects respectively; in the AD patients) (Table 4-1, Table 4-2). In chronic diseases, there was no great difference between AD patients and non-AD group, except for the higher prevalence of diabetes mellitus in AD patients. The proportion of excessive use of strong anticholinergics (≥ 90 doses per year) was higher in AD patients (15.6 vs. 28.2%, in non-AD group, AD group, respectively) (Table 4-2).

Table 4-2. Characteristics of Alzheimer's disease group and non-Alzheimer's disease group in the subjects who took the general health examination in 2011 or 2012 year (n=110520)

		Non-Alzheimer's disease (%)	**Alzheimer's disease (%)**
		n=108985 (98.6)	n=1535 (1.4)
Sex	Male	49123 (44.9)	463 (30.2)
	Female	59862 (55.1)	1072 (69.8)
Age	mean±SD	74.8±4.2	78.5±5.4
	70-74	60274 (55.3)	402 (26.2)
	75-79	34417 (31.6)	541 (35.2)
	80-84	10770 (9.9)	373 (24.3)
	≥ 85	3514 (3.2)	219 (14.3)
Income	0 (Medical aid)	584 (0.5)	9 (0.6)
	4/10 percentile	28,080 (25.8)	362 (23.6)
	8/10 percentile	34165 (31.4)	495 (32.3)
	10/10 percentile	46156 (42.6)	669 (43.6)
Prescribed doses of strong anticholinergics	mean±SD	59.7±144.9	111.2±222.3
	median	15.0	19.0
	0-14	53906 (49.5)	714 (46.5)
	15-89	38101 (35.0)	388 (25.3)
	90-179	8117 (7.5)	131 (8.5)
	≥ 180	8861 (8.1)	302 (19.7)
Prescribed doses of weak anticholinergics	mean±SD	95.2±181.2	132.2±227.9
	median	20.0	44.0

	Non-Alzheimer's disease (%)	**Alzheimer's disease (%)**
	n=108985 (98.6)	n=1535 (1.4)
Polypharmacy	38121 (35.0)	953 (62.1)
Other non-anticholinergics that could impair cognitive functions*	2.3±5.8	5.5±9.1
BMI	24.0±3.2	23.1±3.4
History of		
Stroke	3733 (3.4)	153 (10.0)
Cardiac disease	10245 (9.4)	140 (9.1)
Hypertension	61870 (56.8)	852 (55.5)
Diabetes mellitus	20579 (18.9)	331 (21.6)
Other diseases including cancer	20384 (18.7)	482 (31.4)
Current smoking	10350 (9.5)	68 (4.4)
Heavy alcohol intake	6086 (5.6)	40 (2.6)
Walking 0-1 day/week	47754 (43.8)	910 (59.3)

*Prescription amount of other non-anticholinergics that could impair cognitive functions was measured by cumulative prescribed doses

The prescription amount of antihistamines accounted for the largest proportion in all strong anticholinergics in the non-AD (33.6 dose/year), while antidepressants were most prescribed in AD patients (30.0 dose/year). The prescription amount of antihistamines did not differ significantly between the two groups (33.6 dose/year in non-AD group vs. 28.5 doses/year in AD patients respectively). However the prescription amount in the AD patients was much higher than that in the non-Alzheimer's group in most of the other anticholinergic drug classes. Especially, prescription amount of antidepressants, antimuscarinics, antiparkinsonians, and anticonvulsants were shown to be much higher in the AD patients (Figure 4-1).

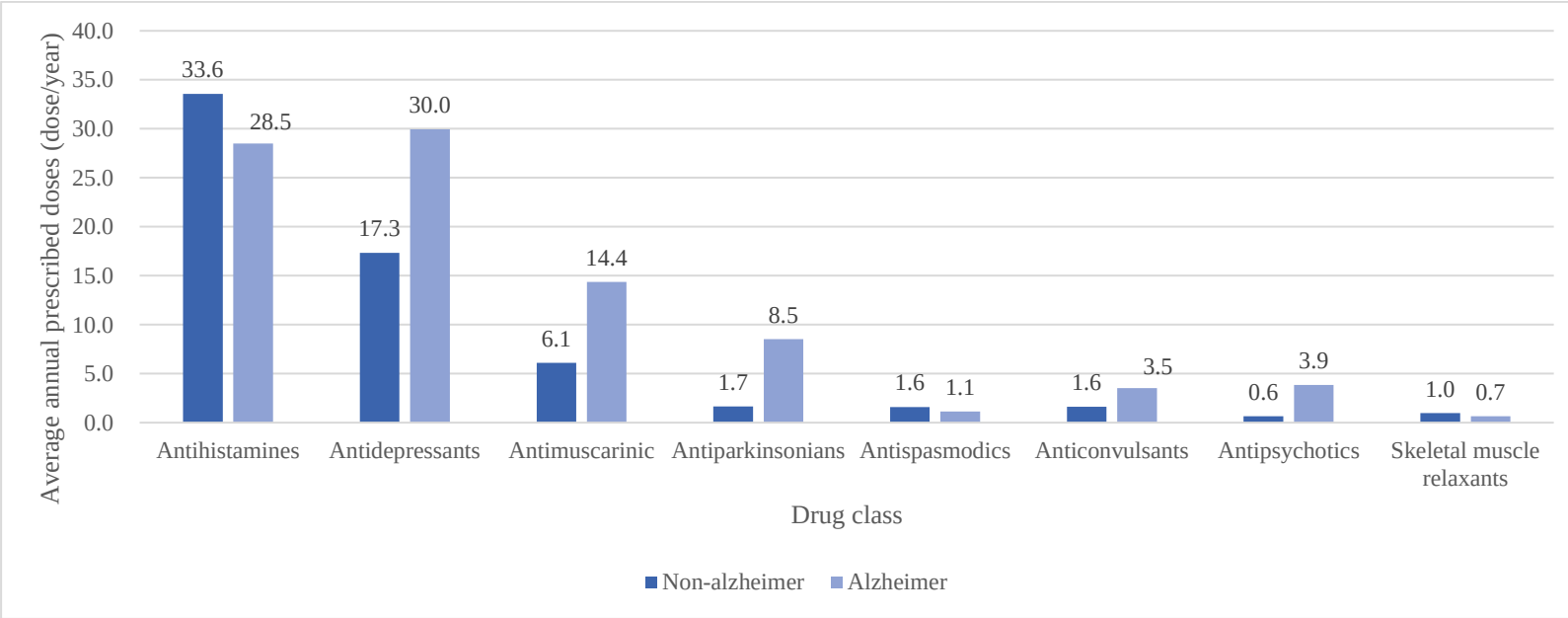


Figure 4-1. Average annual prescribed doses of strong anticholinergics by drug class in Alzheimer's disease group and non-Alzheimer's disease group

When calculating the average amount of prescription for each drug class in those who got the prescription of the corresponding drug at least once, average annual doses of the anticholinergics which were thought to be required long-term daily use, such as antidepressants, antimuscarinics and antiparkinsonians were greatly increased. The big differences in the prescription amount between non-AD group and AD patients in those drug classes became narrowed (Figure 4-1, Figure 4-2). In case of antihistamines, which would be frequently used in intermittent way for mild diseases such as common cold and allergic conditions, have a relatively small increase in their extent (Figure 4-2).

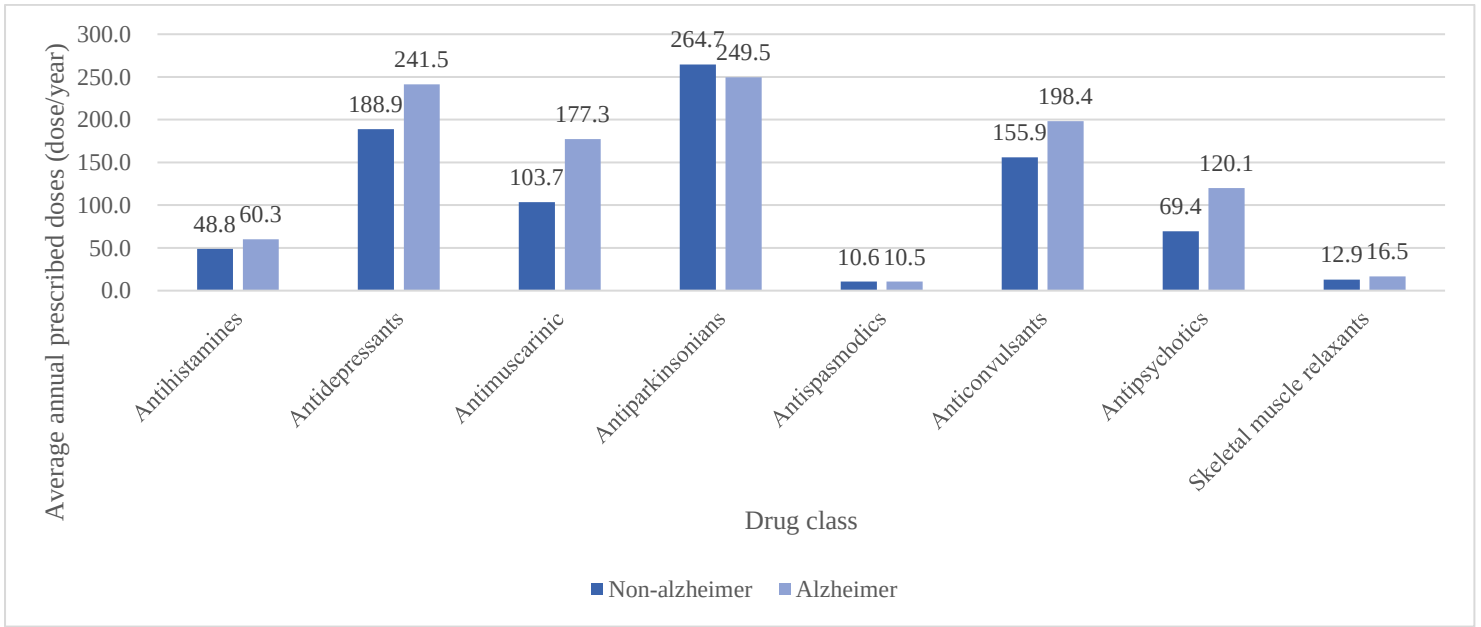


Figure 4-2. Average annual prescribed doses of strong anticholinergics by drug class in the Alzheimer's disease group and the non-Alzheimer's disease group among those who were prescribed the corresponding drug at least once

In overall, the drugs in the 10th place were similar in the non-AD group and the AD group, but there were differences in the drug-specific proportions. In the non-AD group, chlorpheniramine had the highest prescription volume and occupying nearly 40% of the total dose of strong anticholinergics. The prescription of amitriptyline was the next highest (21.8%). In the AD group, amitriptyline ranked the the highest prescription amount (20.4%), followed by chlorpheniramine (19.6%) and another antidepressant, paroxetine (8.5%). The three antimuscarinic agents used in urological diseases such as tolterodine, solifenacin, and fesoterodine were also in the top 10 of the prescriptions in the both groups. In both groups, these top ten drugs accounted for over 80% of the prescription amount of strong anticholinergics (Table 4-3).

Table 4-3. Rank of strong anticholinergics by prescribed doses in the Alzheimer' disease group and the non-Alzheimer's disease group

	Non-Alzheimer's disease group			Alzheimer's disease group		
Rank	Drug	Proportion (%)	Cumulative proportion (%)	Drug	Proportion (%)	Cumulative proportion (%)
1	Chlorpheniramine	39.8	39.8	Amitriptyline	20.4	20.4
2	Amitriptyline	21.8	61.5	Chlorpheniramine	19.6	40.0
3	Dimenhydrinate	6.9	68.5	Paroxetine	8.5	48.6
4	Hydroxyzine	5.9	74.4	Dimenhydrinate	6.7	55.3
5	Tolterodine	3.4	77.8	Tolterodine	5.5	60.7
6	Solifenacin	2.7	80.5	Hydroxyzine	5.1	65.9
7	Paroxetine	2.5	83.1	Solifenacin	4.6	70.4
8	Carbamazepine	2.3	85.4	Amantadine	4.2	74.6
9	Scopolamine	2.1	87.5	Benztropine	4.1	78.7
10	Fesoterodine	1.7	89.3	Fesoterodine	3.9	82.6

The multiple logistic regression analysis was performed to identify how much the odds of excessive use of strong anticholinergics were increased in AD patients in both all subjects and members who took the general health screening examinations. The odds for the excessive use of those drugs in AD patients was increased 36% after adjusting for age, sex, and level of income in all subjects comparing to non-AD group. When the multiple logistic regression analysis was conducted for the subjects who have taken the general health examinations after controlling the additional covariances of comorbidities and life styles, the odds increased further by 77% in the AD group compared to the non-AD group. In both analyzes, odds for the excessive use was increased until 84 years of age and then decreased after reaching at the age of the oldest old (≥ 85 years). The risk of the excessive use was also higher in the beneficiaries of Medical aid, the lowest income group compared to the highest income group. Some main diseases in elderly people, such as stroke, cardiovascular disease, and diabetes mellitus were associated with the excessive use (Table 4-4).

Table 4-4. Association of Alzheimer's Disease with excessive use of strong anticholinergic agents, analyzed in the all subjects and the general health screening examinations recipients, respectively

		Excessive use of strong anticholinergics*	
		All subjects (n=329043)	**General health screening examinations recipients (n=110520)**
		Odds ratio (95% Confidence interval)	
Crude model			
Alzheimer's disease		1.48 (1.41-1.56)	2.13 (1.90-2.38)
Covariates model			
Alzheimer's disease		1.36 (1.29-1.43)	1.77 (1.58-1.99)
Age	70-74	Reference	Reference
	75-79	1.19 (1.17-1.22)	1.21 (1.16-1.25)
	80-84	1.28 (1.25-1.31)	1.39 (1.32-1.46)
	≥85	1.07 (1.03-1.11)	1.30 (1.19-1.42)
Sex, Female		1.00 (0.98-1.02)	0.92 (0.88-0.96)
Income	10/10 percentile	Reference	Reference
	8/10 percentile	1.01 (0.98-1.03)	1.02 (0.98-1.06)
	4/10 percentile	1.07 (1.04-1.09)	1.08 (1.04-1.13)
	0 (Medical aid)	1.72 (1.66-1.77)	1.78 (1.47-2.15)
BMI		-	1.01 (1.01-1.02)
Histories of			

		Excessive use of strong anticholinergics*	
		All subjects (n=329043)	**General health screening examinations recipients (n=110520)**
		Odds ratio (95% Confidence interval)	
	Stroke		1.55 (1.44-1.68)
	Cardiac disease	-	1.23 (1.17-1.30)
	Hypertension	-	1.14 (1.10-1.17)
	Diabetes mellitus	-	1.25 (1.20-1.30)
	Dyslipidemia	-	1.01 (0.94-1.08)
	Other diseases including cancer	-	1.60 (1.54-1.67)
Current smoking		-	1.16 (1.09-1.24)
Heavy alcohol intake		-	0.68 (0.63-0.74)
Walking 0-1 day/week		-	1.14 (1.10-1.19)

*Excessive use of strong anticholinergics (≥ 90 dose/year): calculated by annual standardized prescribed doses.

Table 4-5 shows if the presence of AD would induce the restraint of anticholinergic prescription. The odds for the excessive use of strong anticholinergics was 48% higher in AD patients compared to the non-AD group in the univariate analysis. However when multivariate analysis was conducted after controlling the almost all diseases requiring strong anticholinergic use, 12% lower odds in AD patients than in the non-AD group for the excessive use of strong

anticholinergics was identified. As expected, most of these diseases for which strong anticholinergics were mostly indicated were the predictors of the excessive use of them. In particular, depression, Parkinson's disease, respiratory disease, dizziness (including by vestibular abnormalities), or genitourinary diseases strongly predicted excessive use of strong anticholinergics (Table 4-5).

Table 4-5. Use of strong anticholinergic agents in Alzheimer's disease before and after controlling the diseases for which strong anticholinergics mainly indicated

	Univariate Analysis	**Multivariate Analysis**
	Odds ratio (95% Confidence interval)	
Alzheimer's disease	1.48(1.41-1.56)	0.88 (0.82-0.93)
Age		
70-74	Reference	Reference
75-79	1.21 (1.18-1.24)	1.11 (1.08-1.13)
80-84	1.34 (1.30-1.37)	1.21 (1.18-1.25)
≥ 85	1.14 (1.11-1.18)	1.24 (1.19-1.28)
Sex, female	1.05 (1.03-1.07)	1.11 (1.08-1.13)
Income		
10/10 percentile	Reference	Reference
8/10 percentile	1.00 (0.97-1.02)	1.05 (1.03-1.08)
4/10 percentile	1.06 (1.04-1.09)	1.11 (1.08-1.14)
0 (Medical aids)	1.76 (1.70-1.82)	1.42 (1.37-147)
Hypertension	1.36 (1.33-1.38)	1.07 (1.05-1.09)
Cardiovascular disease	2.03 (1.98-2.08)	1.37 (1.33-1.41)

	Univariate Analysis	Multivariate Analysis
	Odds ratio (95% Confidence interval)	
Myocardial infarction	1.31 (1.25-1.37)	1.03 (0.98-1.09)
Diabetes mellitus	1.37 (1.34-1.40)	1.15 (1.12-1.18)
Depression	4.61 (4.51-4.71)	3.75 (3.62-3.88)
Anxiety	3.61 (3.52-3.71)	0.71 (0.68-0.74)
Genitourinary disease	2.92 (2.86-2.98)	2.44 (2.37-2.50)
Dizziness*	3.45 (3.37-3.53)	2.30 (2.24-2.37)
Sleep disorder	3.14 (3.06-3.23)	1.54 (1.50-1.59)
Neuralgia	1.98 (1.94-2.02)	1.34 (1.31-1.37)
Respiratory disease	2.71(2.66-2.76)	2.22 (2.18-2.27)
Dermatological disease	2.70 (2.64-2.76)	2.06 (2.01-2.11)
Parkinson's disease	4.59 (4.32-4.87)	3.38 (3.15-3.62)
Psychosis	3.89 (3.57-4.25)	1.46 (1.32-1.62)

*Dizziness including by vestibular abnormalities

4-4. Discussion

The quantitative comparison of the use of strong anticholinergics in the AD patients and the non-AD group in the large elderly population showed that more anticholinergic drugs were prescribed in the AD patients than in the non-AD elderly. Since the studies of the anticholinergic medications in patients with dementia were very limited and there was a large difference between the studies in the aspects of subjects population and estimation of exposure amount, direct comparison of this study with previous ones was cautious. However, in regarding a recent study, 23.3% of non-institutionalized elderly people with dementia were reported to have been using clinically significant anticholinergic agents (Sura et al. 2013) and a retrospective study found that the prevalence of anticholinergic medications in 418 older adults who were using donepezil was 33% (Roe, Anderson, and Spivack 2002), the prevalence and prescription amount of the strong anticholinergics shown in this study were fairly high level.

After adjusting for basic demographic variables such as age, sex and level of income, the odds for excessive use of strong anticholinergics was 36% higher in AD patients than in the non-AD control group. When the subset analysis in those who took general health screening examinations in 2011-2012 was conducted after controlling the additional covariates such as BMI, hypertension, diabetes mellitus, smoking status etc., the odds increased further by 77% in the AD group compared to the non-AD group. Those analysis was actually carried out as part of sensitivity test. Consistent and enhanced results in this subset analysis supported the robustness of this study. The members of the subset group were generally younger and have fewer Medical aid then they might be healthier compared to the all subjects. They could be

more tolerable to the adverse effects of anticholinergic agents, so it can be assumed that they were given a more generous prescription. However, the majority of strong anticholinergics require long-term use, and less frequent short-term adverse events will not guarantee the safer condition in long-term. Efforts to minimize the use of strong anticholinergics should be taken earlier as a preventive measure.

Compared with the AD group, the antihistamines including chlorpheniramine, dimenhydrinate, and hydroxyzine accounted for more than 60% of the total strong anticholinergic prescription and the proportion of amitriptyline was also high (21.8%) in non-AD group. In contrast, amitriptyline and paroxetine, which belong to the antidepressants, was accounted for 30% of the total in AD group. the prescription amount of urological antimuscarinics was also remarkably high in both groups. When comparing the average amount of prescription for each drug class in those who were prescribed the corresponding drug at least once, the difference between the two groups was greatly reduced, although still higher in AD group for most of all drug classes suggesting that the AD patients were being prescribed long-term anticholinergics with higher doses than non-AD subjects.

The average prescribed doses of the strong anticholinergic agent was very high in both the AD patients and non-AD group, about 50% higher in the AD group than in the non-AD group. However, conversely, the median in the AD group was half that of the non-AD group. In addition, over half of the elderly were in the lowest exposure level (0-14 doses) in both groups, and the proportion was higher in the AD group than in the control group (51.5% vs. 58.3%, in non-AD group and AD group, respectively). These results may indicate that the majority of the elderly are not exposed to excessive amount of strong anticholinergics, but the problem is serious in some older people. Among elderly people who were exposed to acceptable level

of strong anticholinergics (0-14 doses), AD patients were being prescribed less. However, when the excessive dose was defined as ≥90 dose/year, the proportion of the corresponding subjects was 16.3% and 22.5% in the non-AD and AD patients, respectively, which is not a minority. As shown in Table 4-4, the exposure was likely to be more than twice as high in the AD group as in the non-AD group. Since the anticholinergic efficacy could be decreased in combination with anti-Alzheimer's drug, there is a possibility that one-time prescription dose itself was set higher in AD to exert equivalent efficacy.

Multivariate analysis which was conducted to examine if the presence of AD would induce the restraint of anticholinergic prescription confirmed 12% lower odds for the exposure to the excessive strong anticholinergics in AD. It could be cautiously interpreted that the extent of prescription reduction of the strong anticholinergics due to affected AD was as about 12%. Considering the potential risks to cognitive function of the potent anticholinergic agents, the effort to reduce it in AD seemed not to be sufficient in clinical field. In patients with severe dementia admitted to a nursing home, sedative and depressant anticholinergics might be overdosed to control the excess mental behaviors which were frequently found in dementia (Kröger et al. 2015). In order to confirm this, follow-up studies such as separate analysis of inpatients and outpatients, and subgroup studies according to severity of AD will be necessary.

Based on the distribution of strong anticholinergic use and the results of the drug-specific prescription ranking in the AD and the non-AD group, and logistic regression analysis, some AD patients seemed to be taking particularly high dose of anticholinergics over a long period of time to treat their comorbidities of AD by concomitant medications, then they are likely to pull up the average prescribed doses

of total anticholinergics in AD group. These results suggest that AD patients may have low overall health status due to the related complications; then they were more likely to develop diseases, such as common cold, pruritus, or depression in which the strong anticholinergics were used. In addition, these patients are required to visit the hospital regularly that they tend to get prescriptions easily even for a mild diseases or conditions.

This study has several advantages and implications. First, by using the large population of over 300,000 elderly people, the results can be applied to the whole Korean older population. Second, the exact prescription amount of anticholinergics was almost fully calculated that the exposure assessment was very reliable. Third, the validity of the results was verified by subgroup analysis in those who took the general health screening examinations. Fourth, by identifying the extent of anticholinergic exposure by drug class and individual drug in AD patients and non-AD group, this study provides the basis for a more specific guide to make reduction the inappropriate anticholinergic use in Alzheimer's disease.

CHAPTER 5. THE ASSOCIATION OF ANTICHOLINERGIC USE WITH INCIDENCE OF ALZHEIMER'S DISEASE

5-1. Background

Although the use of inappropriate anticholinergics in the older adults is known to have a negative impact on cognitive function (Ruxton, Woodman, and Mangoni 2015, Collamati et al. 2016, Risacher et al. 2016), there are controversy and little research as to whether it could affect the risk of AD (incidence of AD). One of the main reasons seemed that the long-term follow-up of exposure to multiple anticholinergics which is crucial for demonstrating the causal relationship between the exposure and incidence of dementia are very demanding.

In a recent prospective cohort study, 3,434 elderly people with the information of past 10-year cumulative doses of anticholinergics were followed up to determine whether the long-term use of anticholinergics was associated with the development of dementia or AD. The result showed that the hazard for incident AD in the highest exposed group was 63% higher than the lowest exposed group (Gray et al. 2015). The study seems most valid among the several studies in that it measured the long-term exposure meticulously by calculating total standardized daily doses and took into account possible biases from prodromal symptoms. However, the authors pointed out that the focus was only on high - potency anticholinergics and that the possibility of generalization was unknown (Gray et al. 2015). In a follow-up study of 6,900 elderly people in three cities in France, the risk of incident dementia

was higher (HR = 1.65, CI = 1.00-2.73) in the consecutive users of anticholinergics, but not in discontinued subjects (HR = 1.28, CI = 0.59-2.76) (Carrière et al. 2009). However, the median follow-up period was only 3.5 years, and the use of anticholinergics by the prodromal symptom was not considered. In addition, the high dropout rate seemed to be a limitation in generalizing the results of the study. A German study of 2,600 elderly people suggested that HR in anticholinergic users was similar to that of ApoE4 (Jessen et al. 2010). However, no exposure was quantified by just defining those who had used anticholinergics as exposed people at any time before the diagnosis of incident dementia. Some studies have shown that the use anticholinergic agents was not associated with the development of dementia (Campbell et al. 2010, Ancelin et al. 2006, Kalisch Ellett et al. 2014). In a 6-year, long-term study of 1,600 African-American elderly people, the use of anticholinergics had a negative impact on cognitive ability, but no association with dementia was identified. However, anticholinergic exposure was only evaluated as medications in subjects' home at the initial in-home evaluation (Campbell et al. 2010).

One of the biggest challenges researches who find relationship between anticholinergic exposure and risk of AD is facing seems to be how to exclude prodromal effects. The clinical stage of AD can be divided into prodromal and dementia stages (Dubois, Hampel, et al. 2016). In the prodromal state prior to the dementia stage, prescription of anticholinergic antidepressants may be increased due to depressive symptoms (Bennett and Thomas 2014), although cognitive performance deterioration already occur (Amieva et al. 2008). In observational studies to elucidate the causal relationship of anticholinergic use with risk of AD, anticholinergic use for the prodromal AD symptoms prior to diagnosis within the

observation period of anticholinergics use should be excluded as much as possible. However only very limited studies (Gray et al. 2015) have considered this carefully. In addition, considering the lag time between the onset of AD clinical phenotype and the initial diagnosis (Dubois, Padovani, et al. 2016), which is usually defined as the occurrence of dementia, a more diverse research designs should be tried to identify the causality in the absence of reverse association.

The purpose of this study was to investigate whether anticholinergic use increases the risk of AD, and how long a period of anticholinergic exposure is associated with the risk of AD in the elderly population. We hypothesized that long-term exposure to excessive amount of strong anticholinergics increases the risk of AD, but not in relatively short term exposure or in the exposure to weak anticholinergics. We especially examined whether the younger elderly were more affected by strong anticholinergic use in risk of AD comparing to the other older elderly.

5-2. Methods

Data source

We conducted a prospective cohort study in a large Korean elderly population by using NHIS Elderly cohort DB. Drug information was obtained from both HIRA and KPIC. Details on the data sources were was stated in Chapter Ⅱ.

Study subjects

Among the elderly who had never been diagnosed with mental and behavioral disability (ICD: F00-F99) and Alzheimer's disease (ICD-10: G30), including all types of dementia as the primary or secondary diagnosis for three years from 2002 to 2004, 342,522 people who are qualified for NHIS in 2005 were selected.

Selection of anticholinergic agents and measurement of prescription amount

Selection and classification of anticholinergic agents were based on Beers Criteria (Radcliff et al. 2015) and Anticholinergic Cognitive Burden (ACB) scale (Boustani et al. 2008). Drugs which were listed on Beers Criteria as 'strong anticholinergic agents' or with ACB score of 2 or 3 were classified into 'strong anticholinergics', while 'weak anticholinergics' were drugs of ACB score 1. Strong anticholinergic agents were classified as inappropriate drugs for the elderly due to the high risk of causing various side effects to those people. Exposure to both strong and weak anticholinergic agents was measured quantitatively using prescription DB from NHIS Elderly cohort and drug DB provided by HIRA. First, the adequate daily dose for the elderly for each anticholinergic agent was set based on the Korean drug formulary from Ministry of Food and Drug Safety (MFDS), Lexicomp® Online, and Micromedex® DRUGDEX. If dosing for geriatrics is available in the Korean drug formulary, it is given priority. If it was not available, the adequate daily dose for the elderly was set considering the lower limit of effective dose. And then the standardized prescribed doses for each anticholinergic agent was calculated using the generic name code, relative dose, dosage unit, daily frequency of administration, and number of prescribed days. Supplementary table 1 presented the list of strong and weak anticholinergic agents and their adequate daily dose for the elderly. The

standardized prescribed doses of anticholinergics from 2002 until the end of individual follow-up was summed. The formula for obtaining the prescription amount was as follows.

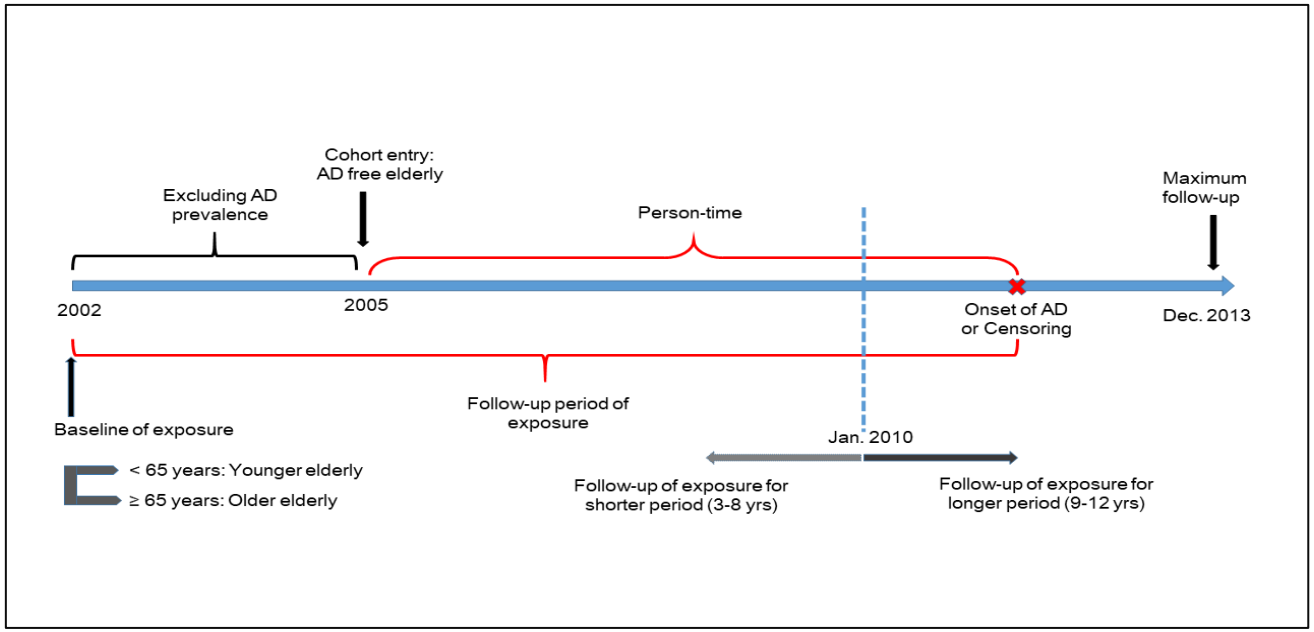
- Relative dose = actual content in prescribed drug / adequate daily dose for the elderly
- Standardized prescribed doses (doses) = relative dose x number of unit of administration x daily frequency of administration x number of prescribed days
- Prescription amount (doses) = ∑ standardized prescribed doses

Definition and follow-up of incidence of Alzheimer's disease

In a follow-up study from 1 January 2005 to 31 December 2013, a person with a diagnosis of AD (F00 or G30) and a prescription of anti-Alzheimer's disease agents, such as donepezil, rivastigmine, galantamine, and memantine at the time of diagnosis was defined as an AD patient and the first day of those was defined as the incident date. In the case of censored participants, the period from 2002 to the earlier date between the date of death and the date of the last visit to the medical facility until 2013 was defined as follow-up period.

Assessment of exposure: Average annual prescription amount and follow-up of exposure

The individual exposure period varies from a minimum of 3 years (2002-2004) to a maximum of 12 years (2002-2013), depending on the end of the follow-up. The average annual prescription amount was calculated by means of dividing the prescription amount by observed period (years) of anticholinergic use from 2002, that is, the follow-up period from 2005 to the event or censored time plus 3 years (2002-2004) for each subject. Subjects were divided into four classes according to the average annual prescription amount of strong anticholinergic agents from 1 January 2002 until the end of the follow-up (0-9 dose/year, 10-49 dose/year, 50-119 dose/year, ≥ 120 dose/year). The strong anticholinergics were classified into nine drug classes according to the drug classification provided by Beers Criteria (Radcliff et al. 2015), and prescription amounts were evaluated by drug class for three classes with high volume of prescription; antihistamines, antidepressants, and urinary antimuscarinics. For weak anticholinergics, the subjects were grouped into four classes by the prescription amount (0-29 dose/year, 30-119 dose/year, 120-299 dose/year, ≥ 300 dose/year) and the same analyses were performed. The follow-ups of anticholinergic exposure and development of AD were simply represented in Figure 5-1.



Abbreviation: AD, Alzheimer's disease

Figure 5-1. Schematic representation of person-time, follow-up period of exposure, and the subgroups by age at the baseline follow-up of exposure

Statistical Analyses

Characteristics of subjects by prescription amount of strong anticholinergics and by incidence of AD were described with mean±SD, median or frequency (proportion). Confidence intervals for incidence rates were calculated assuming poisson distribution. Proportional hazard regression model was used to assess the association between anticholinergic use and incidence of AD. To verify proportional hazard assumption, log-negative-log of Kaplan-Meier estimator of the survival function was applied.

Stratification by time scales (follow-up period and age)

Subjects were stratified according to the follow-up period of exposure and age at the baseline of exposure (Szklo, Nieto, and Miller 2007) for the following reasons. First, in this study, the follow-up period for anticholinergics varies from person to person, shortly 3 years, up to 12 years and the exposure was evaluated as average annual doses. Hence even among subjects with the same average annual exposure, those with longer follow-up periods may be more likely to be affected by anticholinergic agents, and for the same reason, those with shorter follow-up periods may not reflect the effects of exposure enough. We observed a proportional hazard from the log-negative-log Kaplan-Meier plot after about 6 years of person-time, i.e., around 9 years from the baseline of exposure, so the subjects were stratified into two groups of shorter (3-8 years) vs. longer (9-12 years) follow-up of exposure. Secondly, it was assumed that event of AD especially increased with time more prominently in younger, healthier elderly, as they are followed up as they age. Thus subjects were also divided into two strata by age at the baseline of exposure. That is, subjects

younger than 65 years of age in 2002, who appeared at age 75 or younger at the time of AD or censoring, were defined as 'the younger elderly', and the other group of subjects, subjects ≥ 65 years of age in 2002, were defined as ‘the older elderly’. Taken together, we constructed two-dimensional strata using these two time scales, then the incidence rate, and the risk of AD according to the strong anticholinergic exposure levels were estimated. A trusted textbook in the field of Epidemiology was referenced to support the rationale for establishing those two-dimensional strata (Szklo, Nieto, and Miller 2007). Especially, since the younger elderly seems to have a shorter lag time from the prodromal state to diagnosis of AD than the older elderly, and the results in this subgroup were assumed to be less biased by comorbidities or multiple medications, we performed all the key analyzes in this subgroup, so that they were compared with the results from all subjects. The analysis was performed even on the entire subjects to see the average effect of anticholinergic exposure in the whole subjects.

Adjustment for potential confounding variables

To identify and control for potential confounding variables, basic demographic variables, such as age, sex, level of income; medical histories, such as hypertension (HTN), diabetes mellitus (DM), myocardial infarction (MI), cardiovascular disease (CVD), Parkinson's disease (PD), epilepsy, neuralgia, dizziness including due to vestibular abnormalities, sleep disorder, genitourinary diseases, skin diseases; use of weak anticholinergics, and use of other non-anticholinergic drugs that could impair cognitive functions, were included as covariates. Age was included as continuous variable. For the level of income, insurance contribution were used as a proxy. The

beneficiaries of the Medical aid program which is a tax-based governmental program for low-income families were classified into the lowest income group. For the information on medical histories, records of ICD diagnostic codes in 2004 year were used as surrogates. In detail, subjects diagnosed with HTN, DM, MI, or CVD, which are main diseases in the elderly; main indications of various strong anticholinergics, such as PD, epilepsy, neuralgia, dizziness including due to vestibular abnormalities, sleep disorder, genitourinary diseases, skin diseases, as primary or secondary diagnoses in 2004 at least three times were considered as having the corresponding medical histories. They were then included in the covariates in the final analysis model (Model Ⅱ). The ICD codes which were used to define each disease (group) were presented in the Appendix 3.

Prescription amount of the weak anticholinergics, cumulative prescribed days of other non-anticholinergic agents that could impair cognitive functions were also included in the analysis model. Weak anticholinergics, like strong anticholinergics, were quantified as standardized prescribed doses and divided into quartiles according to the annual prescription amount. The use of 'other non-anticholinergic drugs that could impair cognitive functions' was quantified by average annual cumulative prescribed days.

Backward elimination was carried out with the significant level of 0.3 for retaining the effects in the model. Some variables, for example, skin diseases or sleep disorder, did not showed the significance with the level in specific strata. However every covariate left as it is since they were all significant in the analyses of all subjects and there was little difference between the results before and after backward elimination. When the exposure of the weak anticholinergics was a variable of interest, the prescription amount of strong anticholinergics was additionally adjusted

for.

Supplementary analyses Ⅰ: To minimize the bias due to prodromal effects

Since the use of anticholinergics may be due to the prodromal symptoms of AD before the first diagnosis, the average dose of anticholinergics were calculated after excluding the amount of prescription during 1 year and 2 years prior to the end of the follow-up respectively. Since depression was highly prevalent in the stage of the prodromal AD, analysis was carried out after excluding 'anticholinergic antidepressants'. Furthermore, analyzes were performed after excluding 'strong anticholinergic prescriptions for one year prior to the end of follow-up' and 'doses of antidepressants for all follow-up period of time' at a time. For drug classes with high volume of prescription among the all anticholinergics, such as antihistamines, antidepressants, and antimuscarinics, the prescription amount was also calculated separately, and then the association of the exposure to the each drug class with risk of AD was examined. In this case, the prescription amount of the drugs belonged to the other drug classes, not the interest drug class was adjusted for. Multivariate proportional hazard regression analyses were carried out for all these additional analyses.

Supplementary analyses Ⅱ: Subset analyses for subjects who participated in the general national health screening programs

The NHIS has provided general national health screening programs to improve the health status of Koreans through the prevention and early detection of diseases. All

insured adults are eligible for a general health screening programs that is biennially conducted (Yang et al. 2015). Among the all subjects, 108,920 elderly have participated in the health screening programs in 2005 or 2006 year, then additional information on basic indices of health status such as body mass index (BMI), systolic blood pressure (SBP), blood glucose level, and total cholesterol level; history of major diseases such as stroke, hepatitis, liver disease, tuberculosis, any type of cancer; variables for life style and behaviors such as smoking status, alcohol intake, exercise habits were available. To examine and to exclude the possible influence of these variables to the results of the study, subset analyses were carried out for these participants. The missing values were treated with mean imputation for successive variables such as BMI and SBP, and with missing-indicator methods for categorical variables such as smoking status, alcohol intake, and exercise habits.

Sensitivity test Ⅰ: Exact matching and propensity score analyses

As part of sensitivity tests, exact matching and propensity score method (PSM) were performed and the results were compared with those from standard covariance adjustment method in multivariate proportional hazard regression. First, to run exact matching method, the continuous variable 'other non-anticholinergics that could impair cognitive functions' was converted into a categorical variable with six classes grouped by average annual prescribed doses (0 dose/year; 1-2 dose/year; 3-14 dose/year; 15-59 dose/year; 60-119 dose/year; ≥ 120 dose/year) to make exact matching possible for all sixteen covariates denoted previously (Burden et al. 2017). Each exposed unit was matched with a reference (control) unit that has exactly the same value on each covariate (Randolph and Falbe 2014, Ho et al. 2018). In PSM,

matching procedure was conducted by using propensity score (PS) regression adjustment method (Elze et al. 2017, Vansteelandt and Daniel 2014). Distributions of propensity score both in the reference and highest exposed group was tested visually by histogram to set the upper limit of propensity score under which the distribution of PS between reference and the highest exposed group was similar. In all subjects, the distribution was found to be very similar between the two groups in propensity score <0.1. Thus PS regression adjustment was conducted for the subset members satisfying the condition of PS <0.1.

Sensitivity test Ⅱ: Applying different criteria to define incidence of Alzheimer's disease

Two approaches were used to examine the validity of the study design by applying various criteria in defining incidence of Alzheimer's disease. First, the incidence of AD was redefined more strictly, as such diagnoses of Alzheimer's disease (ICD: G30) or Alzheimer's dementia (ICD: F00) more than twice or three times, and at each diagnosis point with a prescription of an anti-Alzheimer's agents. Then the results were compared with those in original definition. Second approach was in order to confirm that the 'three-year exclusion' which was adopted criterion in this study to exclude people already suffering from Alzheimer's disease, was long enough to rule out those people. To test this, after eliminating people with AD diagnostic codes from a minimum of 1 year to a maximum of 5 years prior to 2007 year, any difference in the proportion of incident AD for 7 years from 2007 to 2013 was examined.

5-3. Results

Descriptive data

In 2005, the number of subjects included in the follow-up was 342,522. 45.1% had low anticholinergic burden of 0-9 doses per year, while 16.0% of the subjects were exposed to large amount of anticholinergics with more than 50 doses per year. 5.9% of the subjects were prescribed a very large amount of strong anticholinergics (≥ 120 doses/yr). In the elderly who were prescribed more strong anticholinergics, both the prescription amount of weak anticholinergics and 'other non-anticholinergics that could impair cognitive functions' were also larger. Antihistamines, antidepressants, and urinary antimuscarinics were prescribed most among strong anticholinergic drug classes. Beneficiaries of the Medical aid were exposed to more anticholinergics. The diseases such as PD, neuralgia, GUD where strong anticholinergics frequently used, and main chronic diseases of elderly people such as HTN, DM were more prevalent in those who used more anticholinergics (Table 5-1).

Table 5-1. General characteristics of subjects by prescription amount of strong anticholinergic agents

	Prescribed doses of strong anticholinergics (dose/year) (n=342522)			
	0-9	**10-49**	**50-119**	**≥ 120**
No. of subjects (%)	154370 (45.1)	131678 (38.4)	36281 (10.1)	20193 (5.9)
Sex, male	71879 (46.6)	57150 (43.4)	16195 (44.6)	9553 (47.3)
female	82491 (53.4)	74528 (56.6)	20086 (55.4)	10640 (52.7)
Age	69.2±7.9	67.5±6.3	68.2±6.3	68.4±6.2
Person-year	2485.5±1070.5	2852.9±799.1	2788.9±826.6	2458.7±833.4
Level of income				
Lowest income, Medical aid	16513 (10.7)	13155 (10.0)	5664 (15.6)	3903 (19.3)
4/10 percentile	42812 (27.7)	36320 (27.6)	9887 (27.3)	5191 (25.7)
8/10 percentile	52734 (34.2)	46189 (35.1)	11828 (32.6)	6241 (30.9)
10/10 percentile	42308 (27.4)	36014 (27.4)	8902 (24.5)	4858 (24.1)
Strong anticholinergics*	3.7±3.0	23.4±10.7	76.0±19.4	243.2±164.0
Weak anticholinergics*	50.2±132.8	79.8±146.3	114.4±213.7	152.0±200.6
0-29	115151 (74.6)	69381 (52.7)	11427 (31.5)	4911 (24.3)

	Prescribed doses of strong anticholinergics (dose/year) (n=342522)			
	0-9	**10-49**	**50-119**	**≥ 120**
30-119	21341 (13.8)	37856 (28.8)	14546 (40.1)	7284 (36.1)
120-299	11397 (7.4)	16399 (12.5)	7125 (19.6)	5163 (25.6)
≥ 300	6481 (4.2)	8042 (6.1)	3183 (8.8)	2835 (14.0)
Total anticholinergics *	53.9±132.8	103.2±147.4	190.4±215.4	395.2±267.5
Antihistamines*	3.0±2.8	18.2±10.6	516±29.8	109.9±119.2
Antidepressants*	0.1±0.7	1.9±5.1	10.6±21.3	74.4±144.6
Urinary antimuscarinics*	0.1±0.6	1.4±4.6	7.3±18.5	26.2±72.1
Other non-anticholinergics that could impair cognitive functions**	6.5±23.3	13.9±33.0	26.0±49.4	40.4±70.4
Medical histories (%)				
Hypertension	29778 (19.3)	34802 (26.4)	10324 (28.5)	5991 (29.7)
Cardiovascular disease	3684 (2.4)	3533 (2.7)	1495 (4.1)	1237 (6.1)
Myocardial infarction	1482 (1.0)	1652 (1.3)	544 (1.5)	361 (1.8)
Diabetes mellitus	11880 (7.7)	13998 (10.6)	4519 (12.5)	3112 (15.4)
Parkinson’s disease	150 (0.1)	124 (0.1)	78 (0.2)	237 (1.2)

	Prescribed doses of strong anticholinergics (dose/year) (n=342522)			
	0-9	**10-49**	**50-119**	**≥ 120**
Epilepsy	170 (0.1)	171 (0.1)	70 (0.2)	190 (0.9)
Neuralgia	2535 (1.6)	5630 (4.3)	2162 (6.0)	1242 (6.2)
Dizziness[†]	1493 (1.0)	2840 (2.16)	1436 (4.0)	1029 (5.1)
Sleep disorder	246 (0.2)	464 (0.4)	238 (0.7)	231 (1.1)
Genitourinary disease	2678 (1.7)	4412 (3.4)	2038 (5.6)	1641 (8.1)
Skin disease	2263 (1.5)	6276 (4.8)	2958 (8.2)	1984 (9.8)

All values were presented with mean±SD or frequency (%)

[*] average annual prescription amount from 2002 to the follow-up period.

[**] calculated as average annual cumulative prescribed days from 2002 to end of follow-up period.

[†] including dizziness due to vestibular abnormalities

The mean follow-up periods were 7.5 years and 5.7 years in the non-incident AD and incident AD group respectively. During the follow-up period, AD occurred in 10.0% of the subjects (34,231 subjects). The incidence of AD was high in female and Medical aid. In the AD incident group, both the median and annual mean dose of strong anticholinergics were higher than in the non-incident AD group. In AD patients, prescription amount of weak anticholinergics were higher than in non-AD incident group. By drug class, antihistamines, antidepressants, and antimuscarinics were the highest in the order of average annual dosage in the both groups and incident AD subjects were more prescribed drugs for all those drug classes. When median of average annual prescription dose was examined by drug class, antihistamines were 8.3 doses and 8.0 doses in non-AD and AD group respectively, while those in the other drug classes were all zero, suggesting that antihistamines were widely prescribed to many older adults, while the drugs belonging to the other drug classes were used in some elderly. DM, PD, neuralgia, and dizziness were more prevalent in AD group (Table 5-2).

Table 5-2. Characteristics of subjects in Non-incident Alzheimer's disease group and incident Alzheimer's disease group

	Non-incident Alzheimer's disease n=308291 (90.0%)		**Incident Alzheimer's disease n=34231 (10.0%)**	
	Frequency (%) Mean±SD	median	Frequency (%) Mean±SD	median
Sex Male	143639 (46.6)	-	11138 (32.5)	-
Sex, Female	164652 (53.4)	-	23093 (67.5)	-
Age	68.0±7.1	66.0	71.6±6.8	71.0
Level of income				
Medical aid	32211 (10.5)	-	7027 (20.5)	-
4/10 percentile	85880 (27.9)	-	8330 (24.3)	-
8/10 percentile	107206 (34.8)	-	9786 (28.6)	-
10/10 percentile	82994 (26.9)	-	9088 (26.6)	-
Person-year (day)	2739.3±943	3261.0	2095.7±823.4	2233.0
Strong anticholinergics*	32.2±68.1	11.9	40.2±85.0	13.5
0-9	139618 (45.3)	-	14752 (43.1)	-
10-49	119352 (38.7)	-	12326 (36.0)	-
50-119	31935 (10.4)	-	4346 (12.7)	-
≥ 120	17386 (5.6)	-	2807 (8.2)	-
Weak anticholinergics*	74.0±156.5	18.4	77.4±145.8	22.3
0-29	181937 (59.0)	-	18933 (55.3)	-
30-119	72194 (23.4)	-	8833 (25.8)	-
120-299	35722 (11.6)	-	4362 (12.7)	-
≥ 300	18438 (6.0)	-	2103 (6.1)	-
Total anticholinergics*	106.3±179.6	41.9	117.5±181.9	50.6
Antihistamines*	20.1±40.6	8.3	22.2±45.5	8.0
Antidepressants*	6.0±38.8	0.0	8.7±48.5	0.0
Urinary antimuscarinics*	2.8±18.2	0.0	4.0±30.2	0.0

	Non-incident Alzheimer's disease n=308291 (90.0%)		Incident Alzheimer's disease n=34231 (10.0%)	
	Frequency (%) Mean±SD	median	Frequency (%) Mean±SD	median
Other non-anticholinergics that could impair cognitive functions**	12.9±35.2	1.7	17.6±42.3	2.3
Medical histories				
Hypertension	72725 (23.6)	-	8170 (23.9)	-
Cardiovascular disease	8666 (2.8)	-	1283 (3.8)	-
Myocardial infraction	3613 (1.2)	-	426 (1.2)	-
Diabetes mellitus	29805 (9.7)	-	3704 (10.9)	-
Parkinson's disease	450 (0.2)	-	139 (0.4)	-
Sleep disorder	1022 (0.3)	-	157 (0.5)	-
Dizziness†	5869 (1.9)	-	929 (2.7)	-
Genitourinary disease	9709 (3.2)	-	1060 (3.1)	-
Epilepsy	517 (0.2)	-	84 (0.3)	-
Neuralgia	10158 (3.3)	-	1414 (4.1)	-
Skin disease	12154 (3.9)	-	1327 (3.9)	-

* average annual prescription amount from 2002 to the end of follow-up period

** calculated as average annual cumulative prescribed days from 2002 to the end of follow-up period.

† including dizziness due to vestibular abnormalities

Outcome, Main results

Proportional hazards assumptions were verified in longer (9-12 years) follow-up exposure and younger aged stratum (Figure 5-2), In case of longer follow-up exposure stratum for all age, the proportionality was generally identified as well, but plots were almost superimposed between 0-9 dose/year group and 10-49 dose/year group, implying little difference between the two groups (Figure 5-3).

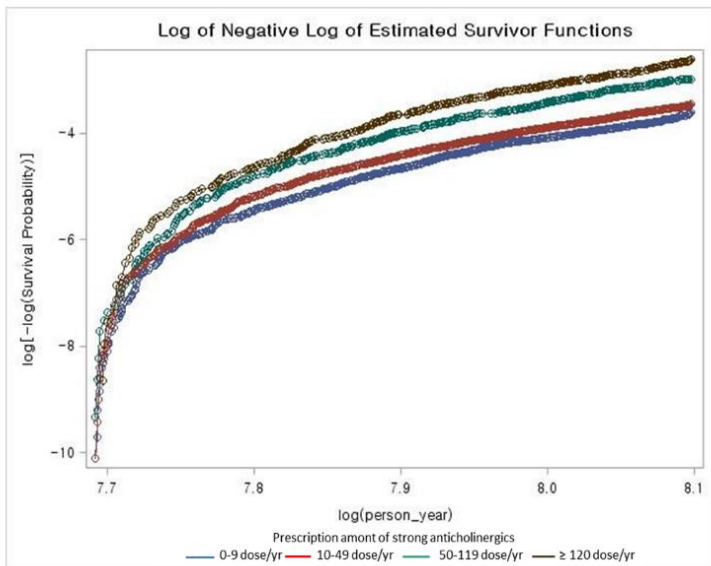


Figure 5-2. Log negative Log estimated survival plot in the longer follow-up period of exposure and younger age stratum

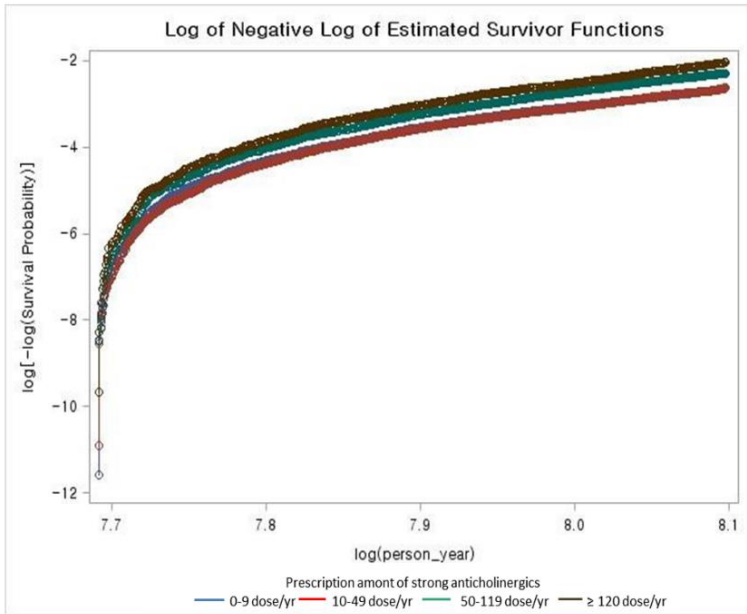


Figure 5-3. Log negative Log estimated survival plot in the longer follow-up period of exposure stratum

The risk of AD by level of prescription amount of strong anticholinergics, in all subjects and two dimensional strata by follow-up period of exposure and age were shown in Table 5-3. Of all 342,522 subjects, 37% (128,216 subjects) belonged to the younger elderly, and 4.5% (5,716 subjects) of the younger elderly developed AD. Majority of people (261,328 subjects, 76.3%) were followed up for longer period of exposure (9-12 years), especially in the younger elderly (114,516 subjects, 89.3%) which seemed to be due to the longer life span and the longer time it takes to develop AD in those people. A crude model and two covariates models were set up. In model Ⅰ, only age, sex, and level of income were included for adjustment. In

model Ⅱ, all sixteen covariates stated in the Methods section were additionally included (Table 5-3).

For all subjects whose exposure were followed up for minimum 9 years to maximum 12 years, the risk of AD was significantly higher in more exposed groups than in reference group (0-10 dose/yr), in both crude and the two covariates models. HRs decreased slightly as the covariates were added. When all subjects were examined regardless of the follow-up period of exposure or age at the baseline of exposure to see the average effect, the risk of AD was only slightly higher in the most exposed group after adjusting for the covariates (HR=1.09, 95% CI, 1.04 to 1.14, in ≥ 120 dose/yr group, Model Ⅱ). In general, those with longer follow-up periods had an increased risk of Alzheimer's disease in proportion to their anticholinergic use, but not in those with shorter follow-up periods (3-8 years). Looking into younger elderly group, the HRs in the younger elderly group followed up for 9-12 years were highest among the 2 dimensional strata [HR (95% CI)=1.07 (0.99-1.16), HR (95% CI)=1.49 (1.34-1.67), HR (95% CI)=1.78 (1.57-2.03); for 10-49 dose/yr, 50-119 dose/yr, and ≥ 120 dose/yr group respectively, in the younger elderly whose exposure were followed up for 9-12 years; Model Ⅱ]. In the longer follow-up periods of exposure, the older elderly group, the risk of AD was increased as the amount of strong anticholinergic use were increased although the effect was less than in the younger elderly. The relevance of the strong anticholinergic use with risk of AD were not found in those who were followed up during shorter periods of time (3-8 years) (Table 5-3).

Table 5-3. Risk of Alzheimer's disease by prescription amount of strong anticholinergics

Followed-up period of exposure	Subjects	Prescription (dose/year)	No. of AD event (%)	Incidence rate per 100,000 person-years	Crude model	Covariates model	
						Model Ⅰ	Model Ⅱ
					Hazard ratio (95% Confidence interval)		
Overall (3-12 yrs) (n=342522)	All subjects (n=342522)	overall	34231 (10.0)	3.74 (3.70-3.78)			
		0-9	14752 (9.6)	3.84 (3.78-3.91)	Reference	Reference	Reference
		10-49	12326 (9.4)	3.28 (3.22-3.34)	0.82 (0.80-0.89)	0.87 (0.85-0.89)	0.86 (0.84-0.88)
		50-119	4346 (12.0)	4.30 (4.17-4.42)	1.08 (1.05-1.12)	1.04 (1.01-1.08)	1.00 (0.97-1.04)
		≥ 120	2807 (13.9)	5.04 (4.85-5.23)	1.28 (1.23-1.34)	1.18 (1.13-1.23)	1.09 (1.04-1.14)
	Younger elderly (n=128216)	overall	5716 (4.5)	1.49 (1.45-1.53)			
		0-9	2164 (3.8)	1.32 (1.26-1.37)	Reference	Reference	Reference
		10-49	2218 (4.2)	1.36 (1.31-1.42)	1.01 (0.95-1.07)	0.96 (0.90-1.01)	0.92 (0.86-0.97)
		50-119	800 (6.5)	2.13 (1.99-2.28)	1.59 (1.47-1.72)	1.40 (1.29-1.52)	1.25 (1.14-1.36)
		≥ 120	534 (9.3)	2.79 (2.55-3.03)	2.10 (1.91-2.31)	1.76 (1.60-1.94)	1.39 (1.26-1.55)
		overall	28515 (13.3)	5.35 (5.29-5.42)			

Followed-up period of exposure	Subjects	Prescription (dose/year)	No. of AD event (%)	Incidence rate per 100,000 person-years	Crude model	Covariates model	
						Model Ⅰ	Model Ⅱ
					Hazard ratio (95% Confidence interval)		
Longer (9-12 yrs) (n=261328) 76.3%	Older elderly (n=214306)	0-9	12588 (12.9)	5.74 (5.64-5.84)	Reference	Reference	Reference
		10-49	10108 (12.8)	4.75 (4.65-4.84)	0.78 (0.76-0.80)	0.84 (0.82-0.86)	0.84 (0.81-0.86)
		50-119	3546 (14.8)	5.57 (5.38-5.75)	0.92 (0.89-0.96)	0.95 (0.91-0.99)	0.94 (0.90-0.98)
		≥ 120	2273 (16.5)	6.21 (5.96-6.47)	1.04 (0.99-1.08)	1.04 (1.00-1.09)	1.01 (0.96-1.06)
	All subjects (n=261328)	overall	17719 (6.8)	2.14 (2.11-2.18)			
		0-9	6485 (6.1)	1.93 (1.88-1.97)	Reference	Reference	Reference
		10-49	6912 (6.3)	1.99 (1.94-2.04)	0.99 (0.96-1.03)	1.02 (0.98-1.05)	0.99 (0.95-1.02)
		50-119	2571 (8.8)	2.80 (2.69-2.90)	1.42 (1.36-1.49)	1.31 (1.25-1.37)	1.22 (1.17-1.28)
		≥ 120	1751 (10.9)	3.49 (3.32-3.65)	1.80 (1.71-1.90)	1.58 (1.50-1.67)	1.41 (1.33-1.49)
	Younger elderly (n=114516)	overall	3433 (3.0)	0.93 (0.90-0.97)			
		0-9	1132 (2.3)	0.73 (0.68-0.77)	Reference	Reference	Reference
		10-49	1412 (2.9)	0.90 (0.85-0.94)	1.20 (1.11-1.29)	1.14 (1.05-1.23)	1.07 (0.99-1.16)
		50-119	523 (4.7)	1.46 (1.33-1.58)	1.96 (1.77-2.17)	1.74 (1.57-1.93)	1.49 (1.34-1.67)

Followed-up period of exposure	Subjects	Prescription (dose/year)	No. of AD event (%)	Incidence rate per 100,000 person-years	Crude model	Covariates model	
						Model Ⅰ	Model Ⅱ
					Hazard ratio (95% Confidence interval)		
		≥ 120	366 (6.4)	2.02 (1.81-2.22)	2.74 (2.44-3.09)	2.34 (2.07-2.63)	1.78 (1.57-2.03)
	Older elderly (n=146812)	overall	14286 (9.7)	3.11 (3.06-3.16)			
		0-9	5353 (9.2)	2.97 (2.89-3.04)	Reference	Reference	Reference
		10-49	5500 (9.1)	2.89 (2.81-2.97)	1.05 (0.97-1.33)	1.06 (0.98-1.14)	0.96 (0.92-1.00)
		50-119	2048 (11.4)	3.65 (3.49-3.81)	1.29 (1.17-1.43)	1.27 (1.14-1.40)	1.15 (1.09-1.21)
		≥ 120	1385 (13.5)	4.32 (4.09-4.55)	1.61 (1.43-1.82)	1.57 (1.39-1.78)	1.30 (1.22-1.39)
Shorter (3-8 yrs) (n=81194) 23.7%	All subjects (n=81194)	overall	16512 (20.3)	18.35 (18.08-18.63)			
		0-9	8267 (17.5)	17.55 (17.17-17.92)	Reference	Reference	Reference
		10-49	5414 (24.0)	19.28 (18.77-19.79)	0.95 (0.92-0.98)	0.94 (0.91-0.98)	0.96 (0.92-0.99)
		50-119	1775 (24.7)	19.18 (18.29-20.07)	0.93 (0.88-0.98)	0.91 (0.86-0.96)	0.94 (0.89-0.99)
		≥ 120	1056 (25.1)	19.17 (18.01-20.33)	0.89 (0.84-0.95)	0.87 (0.82-0.93)	0.90 (0.84-0.96)
	Younger elderly (n=13700)	overall	2283 (16.7)	13.98 (13.41-14.56)			
		0-9	1032 (13.6)	12.41 (11.66-13.17)	Reference	Reference	Reference

Followed-up period of exposure	Subjects	Prescription (dose/year)	No. of AD event (%)	Incidence rate per 100,000 person-years	Crude model	Covariates model	
						Model Ⅰ	Model Ⅱ
					Hazard ratio (95% Confidence interval)		
		10-49	806 (19.2)	14.95 (13.92-15.98)	1.09 (0.99-1.19)	0.99 (0.90-1.08)	1.00 (0.90-1.10)
		50-119	277 (23.0)	16.84 (14.86-18.83)	1.19 (1.04-1.35)	1.05 (0.92-1.20)	1.07 (0.93-1.03)
		≥ 120	168 (23.8)	17.21 (14.61-19.81)	1.14 (0.97-1.34)	0.97 (0.82-1.15)	0.94 (0.78-1.12)
	Older elderly (n=67494)	overall	14229 (21.1)	19.32 (19.01-19.64)			
		0-9	7235 (18.2)	18.65 (18.22-19.08)	Reference	Reference	Reference
		10-49	4608 (25.1)	20.31 (19.72-20.90)	0.82 (0.75-0.89)	0.83 (0.76-0.90)	0.94 (0.90-0.97)
		50-119	1498 (25.0)	19.68 (18.69-20.68)	0.87 (0.77-0.98)	0.88 (0.78-1.00)	0.89 (0.84-0.95)
		≥ 120	888 (25.3)	19.59 (18.31-20.88)	0.75 (0.64-0.89)	0.80 (0.67-0.94)	0.87 (0.81-0.94)

Model Ⅰ: Adjusted for age, sex and level of income

Model Ⅱ: Adjusted for Model Ⅰ + diabetes mellitus, hypertension, myocardial infarction, cardiovascular diseases, dizziness, genitourinary diseases, epilepsy, Parkinson's disease, neuralgia, skin disease, sleep disorder, prescribed doses of weak anticholinergics, and cumulative prescribed days of other non-anticholinergics that could impair cognitive functions (all psychotic diseases including depression, psychosis, anxiety were excluded in the step of participant selection in advance)

Whether exposure to weak anticholinergic drugs increase the risk of AD was presented in Table 5-4. Especially for subjects whose follow-up periods of exposure were longer (9-12 years) and/or in the younger elderly group, the HRs were higher in the more exposed groups in the crude model and model Ⅰ. However no associations were found in the final model where prescription amount of strong anticholinergics and other non-anticholinergic agents that could impair cognitive functions, were further adjusted for (Table 5-4).

Table 5-4. Risk of Alzheimer's disease by prescription amount of weak anticholinergics

Followed-up period of exposure	Subjects	Amount of weak anticholinergic use (dose/yr)	No. of AD event (%)	Incidence rate per 100,000 person-years	Crude Model	Covariates Model	
						Model Ⅰ	Model Ⅱ
					Hazard ratio (95% Confidence interval)		
Overall (3-12 yrs) (n=342522)	All subjects (n=342522)	overall	8,321 (7.6)	3.74 (3.70-3.78)			
		0-29	4,382 (7.1)	3.63 (3.58-3.68)	Reference	Reference	Reference
		30-119	2,403 (8.5)	3.88 (3.80-3.96)	1.05 (1.02-1.08)	0.99 (0.97-1.02)	0.96 (0.93-0.98)
		120-299	1,050 (8.3)	3.90 (3.79-4.02)	1.06 (1.03-1.09)	0.98 (0.95-1.01)	0.91 (0.88-0.95)
		≥ 300	486 (8.4)	3.82 (3.66-3.99)	1.05 (1.01-1.10)	1.00 (0.96-1.05)	0.90 (0.85-0.94)
	Younger elderly (n=128216)	overall	2011 (3.8)	1.49 (1.45-1.53)			
		0-29	1073 (3.4)	1.32 (1.27-1.37)	Reference	Reference	Reference
		30-119	581 (4.5)	1.72 (1.64-1.81)	1.29 (1.21-1.37)	1.18 (1.11-1.25)	1.19 (1.10-1.30)
		120-299	246 (4.5)	1.77 (1.64-1.90)	1.33 (1.23-1.44)	1.20 (1.11-1.30)	1.09 (0.97-1.21)
		≥ 300	111 (4.7)	1.86 (1.67-2.05)	1.41 (1.27-1.57)	1.29 (1.16-1.44)	1.14 (0.99-1.32)
Longer (9-12 yrs) (n=261328)	All subjects (n=261328)	overall	4899 (5.1)	2.14 (2.11-2.18)			
		0-29	2446 (4.4)	1.92 (1.88-1.96)	Reference	Reference	Reference
		30-119	1508 (6.0)	2.43 (2.36-2.50)	1.28 (1.21-1.29)	1.14 (1.10-1.18)	1.06 (1.02-1.10)
		120-299	654 (5.8)	2.46 (2.37-2.56)	1.26 (1.21-1.32)	1.13 (1.08-1.18)	1.02 (0.97-1.07)

	≥ 300	291 (5.9)	2.42 (2.28-2.55)	1.26 (1.19-1.34)	1.16 (1.09-1.24)	1.02 (0.96-1.09)
Younger elderly (n=114516)	overall	1261 (2.6)	0.93 (0.90-0.97)			
	0-29	642 (2.2)	0.77 (0.73-0.81)	Reference	Reference	Reference
	30-119	394 (3.2)	1.18 (1.11-1.26)	1.51 (1.39-1.63)	1.38 (1.28-1.49)	1.20 (1.10-1.30)
	120-299	155 (3.0)	1.16 (1.06-1.27)	1.48 (1.34-1.64)	1.34 (1.21-1.49)	1.09 (0.97-1.22)
	≥ 300	70 (3.3)	1.25 (1.09-1.41)	1.60 (1.40-1.84)	1.48 (1.29-1.69)	1.14 (0.99-1.32)

Model Ⅰ: Adjusted for age, sex and level of income

Model Ⅱ: Adjusted for Model Ⅰ + diabetes mellitus, hypertension, myocardial infarction, cardiovascular diseases, dizziness, genitourinary diseases, epilepsy, Parkinson's disease, neuralgia, skin disease, sleep disorder, prescribed doses of strong anticholinergics, and cumulative prescribed days of other non-anticholinergics that could impair cognitive functions (all psychotic diseases including depression, psychosis, anxiety were excluded in the step of participant selection in advance)

Results from supplementary analyses Ⅰ: To minimize the bias due to prodromal effects.

Since anticholinergic drugs may be used to treat pre-existing symptoms such as depression, urinary incontinence etc., prior to the diagnosis of AD, the average prescribed doses of anticholinergic agents were calculated after excluding the amount of prescription during 1 year and 2 years prior to the end of the follow-up respectively, then the association with developing AD was assessed. As a result, the longer the period of time excluded, the lower the association between strong anticholinergic exposure and AD. However, in overall, the significances were still maintained and the risk of AD was still highest in the younger elderly who were followed up for longer period of time [HR (95% CI)=1.66 (1.45-1.89), (HR (95% CI)=1.43 (1.24-1.64); ≥ in 120 dose/year group after excluding the amount of prescription during 1 year, 2 years prior to the end of the follow-up respectively; in the longer followed exposure period, younger elderly; Model Ⅱ]. In particular, even after excluding the exposure of anticholinergic antidepressants which were thought to be used frequently in the prodromal symptoms of AD, the risk of AD was still significantly higher in the more exposed groups than the reference group (0-24 dose/yr) [HR (95% CI)=1.12 (1.03-1.23), HR (95% CI)=1.49 (1.35-1.65), in the longer follow up of exposure, younger elderly group; Model Ⅱ]. To further confirm these, analyzes were performed after excluding 'strong anticholinergic prescriptions for one year prior to end of follow-up' and 'dose of antidepressants for all follow-up period of time' at a time. Consequently, overall HR became lower, but HR was still higher in the more exposed group than the reference group [HR (95% CI)=1.10 (1.01-1.20), HR (95% CI)=1.44 (1.30-1.60), in the longer follow up of exposure,

younger elderly group; in 25-59 dose/year and, ≥ 60 dose/year respectively; Model Ⅱ] (Table 5-5).

When the exposure was limited to antidepressants or antimuscarinics which were more used in AD patients, the risk of AD was obviously lowered comparing to the risks where the whole strong anticholinergic exposure were counted. At first, the hypothesis was as such that if the bias due to the prodromal effect is large, the size of incident AD by these drug classes might be similar to or larger than those by whole strong anticholinergic exposure, but it was not as expected [HR (95% CI)=1.32 (1.26-1.39) in antidepressants ≥ 10 (dose/yr) group; [HR (95% CI)=1.28 (1.22-1.34) in urinary antimuscarinics ≥ 3 (dose/yr) group, for all subjects who were followed up for 9-12 years]. When the exposure parameter was limited to antihistamines alone, which seemed to be least related to the treatment of prodromal AD symptoms and prescribed doses were most similar between AD and non-AD incident groups among the strong anticholinergic drug classes, the risk of AD was still significantly higher in the more exposed group even though the effect size was the smallest comparing to antidepressants or urinary antimuscarinics [HR (95% CI)=1.14 (1.09-1.19), HR (95% CI)=1.14 (1.02-1.27) for for all subjects who were followed up for 9-12 years, in antihistamines ≥ 50 (dose/yr)]. In case of other anticholinergic drug classes, additional analyses were not performed, since the proportions of total prescriptions in those drug classes were very small. The weak anticholinergics did not show any association with total anticholinergic agents, so no analyses by individual drug (class) were performed (Table 5-4).

Table 5-5. Risk of of Alzheimer's disease by various exposure criteria of strong anticholinergic agents in the all subjects and the younger elderly group

		All Subjects (n=342522)				Younger elderly (n=128216)			
		All subjects (n=342522)		Subjects with longer followed-up of exposure (9-12 yrs) (n=261328)		All younger elderly (n=128216)		Subjects with longer followed-up of exposure (9-12 yrs) (n=114516)	
Prescription amount* (dose/yr)		No. of AD event (%)	HR (CI)	No. of AD event (%)	HR (CI)	No. of AD event (%)	HR (CI)	No. of AD event (%)	HR (CI)
Total strong anticholinergics-recent 1 year†	0-9	13246 (9.9)	Reference	7023 (6.2)	Reference	2464 (4.1)	Reference	1257 (2.4)	Reference
	10-49	11729 (9.2)	0.79 (0.77-0.81)	6769 (6.3)	0.95 (0.92-0.98)	2117 (4.1)	0.81 (0.77-0.87)	1375 (2.9)	1.00 (0.93-1.08)
	50-119	3855 (11.7)	0.90 (0.86-0.93)	2363 (8.8)	1.15 (1.09-1.20)	677 (6.1)	1.01 (0.93-1.10)	466 (4.5)	1.33 (1.18-1.48)
	≥ 120	2421 (13.5)	0.96 (0.95-1.00)	1564 (10.8)	1.30 (1.23-1.38)	458 (8.0)	1.16 (1.04-1.29)	335 (6.5)	1.66 (1.45-1.89)
Total strong anticholinergics-recent 2 year‡	0-9	20465 (9.8)	Reference	9186 (6.2)	Reference	3258 (4.2)	Reference	1725 (2.6)	Reference
	10-49	9156 (9.5)	0.81 (0.79-0.83)	5518 (6.8)	0.99 (0.96-1.02)	1623 (4.3)	0.82 (0.77-0.87)	1094 (3.1)	1.01 (0.93-1.09)
	50-119	2530 (11.6)	0.88 (0.84-0.92)	1632 (9.0)	1.16 (1.10-1.22)	460 (6.3)	1.02 (0.92-1.13)	336 (5.0)	1.37 (1.21-1.55)

		All Subjects (n=342522)				Younger elderly (n=128216)			
		All subjects (n=342522)		Subjects with longer followed-up of exposure (9-12 yrs) (n=261328)		All younger elderly (n=128216)		Subjects with longer followed-up of exposure (9-12 yrs) (n=114516)	
	≥ 120	2080 (12.8)	0.91 (0.87-0.96)	1383 (10.4)	1.24 (1.17-1.32)	375 (7.3)	1.02 (0.90-1.14)	278 (5.9)	1.43 (1.24-1.64)
Total strong anticholinergics-dose of antidepressants	0-24	23680 (9.5)	Reference	11477 (6.2)	Reference	3863 (4.1)	Reference	2189 (2.6)	Reference
	25-59	5784 (10.2)	0.95 (0.92-0.98)	3379 (7.3)	1.10 (1.05-1.15)	1017 (4.8)	0.98 (0.91-1.05)	686 (3.5)	1.12 (1.03-1.23)
	≥ 60	4767 (12.8)	1.10 (1.07-1.14)	2863 (9.8)	1.29 (1.23-1.34)	836 (7.2)	1.30 (1.20-1.41)	556 (5.4)	1.49 (1.35-1.65)
Total strong anticholinergics-Recent 1 year† – Antidepressants	0-24	24682 (9.6)	Reference	4061 (4.2)	Reference	11848 (6.2)	Reference	2275 (2.6)	Reference
	25-59	5320 (10.1)	0.98 (0.91-1.05)	930 (4.7)	1.05 (1.00-1.09)	3230 (7.3)	0.95 (0.92-0.98)	649 (3.5)	1.10 (1.01-1.20)
	≥ 60	4229 (12.6)	1.30 (1.20-1.41)	725 (6.9)	1.26 (1.21-1.32)	2641 (9.9)	1.10 (1.07-1.14)	509 (5.4)	1.44 (1.30-1.60)
Antidepressants	0-9	30776 (9.7)	Reference	15600 (6.5)	Reference	4912 (4.1)	Reference	2904 (2.7)	Reference
	≥ 10	3455 (13.7)	1.20 (1.16-1.25)	2119 (10.3)	1.32 (1.26-1.39)	804 (8.9)	1.55 (1.43-1.67)	529 (6.3)	1.64 (1.48-1.81)
Antihistamines	0-49	30288 (9.8)	Reference	15349 (6.5)	Reference	5107 (4.3)	Reference	3027 (2.6)	Reference
	≥ 50	3943 (12.1)	1.03 (0.99-1.07)	2370 (9.3)	1.14 (1.09-1.19)	609 (6.0)	1.07 (0.98-1.16)	406 (4.5)	1.14 (1.02-1.27)

		All Subjects (n=342522)				Younger elderly (n=128216)			
		All subjects (n=342522)		Subjects with longer followed-up of exposure (9-12 yrs) (n=261328)		All younger elderly (n=128216)		Subjects with longer followed-up of exposure (9-12 yrs) (n=114516)	
Urinary antimuscarinics	0-2	30447 (9.7)	Reference	15400 (6.5)	Reference	5025 (4.3)	Reference	2951 (2.8)	Reference
	≥ 3	3784 (12.6)	1.11 (1.07-1.15)	2319 (9.3)	1.28 (1.22-1.34)	691 (6.6)	1.25 (1.15-1.35)	482 (4.9)	1.42 (1.29-1.57)

* Prescription amount: all of the values of prescription amounts was calculated as average annual dose. Unit is dose/yr

† Recent 1 year: prescription amount of during 1 year prior to the end of the follow-up.

‡ Recent 2 years: prescription amount of during 2 years prior to the end of the follow-up

Results from supplementary analyses Ⅱ: Subset analyses for subjects who participated in the general national health screening programs

Survival analysis was performed after controlling the additional covariates obtained from the NHIS health screening data in a subset population who took NHIS heath screening examination in 2005-2006 year. The recipients of the NHIS health screening subjects had a higher proportion of younger elderly people (37.4% vs. 48.4 % in the all study subject, NHIS health screening examination recipients respectively), and longer follow-up period (76.3% vs. 88.5%; in the all study subject, and NHIS health screening examination recipients respectively). As a result, when the variables in these health screening data were additionally controlled, the relationship between the use of strong anticholinergics and the risk of AD became greater in longer follow-up of exposure or younger elderly in which the associations were significant in the previous main analyses as presented in Table 5-3. In the younger elderly whose exposure were followed up for 9-12 years, The risk of developing AD was nearly double that of the reference group in those who used the strong anticholinergics the most (≥ 120 dose/year) [HR (95% CI)=1.9 (1.51-2.37)] (Table 5-6).

Table 5-6. Risk of Alzheimer's disease by prescription amount of strong anticholinergics in general health screening recipients in 2005-2006

Followed-up period of exposure	Subjects	Prescription (dose/year)	No. of AD event (%)	Incidence rate per 100,000 person-years	Crude model	Covariates model	
						Model Ⅰ	Model Ⅱ
					Hazard ratio (95% Confidence interval)		
Overall (3-12 yrs) (n=108920)	All subjects (n=108920)	overall	8,321 (7.6)	2.56 (2.50-2.61)			
		0-9	2,973 (7.1)	2.41 (2.33-2.50)	Reference	Reference	Reference
		10-49	3,516 (7.2)	2.36 (2.29-2.44)	0.82 (0.80-0.89)	0.87 (0.85-0.89)	0.93 (0.88-0.98)
		50-119	1,161 (9.6)	3.23 (3.04-3.42)	1.08 (1.05-1.12)	1.04 (1.01-1.08)	1.16 (1.04-1.20)
		≥ 120	671 (11.2)	3.79 (3.50-4.07)	1.28 (1.23-1.34)	1.18 (1.13-1.23)	1.20 (1.10-1.31)
	Younger elderly (n=52728)	overall	2,011 (3.8)	1.23 (1.18-1.28)			
		0-9	695 (3.3)	1.06 (0.98-1.14)	Reference	Reference	Reference
		10-49	854 (3.6)	1.14 (1.06-1.21)	1.01 (0.95-1.07)	0.96 (0.90-1.01)	0.97 (0.87-1.07)
		50-119	291 (5.7)	1.83 (1.62-2.04)	1.59 (1.47-1.72)	1.40 (1.29-1.52)	1.39 (1.20-1.61)
		≥ 120	171 (7.3)	2.35 (2.00-2.70)	2.10 (1.91-2.31)	1.76 (1.60-1.94)	1.57 (1.31-1.89)
		overall	6310 (11.2)	3.90 (3.80-4.00)			
		0-9	2278 (11.1)	3.94 (3.78-4.10)	Reference	Reference	Reference

Followed-up period of exposure	Subjects	Prescription (dose/year)	No. of AD event (%)	Incidence rate per 100,000 person-years	Crude model	Covariates model	
						Model Ⅰ	Model Ⅱ
					Hazard ratio (95% Confidence interval)		
	Older elderly (n=56192)	10-49	2662 (10.6)	3.62 (3.48-3.76)	0.90 (0.85-0.95)	0.92 (0.87-0.97)	0.91 (0.86-0.97)
		50-119	870 (12.5)	4.34 (4.05-4.63)	1.09 (1.01-1.18)	1.08 (1.00-1.17)	1.03 (0.95-1.12)
		≥ 120	500 (13.8)	4.79 (4.37-5.21)	1.21 (1.10-1.33)	1.20 (1.09-1.32)	1.09 (1.99-1.21)
Longer (9-12 yrs) (n=96448)	All subjects (n=96448)	overall	4899 (5.08)	1.59 (1.27-1.40)			
		0-9	1549 (4.25)	1.33 (1.47-1.60)	Reference	Reference	Reference
		10-49	2179 (4.83)	1.54 (1.96-2.27)	0.99 (0.96-1.03)	1.02 (0.98-1.05)	1.07 (1.00-1.14)
		50-119	715 (6.75)	2.12 (2.49-3.00)	1.42 (1.36-1.49)	1.31 (1.25-1.37)	1.28 (1.17-1.41)
		≥ 120	456 (8.71)	2.75 (1.54-1.63)	1.80 (1.71-1.90)	1.58 (1.50-1.67)	1.54 (1.38-1.73)
	Younger elderly (n=49299)	overall	1261 (2.56)	0.79 (0.75-0.84)			
		0-9	386 (1.96)	0.61 (0.55-0.67)	Reference	Reference	Reference
		10-49	569 (2.51)	0.78 (0.71-0.84)	1.20 (1.11-1.29)	1.14 (1.05-1.23)	1.12 (0.98-1.28)
		50-119	188 (3.94)	1.22 (1.05-1.40)	1.96 (1.77-2.17)	1.74 (1.57-1.93)	1.54 (1.28-1.55)
		≥ 120	118 (5.41)	1.69 (1.38-1.99)	2.74 (2.44-3.09)	2.34 (2.07-2.63)	1.90 (1.51-2.37)
		overall	3638 (7.7)	2.44 (2.36-2.51)			
		0-9	1163 (7.0)	2.20 (2.07-2.32)	Reference	Reference	Reference

Followed-up period of exposure	Subjects	Prescription (dose/year)	No. of AD event (%)	Incidence rate per 100,000 person-years	Crude model	Covariates model	
						Model Ⅰ	Model Ⅱ
					Hazard ratio (95% Confidence interval)		
	Older elderly (n=47149)	10-49	1610 (7.5)	2.35 (2.24-2.47)	1.05 (0.97-1.33)	1.06 (0.98-1.14)	1.04 (0.97-1.13)
		50-119	527 (9.0)	2.86 (2.62-3.11)	1.29 (1.17-1.43)	1.27 (1.14-1.40)	1.19 (1.07-1.33)
		≥ 120	338 (11.1)	3.52 (2.36-2.51)	1.61 (1.43-1.82)	1.57 (1.39-1.78)	1.43 (1.26-1.63)
Shorter (3-8 yrs) (n=12472)	All subjects (n=12472)	overall	3422 (27.4)	19.86 (19.20-20.53)			
		0-9	1424 (26.5)	20.31 (19.26-21.37)	Reference	Reference	Reference
		10-49	1337 (27.5)	19.25 (18.22-20.28)	1.09 (0.99-1.19)	1.10 (0.90-1.08)	1.87 (0.80-0.94)
		50-119	446 (30.2)	20.72 (18.79-22.64)	1.19 (1.04-1.35)	1.05 (0.92-1.20)	0.99 (0.88-1.11)
		≥ 120	215 (28.3)	19.22 (16.65-21.79)	1.14 (0.97-1.34)	0.97 (0.82-1.15)	0.86 (0.73-1.00)
	Younger elderly (n=3429)	overall	750 (21.9)	15.70 (14.58-16.83)			
		0-9	309 (19.6)	14.79 (13.14-16.44)	Reference	Reference	Reference
		10-49	285 (21.7)	15.25 (13.48-17.02)	1.09 (0.99-1.19)	0.99 (0.90-1.08)	0.87 (0.74-1.04)
		50-119	103 (28.6)	19.12 (15.43-22.81)	1.19 (1.04-1.35)	1.05 (0.92-1.20)	1.14 (0.90-1.45)
		≥ 120	53 (29.6)	18.96 (13.86-24.06)	1.14 (0.97-1.34)	0.97 (0.82-1.15)	0.85 (0.60-1.19)
		overall	2672 (29.6)	19.31 (20.65-22.27)			
		0-9	1115 (29.4)	22.65 (21.32-23.98)	Reference	Reference	Reference

Followed-up period of exposure	Subjects	Prescription (dose/year)	No. of AD event (%)	Incidence rate per 100,000 person-years	Crude model	Covariates model	
						Model Ⅰ	Model Ⅱ
					Hazard ratio (95% Confidence interval)		
	Older elderly (n=9043)	10-49	1052 (29.6)	20.73 (19.47-21.98)	0.82 (0.75-0.89)	0.83 (0.76-0.90)	0.85 (0.78-0.93)
		50-119	343 (30.7)	21.24 (19.00-23.50)	0.87 (0.77-0.98)	0.88 (0.78-1.00)	0.95 (0.83-1.08)
		≥ 120	162 (27.9)	19.31 (16.34-22.29)	0.75 (0.64-0.89)	0.80 (0.67-0.94)	0.83 (0.70-1.10)

Model Ⅰ: Adjusted for age, sex and level of income

Model Ⅱ: Adjusted for Model Ⅰ + diabetes mellitus, hypertension, myocardial infarction, cardiovascular diseases, dizziness, genitourinary diseases, epilepsy, Parkinson's disease, neuralgia, skin disease, sleep disorder, prescribed doses of weak anticholinergics, and cumulative prescribed days of other non-anticholinergics that could impair cognitive functions, BMI, blood glucose level, total cholesterol level, systolic blood pressure, medical histories of tuberculosis, hepatitis, hepatic disease, stroke, caner; smoking status, alcohol intake, level of exercise (all psychotic diseases including depression, psychosis, anxiety were excluded in the step of participant selection in advance)

Results from sensitivity test Ⅰ: Exact matching and propensity score analyses

The results obtained from using the exact matching and the propensity score method were shown in Table 5-7 together with the those from the standard adjustment model. The proportions of incident AD in the highest exposed group in both the matched groups and the subsets of PS <0.1 were consistently higher than the control groups. In overall, HRs were slightly higher when using exact matching or PS method than in the standard adjustment [(HR (95% CI)=1.09 (1.04-1.14) in standard adjustment; (HR (95% CI)=1.34 (1.28-1.41) in exact matching; (HR (95% CI)=1.20 (1.11-1.31) in PS regression adjustment within the subset of PS <0.1, for all subjects]. Especially, among the three analytical methods, the highest values were found in the exact matching and the increases were more noticeable in the younger elderly who were followed up for longer period of time [(HR (95% CI)=1.78 (1.57-2.03) in standard adjustment; (HR (95% CI)=2.73 (2.38-3.14) in exact matching] (Table 5-7).

Table 5-7. Risk of Alzheimer's disease by prescription amount of strong anticholinergics in exact matching and propensity score analyses vs. standard covariates adjustment.

Follow-up period of time	Subjects	strong anticholinergics (dose/yr) *	Standard covariates adjustment (Model Ⅱ) **			Exact matching ** †			Propensity score regression adjustment for subset of PS <0.1		
			No. of subjects	No of events (%)	HR (CI)	No. of subjects	No of events (%)	HR (CI)	No. of subjects	No of events (%)	HR (CI)
Overall (3-12 yrs)	All subjects	0-9	154370	14752 (9.6)	Reference	113825	10379 (9.1)	Reference	111783	10678 (9.6)	Reference
		≥ 120	20193	2807 (13.9)	1.09 (1.04-1.14)	13475	1838 (13.6)	1.34 (1.28-1.41)	3685	449 (12.2)	1.20 (1.11-1.31)
	Younger elderly	0-9	56503	2164 (3.8)	Reference	46964	1708 (3.6)	Reference	41242	1525 (3.7)	Reference
		≥ 120	6386	534 (9.3)	1.39 (1.26-1.55)	4557	373 (8.2)	2.13 (1.91-2.38)	1213	78 (6.4)	1.54 (1.21-1.95)
	Older elderly	0-9	97867	12588 (12.9)	Reference	23316	1382 (5.9)	Reference	70154	9153 (13.0)	Reference
		≥ 120	13807	2273 (16.5)	1.01 (0.96-1.06)	3181	200 (6.3)	1.04 (0.99-1.09)	2472	371 (15.0)	1.09 (0.98-1.22)

Longer (9-12 yrs)	All subjects	0-9	107114	6485 (6.1)	Reference	78654	4253 (5.4)	Reference	75650	4606 (6.1)	Reference
		≥ 120	15977	1751 (10.9)	1.41 (1.33-1.49)	10509	1117 (10.6)	1.95 (1.82-2.08)	2846	266 (9.4)	1.49 (1.31-1.70)
	Younger elderly	0-9	48909	3433 (3.0)	Reference	40221	900 (2.2)	Reference	35683	802 (2.3)	Reference
		≥ 120	5681	366 (6.4)	1.78 (1.57-2.03)	4042	255 (6.3)	2.73 (2.38-3.14)	1080	48 (4.4)	1.74 (1.29-2.35)
	Older elderly	0-9	58205	5353 (9.2)	Reference	38433	3353 (8.7)	Reference	39967	3804 (9.5)	Reference
		≥ 120	10296	1385 (13.5)	1.30 (1.22-1.39)	6467	862 (13.3)	1.51 (1.40-1.62)	1766	218 (12.3)	1.25 (1.08-1.45)

* Standardized prescribed doses of strong anticholinergics (dose/year)

** Covariates adjusted for or matched are the same with those in standard adjustment model (Model Ⅱ); age, sex and level of income, diabetes mellitus, hypertension, myocardial infarction, dizziness, genitourinary diseases, epilepsy, Parkinson's disease, prescribed doses of strong anticholinergics, and cumulative prescribed days of other non-anticholinergics that could impair cognitive functions (all psychotic diseases including depression, psychosis, anxiety were excluded in the step of participant selection in advance).

† The covariate 'other non-anticholinergics that could impair cognitive functions' which were included as continuous variable in Model Ⅱ was converted into a six class-variable with 6 categories for performing exact matching.

Results from sensitivity test Ⅱ: Applying different criteria to define incidence of Alzheimer's disease

The incidence of AD was redefined more strictly, as such diagnoses of Alzheimer's disease (ICD: G30) or Alzheimer's dementia (ICD: F00) more than twice or three times, and at each diagnosis point with a prescription of an anti-Alzheimer's agents then the results were compared with those in original definition, i.e., more than one time. As a results, the incidence of AD was reduced by 16.3% and 26.9%, when the criteria were changed from 'more than one time' to 'more than two time' or 'more than three times' respectively. The majority were expected to be censored for 'death or termination of follow-up' after the first or second diagnoses plus prescription. In order to confirm this, 9,219 patients who were excluded when the criteria to identify incident AD was changed from 'more than one time' to 'more than three times' were selected. And then the proportion of people with less than three months (90 days) of time interval between the day of first diagnose plus prescription and day of censoring by death, end of visit or reaching at the end of study (December 31, 2013) was examined. As a result, 6,834 subjects (74.2%) of them were belonged to these cases confirming that the decrease in number of AD events according to modifying the case definition was mainly due to censoring. Although the proportion of AD events were declined as such, risk of AD were little different from the original analysis by 'more than one time' criteria in all subjects and all strata (Table 5-8).

Table 5-8. Risk of Alzheimer's disease by prescription amount of strong anticholinergics in different defining of incident AD by frequency of diagnose and prescription at the time of the diagnose

Followed-up period of exposure	Subjects	strong anticholinergics (dose/year)	Definition of incident AD by frequency of diagnose and prescription at the time of diagnose								
			≥ one time			≥ two times			≥ three times		
			No of AD events (%)	Model Ⅰ	Model Ⅱ	No of AD events (%)	Model Ⅰ	Model Ⅱ	No of AD events (%)	Model Ⅰ	Model Ⅱ
Overall (3-12 yrs)	All subjects	overall	34231 (10.0)			28646 (8.5)			25019 (7.5)		
		0-9	14752 (9.6)	Reference	Reference	12393 (8.2)	Reference	Reference	10793 (7.2)	Reference	Reference
		10-49	12326 (9.4)	0.87 (0.85-0.89)	0.86 (0.84-0.88)	10280 (7.9)	0.87 (0.85-0.89)	0.85 (0.83-0.88)	9010 (7.0)	0.88 (0.85-0.90)	0.86 (0.84-0.88)
		50-119	4346 (12.0)	1.04 (1.01-1.08)	1.00 (0.97-1.04)	3650 (10.3)	1.05 (1.01-1.09)	1.01 (0.97-1.05)	3189 (9.9)	1.06 (1.02-1.10)	1.01 (0.97-1.05)

Followed-up period of exposure	Subjects	strong anticholinergics (dose/year)	Definition of incident AD by frequency of diagnose and prescription at the time of diagnose								
			≥ one time			≥ two times			≥ three times		
			No of AD events (%)	Model Ⅰ	Model Ⅱ	No of AD events (%)	Model Ⅰ	Model Ⅱ	No of AD events (%)	Model Ⅰ	Model Ⅱ
	Younger elderly	≥ 120	2807 (13.9)	1.18 (1.13-1.23)	1.09 (1.04-1.14)	2320 (11.8)	1.17 (1.12-1.23)	1.08 (1.03-1.13)	2027 (10.4)	1.18 (1.13-1.24)	1.08 (1.03-1.14)
		overall	5716 (4.5)			4708 (3.7)			4080 (3.2)		
		0-9	2164 (3.8)	Reference	Reference	1807 (3.2)	Reference	Reference	1583 (2.8)	Reference	Reference
		10-49	2218 (4.2)	0.96 (0.90-1.01)	0.92 (0.86-0.97)	1809 (3.4)	0.46 (0.88-1.00)	0.90 (0.84-0.96)	1563 (3.0)	0.93 (0.87-1.00)	0.89 (0.83-0.95)
		50-119	800 (6.5)	1.40 (1.29-1.52)	1.25 (1.14-1.36)	664 (5.4)	1.40 (1.28-1.53)	1.25 (1.14-1.37)	566 (4.7)	1.37 (1.24-1.51)	1.21 (1.09-1.34)
		≥ 120	534 (9.3)	1.76 (1.60-1.94)	1.39 (1.26-1.55)	428 (6.8)	1.71 (1.54-1.90)	1.31 (1.21-1.52)	369 (5.9)	1.68 (1.50-1.89)	1.32 (1.26-1.49)
	Older elderly	overall	28515 (13.3)			23938 (11.4)			20939 (10.1)		

Followed-up period of exposure	Subjects	strong anticholinergics (dose/year)	Definition of incident AD by frequency of diagnose and prescription at the time of diagnose								
			≥ one time			≥ two times			≥ three times		
			No of AD events (%)	Model Ⅰ	Model Ⅱ	No of AD events (%)	Model Ⅰ	Model Ⅱ	No of AD events (%)	Model Ⅰ	Model Ⅱ
		0-9	12588 (12.9)	Reference	Reference	10586 (11.0)	Reference	Reference	9210 (9.8)	Reference	Reference
		10-49	10108 (12.8)	0.84 (0.82-0.86)	0.84 (0.81-0.86)	8471 (11.0)	0.84 (0.81-0.86)	0.83 (0.81-0.86)	7447 (9.8)	0.92 (0.87-0.97)	0.84 (0.81-0.86)
		50-119	3546 (14.8)	0.95 (0.91-0.99)	0.94 (0.90-0.98)	2989 (12.8)	0.95 (0.92-0.99)	0.94 (0.90-0.98)	2623 (11.4)	1.08 (1.00-1.17)	0.94 (0.90-0.98)
		≥ 120	2273 (16.5)	1.04 (1.00-1.09)	1.01 (0.96-1.06)	1892 (14.1)	1.04 (0.99-1.09)	1.10 (0.95-1.05)	1659 (12.6)	1.20 (1.09-1.32)	1.01 (0.96-1.06)
Longer (9-12 yrs)	All subjects	overall	17719 (6.8)			14520 (5.6)			12356 (4.8)		
		0-9	6485 (6.1)	Reference	Reference	5347 (5.1)	Reference	Reference	4544 (4.3)	Reference	Reference

Followed-up period of exposure	Subjects	strong anticholinergics (dose/year)	Definition of incident AD by frequency of diagnose and prescription at the time of diagnose								
			≥ one time			≥ two times			≥ three times		
			No of AD events (%)	Model Ⅰ	Model Ⅱ	No of AD events (%)	Model Ⅰ	Model Ⅱ	No of AD events (%)	Model Ⅰ	Model Ⅱ
		10-49	6912 (6.3)	1.02 (0.98-1.05)	0.99 (0.95-1.02)	5625 (5.2)	1.01 (0.97-1.05)	0.98 (0.94-1.02)	4793 (4.9)	1.02 (0.98-1.06)	0.99 (0.95-1.03)
		50-119	2571 (8.8)	1.31 (1.25-1.37)	1.22 (1.17-1.28)	2129 (7.4)	1.33 (1.27-1.40)	1.24 (1.18-1.31)	1812 (6.4)	1.34 (1.27-1.42)	1.24 (1.17-1.32)
		≥ 120	1751 (10.9)	1.58 (1.50-1.67)	1.41 (1.33-1.49)	1419 (9.1)	1.58 (1.49-1.68)	1.40 (1.31-1.49)	1207 (7.8)	1.59 (1.49-1.70)	1.40 (1.30-1.50)
	Younger elderly	overall	3433 (3.0)			2755 (2.4)			2320 (2.1)		
		0-9	1132 (2.3)	Reference	Reference	924 (1.9)	Reference	Reference	786 (1.6)	Reference	Reference
		10-49	1412 (2.9)	1.14 (1.05-1.23)	1.07 (0.99-1.16)	1115 (2.3)	1.11 (1.02-1.21)	1.04 (0.95-1.14)	940 (2.0)	1.10 (1.00-1.21)	1.03 (0.94-1.14)

Followed-up period of exposure	Subjects	strong anticholinergics (dose/year)	Definition of incident AD by frequency of diagnose and prescription at the time of diagnose								
			≥ one time			≥ two times			≥ three times		
			No of AD events (%)	Model Ⅰ	Model Ⅱ	No of AD events (%)	Model Ⅰ	Model Ⅱ	No of AD events (%)	Model Ⅰ	Model Ⅱ
		50-119	523 (4.7)	1.74 (1.57-1.93)	1.49 (1.34-1.67)	432 (3.9)	1.78 (1.59-2.00)	1.52 (1.35-1.72)	358 (3.3)	1.74 (1.53-1.97)	1.47 (1.29-1.68)
		≥ 120	366 (6.4)	2.34 (2.07-2.63)	1.78 (1.57-2.03)	284 (5.1)	2.27 (1.98-2.59)	1.72 (1.49-2.00)	236 (4.6)	2.22 (1.91-2.57)	1.64 (1.40-1.93)
		overall	14286 (9.7)			11765 (8.2)			10036 (7.0)		
	Older elderly (n=146812)	0-9	5353 (9.2)	Reference	Reference	4423 (7.7)	Reference	Reference	3758 (6.6)	Reference	Reference
		10-49	5500 (9.1)	1.06 (0.98-1.14)	0.96 (0.92-1.00)	4510 (7.6)	0.97 (0.93-1.01)	0.96 (0.92-1.00)	3853 (6.6)	0.98 (0.94-1.03)	0.96 (0.92-1.01)
		50-119	2048 (11.4)	1.27 (1.14-1.40)	1.15 (1.09-1.21)	1697 (9.7)	1.21 (1.14-1.28)	1.16 (1.09-1.23)	1454 (8.4)	1.22 (1.15-1.30)	1.17 (1.10-1.25)
		≥ 120	1385 (13.5)	1.57 (1.39-1.78)	1.30 (1.22-1.39)	1135 (11.3)	1.41 (1.30-1.50)	1.30 (1.21-1.40)	971 (9.8)	1.42 (1.33-1.53)	1.31 (1.22-1.42)

Model Ⅰ: Adjusted for age, sex and level of income
Model Ⅱ: Adjusted for Model Ⅰ + diabetes mellitus, hypertension, myocardial infarction, cardiovascular diseases, dizziness, genitourinary diseases, epilepsy, Parkinson's disease, neuralgia, skin disease, sleep disorder, prescribed doses of weak anticholinergics, and cumulative prescribed days of other non-anticholinergics that could impair cognitive functions (all psychotic diseases including depression, psychosis, anxiety were excluded in the step of participant selection in advance)

Incident cases were defined as those who have been diagnosed with AD for the first time since 2005 by excluding those with AD diagnoses for three years from 2002 to 2004. In order to see whether three-years' exclusion was long enough, the inclusion criteria were varied by excluding people with AD diagnostic codes in the last one to five right before 2007, then the number of incident AD from 2007 to 2013 were examined. As a result, there was only a difference of 0.04 percentage points in the proportion of Alzheimer's patients over the next seven years (2007-2013) when comparing the three-year exclusion with the five-year exclusion. This suggests that 'excluding three years' is enough to rule out the AD prevalent people at the study entry.

Table 5-9. Proportion of incident AD by inclusion criteria to identify incident Alzheimer's disease

Inclusion criteria*	No. of subjects	No. of AD events (%)
1 year (2006)	479712	52040 (10.85)
2 years (2005-2006)	478159	51509 (10.77)
3 years (2004-2006)	477158	51199 (10.73)
4 years (2003-2006)	476474	51017 (10.71)
5 years (2002-2006)	476042	50906 (10.69)

*Inclusion criteria: people without diagnose of Alzheimer's disease (ICD: G30) or Alzheimer's dementia (ICD: F00) during the corresponding period of time.

5-4. Discussion

Using the NHIS elderly cohort DB in 2002-2013, we found that the excessive use of strong anticholinergic agents for long period of time (9-12 years) increased the risk of developing AD and the association was greater in the younger elderly. These findings support the previous studies suggesting that the long-term use of potent anticholinergics was associated with the incident dementia among studies showing mixed results. The risk for AD in the elderly subjects who used strong anticholinergics the most (≥ 120 dose/year) was comparable to those of Gray et al. in which the measurement of anticholinergic exposure was similar to our study (Gray et al. 2015), although the study populations and designs are quite different each other.

Overall, there was little difference between the lowest exposed control group (0-9 dose/year) and the next lowest exposed group (10-49 dose/year) in the risk of AD. However it was increased in groups exposed to ≥ 50 dose/year, and the hazard in the elderly with ≥ 120 dose/year was increased particularly high. Approximately 16.0% of the elderly were exposed to ≥ 50 dose/yr of strong anticholinergic agents, suggesting that quite a few elderly people are at risk of developing Alzheimer's disease due to the excessive use of strong anticholinergics.

It is not known how long a period of anticholinergic exposure is associated with the onset of AD. However, studies in which the anticholinergic use was measured for a relatively short period of time (6 years) did not confirm the association with incidence of dementia (Campbell et al. 2010), and a 10-year long-term exposure study reported increased risk of dementia (Gray et al. 2015). In this study, individuals were assessed for exposure from 2002 to the end of follow-up, and then by calculating the average annual exposure, the follow-up period for use of

anticholinergics varies from person to person, shortly 3 years, up to 12 years. In subjects with shorter follow-up periods, – this mainly seems because AD had occurred or has died shortly after the start of follow-up, and they might be predominantly older elderly – the anticholinergic effect would not be reflected enough comparing to the others whose anticholinergic exposure was tracked longer. It can be stated that, because of this small number of subjects (11.5% of all subjects), proportional hazards just began to emerge 6 years later after the study entry, i.e., 9 years after the exposure. More importantly, the results from proportional hazard regression analyses showed that the higher risk of AD in excessive use of strong anticholinergics was evident in the subjects who were exposed to strong anticholinergic agents for more than 9 years, but not in those exposed for less than 9 years.

When the same analysis was conducted with only younger elderly people aged under 65 years at the time of 2002, the risk of AD by level of exposure were consistently higher compared to the results from the whole subjects. Although the reason why the risk of AD by strong anticholinergic use was greater in the younger elderly is hard to presume currently, the two followings assumption is likely possible. First, the younger elderly were exposed to strong anticholinergics for longer period of time, since the time to onset of Alzheimer's disease or censoring will be relatively longer than the older elderly. This could be supported by the fact that the proportion of people with longer exposure is higher in the younger elderly than in the older elderly (93.5% in the younger elderly subjects vs. 83.9% in the older elderly subjects). Second, it is possible that the phenotypic expression of AD is more prominent in the younger aged, as the decline of AD were reported with age among aged people (Holland et al. 2012). The age of the AD incident subjects in the younger

elderly subgroup become between 63 and 75 years old, which means they might have less prodromal period than the older elderly and they have less potential comorbidities and medications. Hence the higher risk of AD in these younger elderly shown in this study could further support that the excessive use of strong anticholinergics is a risk factor for the development of AD. In addition, the younger elderly are likely to be in the early stage of AD and have longer life span, then they can have more benefit from preventive intervention. In other words, the higher risk of AD due to inappropriate use of anticholinergic agents in these subgroups suggests that the minimizing the inappropriate anticholinergic use could prevent or delay the risk of developing AD. Even in supplementary analyzes in which the exposure criteria were varied to minimize the prodromal effects, the relevance to Alzheimer's disease remained significant, demonstrating the validity of this study.

In the present study, the effect of weak anticholinergic agents on AD incidence was also evaluated. However, no association was found between them after prescription amount of strong anticholinergics and ‘other non-anticholinergic agents that could impair cognitive functions’ were additionally adjusted for. It could be stated that at least, weak anticholinergic agents do not have a clinically negative effect on cognitive function to the extent of increasing the risk of developing AD. However, these results should not be extrapolated as such that the weak anticholinergics will not affect the course of mild cognitive impairment (MCI) or AD.

This study has the following advantages compared to previous studies. First, it targeted a large population of over 340,000 people. Second, the prescribed doses of all anticholinergic agent were accurately measured. Third, this study was the first to find out how long a period of anticholinergic exposure was associated with the

onset of AD by way of methodological strengths. Fourth, the study simply demonstrated the effect of strong anticholinergics and weak anticholinergics on risk of AD separately. Furthermore, the other non-anticholinergics that could impair cognitive functions were counted and controlled for the analyses. Fifth, it was also the first study to confirm that the association of excessive use of strong anticholinergics with developing AD was greater in the younger elderly. Sixthly, by excluding all elderly people who have had a diagnoses of mental and behavioral disorders as well as all kinds of dementia and cognitive impairment disorders from the study subjects, it was tried to examine whether the excessive use of anticholinergics increase the risk of developing AD, not progression of AD as much as possible. Finally, significance in additional analyzes which were performed to exclude the possibility of reverse association with prodromal symptoms further demonstrated the causality between the exposure and and the development of AD. In addition, various sensitivity tests, including analyses after applying exact matching and propensity score method supported the validity of the study results as well.

This study has several limitations. First, as with other studies using health insurance claim data, the inaccuracy due to modification of diagnostic codes or misdiagnosis could not be ruled out even if the cases were rare. However, although the validity of health claim data varies from study to study, accuracy has been reported more than 90% and sensitivity varies widely but many studies reported as 70% (Tu et al. 2007, Wilchesky, Tamblyn, and Huang 2004). Only about 9% of people with dementia-like symptoms are misdiagnosed as dementia (Clarfield 2003). Second, this study did not include use of non-prescription drugs. However, most of the strong anticholinergics are classified as prescription drugs in Korea, and

prescription drugs were counted with few exceptions in administrative data. Therefore, these limitations do not seem to have a significant impact on the results. Third, prescription and actual medication may not coincide. Fourth, although the careful attention was paid to control the other factors affecting the anticholinergic use and incidence of AD, the possibility of residual confounding would be still remained. However, it is less likely that the results were seriously distorted by them since the effect size has increased after using the exact matching and the propensity score method to balance the covariances between the exposed groups. Fifth, although it was tried to exclude the inverse correlation by varying the exposure criteria, the possibility might still remain, since preclinical and prodromal stages in AD are very long in nature (Dubois, Hampel, et al. 2016, Ward et al. 2013). However, large-scaled population, precise assessment of exposure, and long time follow-up of this study seem to offset these limitations. Finally, Because of the wide variety of anticholinergic agents and indications, this study could not establish a washout period for drug exposures. However, it would be compensated with long-term follow-up as well.

Considering that risk of AD is known to be three times higher in a person with one APOE ε4 gene (Holtzman, Herz, and Bu 2012) and twice as high in a family history (Loy et al. 2014) , the effect of anticholinergic exposure is not negligible. It is important to note that exposure to anticholinergic agents is a preventable and controllable, while aging, family history, and heredity are uncontrollable risk factors. In addition, it can be interpreted that the burden of disease can be reduced by prolonging the maintenance period to the preclinical stage of AD or reversible mild cognitive impairment state, and delaying the irreversible clinical manifestation of AD when minimizing the excessive use of inappropriate anticholinergics in older

adults.

Clinical implications

It was found that the prescription amount of strong anticholinergics was very large in Korean elderly people, especially in AD patients who should avoid those drugs due to the drug-disease interactions. The longitudinal cohort study with the follow-period of a minimum of 3 years to a maximum of 12 years also showed that excessive use of a strong anticholinergic agent may increase the risk of AD and may be more relevant in the younger elderly.

In studies investigating the association of PIMs with progression or worsening of AD, various manipulative definitions could be used as outcome variables making it easier to demonstrate the relevance. However, to prove whether the PIMs could be a risk for the development of AD is more demanding, since it requires large population, long-term follow-up, and identifying the initial diagnosis. This study has shown that the anticholinergic effects of older adults on cognitive functioning may be more severe than our previous knowledge by demonstrating that anticholinergics can affect the development of AD. Actually it is difficult to distinguish the onset of AD from its' progression. However, the fact that excessive use of strong anticholinergics could affect the incidence of AD, could be interpreted that these drugs could make cognitive function worse enough to accelerate Alzheimer's diagnosis.

The prevalence of overuse of strong anticholinergics in the Korean elderly was high. More efforts should be made to reduce it. The higher the association between anticholinergics and risk of AD in the younger elderly means the greater the

utility of reducing anticholinergic activity. From a preventive point of view, it will be necessary to prescribe and use strong anticholinergic drugs more strictly from the time of the younger elderly.

This study could provide a very specific guidance for reducing the inappropriate use of anticholinergic agents. The prescription amount of weak anticholinergics was nearly twice that of strong anticholinergics, but it was not related to the risk of AD. Therefore, efforts to reduce the use of strong anticholinergics should be prioritized. Drug (classes) such as antihistamines, antidepressants and antimuscarinics for urinary diseases and chlorpheniramine, diphenhydramine, amitriptyline, paroxetine, and tolterodine as individual drugs accounted for a large portion of the anticholinergic burden in the elderly population. If strategies and institutional arrangements could be made to focus on the use of some of these drugs, the anticholinergic burden can be effectively reduced in a shorter period of time.

In the future, the following researches will be needed: In patients with severe dementia admitted to a nursing home, a strong anticholinergics with sedation may be overdosed to control the excess mental behavior disorders ((Nyborg et al. 2017). In order to confirm this, follow-up studies such as separate analysis of inpatients and outpatients, and subgroup study according to severity of AD will be necessary. It is also necessary to investigate whether the risk of AD could reduced when older adults who have been exposed to the strong anticholinergics prolonged time stop or reduce the medications.

Conclusion

Excessive use of strong anticholinergics increased the risk of AD. The risk was more prominent in long-term medication and / or in younger elderly people. Strong anticholinergics may affect not only the progression but also development of AD. Reducing the use of strong anticholinergics may contribute to preventing or delaying incident AD.

CHAPTER 6. OVERALL DISCUSSION AND CONCLUSION

6-1. More precise measurement of anticholinergic exposure using the National Health Insurance data

Precise measurement of exposure in studies of PIMs is one of the most critical factors in ensuring both the internal and external validity. However, it is difficult to estimate the actual amount of exposure as the sample size is larger, the types of drugs are more different, and the research period is longer. Thus, most of these studies have evaluated exposure to drugs semi-quantitatively by exposure periods or just identifying the exposure dichotomously at a specific point in time. In this study, we used the prescription data of the National Health Insurance Service, which has strengths in the aspect of accuracy and detailedness by characteristics of administrative data, to measure the closest anticholinergic exposure to the actual dose.

Among the studies on inappropriate exposure to anticholinergics, several studies developed the anticholinergic scales (Hilmer et al. 2007, Carnahan et al. 2006, Ancelin et al. 2006, Rudolph et al. 2008), and there were also some studies compared them (Salahudeen, Duffull, and Nishtala 2015). However researchers seemed not to be much interested in how to make the anticholinergic exposure measurements more reliable, although a reasonable measurement of anticholinergic use should be taken precedence before determining the anticholinergic scale. This study provides guidance on how to evaluate anticholinergic exposure. The standardized prescribed

doses and the cumulative prescribed days were highly correlated that they could be used interchangeably each other. The cumulative prescribed days were closer estimation to the standardized prescribed doses rather than the prescribed days.

6-2. Large prescription amount of the both strong and weak anticholinergics in the elderly

We found that the anticholinergic medications were very prevalent in Korean elderly population and the efforts to reduce them were needed. An excessive use of anticholinergics was more prevalent in elderly patients with indications for these drugs. In addition, the great association with polypharmacy and a very large prescription amount in some elderly persons suggest that multiple medications of different anticholinergics contribute to this overuse. In these elderly patients, the anticholinergic burden can be significantly reduced if the medicines could be replaced with those with non or low anticholinergic properties as much as possible. The prescription amount of chlorpheniramine ranked the highest and it has been found that the agent was widely prescribed in relatively less severe, short-term conditions implying that they may be more resilient to reduce the prescriptions than other anticholinergics which were mostly used in more severe chronic diseases. Switching to second-generation antihistamines could be a better choice. Amitriptyline was being frequently used in neuropathic as well as psychiatric disorders such as depression. Amitriptyline is one of the most potent anticholinergics that it is necessary to analyze the reason why the volume of the prescription of this medicine was prominently high as such. There are several plausible reasons for this: First, amitriptyline is a typical and conventional antidepressant, so there may be

stickiness to the prescription. Second, despite the availability of alternative drugs with low anticholinergic burden, higher cost could be a barrier to prescription replacement. Finally, low physicians' perceptions of the severity of anticholinergic adverse effects in the elderly may be probable. More than 80% of the total anticholinergics were respiratory, psychiatric, and urinary tract diseases. More attention should be paid in these medical divisions.

6-3. The higher risk of exposure to excessive amount of strong anticholinergics in Alzheimer's disease

It is generally accepted that a great deal of anticholinergics may aggravate AD and should be avoided for AD patients. Moreover, most of anti-Alzheimer drugs except memantine are cholinesterase-inhibitors to increase the level of acetylcholine, which is used for synaptic transmission in the CNS. Since anti-dementia drugs and anticholinergics are pharmacologically antagonistic and interferes with their efficacies each other, the use of anticholinergics should be avoided in Alzheimer's disease to ensure that the anti-dementia drugs work properly (Johnell and Fastbom 2008). However, AD prevalence was associated with excessive use of strong anticholinergics, and the proportion of elderly persons exposed to the excessive doses was 22.5% in the elderly group, which is not a minority. In AD, the prescription amount of antidepressants, antiparkinsonians, and urinary antimuscarinics were especially larger compared to non-AD. As such, prescription patterns of strong anticholinergics in AD patients were different from non-AD group. It will be necessary to understand the real condition and cause of the inappropriate anticholinergics prescription in AD and then try to minimize it.

6-4. The excessive use of strong anticholinergic agents increases the risk of Alzheimer's disease

Considering that Alzheimer's risk is three times higher in a persons with one APOE ε4 gene and twice as high in a family history (Holtzman, Herz, and Bu 2012, Loy et al. 2014), the effect of anticholinergic exposure on incident AD is not negligible. It is important to note that exposure to strong anticholinergics is a preventable and modifiable, while age, family history, and heredity are the most important but uncontrollable risk factors. In addition, it can be interpreted that the burden of disease could be reduced by prolonging the preclinical stage of AD or reversible mild cognitive impairment state, or delaying transition to the irreversible clinical manifestation of AD when the minimizing the excessive use of inappropriate anticholinergics in older adults.

Although it was tried to exclude the inverse correlation by varying the exposure criteria, the possibility might still remain, since preclinical and prodromal stages in AD are very long in nature (Dubois, Hampel, et al. 2016, Ward et al. 2013). However, large-scaled population, more precise estimation of exposure, and long time follow-up of this study seem to offset these limitations.

6-5. Implications and future research

We found that the prescription of anticholinergics was very high in Korean elderly people, especially in AD patients who should avoid their use due to drug-disease interactions. The longitudinal cohort study with the follow-period of a minimum of 3 years to a maximum of 12 years also showed that excessive use of a strong

anticholinergic agent may increase the risk of developing AD and may be more relevant in younger elderly patients.

In studies investigating the association of PIMs with progression or worsening of AD, various manipulative definitions can be used as outcome variables, and it could be easy to demonstrate the relevance. However, to prove whether the PIMs is a risk factor for the development of AD is more demanding since it requires large population, long-term follow up at least for a few years, and identifying the initial diagnosis. This study has shown that the anticholinergic effects of older adults on cognitive functioning may be more severe than our previous knowledge by demonstrating that anticholinergics can affect the development of Alzheimer's disease. Of course, it is neither possible nor reasonable to separate causing AD from aggravating it clearly. However, the fact that excessive doses of strong anticholinergics could affect the development of AD, could be interpreted as those medicines can make cognitive function worse enough to accelerate Alzheimer's diagnosis.

The prevalence of overuse of strong anticholinergics in the Korean elderly was very high, especially in AD patients who are much vulnerable to the cognitive side effect of strong anticholinergics. More efforts should be made to reduce it. The higher the association between strong anticholinergic use and Alzheimer's disease in the younger elderly means the greater the utility of reducing anticholinergic activity. From a preventive point of view, it will be necessary to strictly prescribe and use potent anticholinergic drugs from the time of the younger elderly.

This study provides a very specific guidance for reducing the inappropriate use of anticholinergic agents. The prescription of weak anticholinergics is nearly twice that of strong anticholinergics, but it was not related to the risk of developing

AD. Therefore, efforts to reduce the use of strong anticholinergics should be prioritized. Drugs such as antihistamines, antidepressants and antimuscarinics for urinary diseases and chlorpheniramine, diphenhydramine, amitriptyline, paroxetine, and tolterodine as individual drugs accounted for a large portion of the anticholinergic burden in the elderly population and the elderly in Alzheimer's. disease. If strategies and institutional arrangements can be made to focus on the use of some of these drugs, the anticholinergic burden could be effectively reduced.

The anticholinergic medication in the elderly is almost entirely dependent on prescribers' decisions. The doctor's prudence and effort for appropriate prescription of anticholinergics are highly required. The pharmacist should pay special attention to double checking the prescriptions. It is also possible to consider using a clinical decision system (CDS), such as the Drug Utilization Review (DUR) system (Yang et al. 2015). In Korea, The Health Insurance Review & Assessment Service (HIRA) introduced alerting for PIMs for older adults to call attention to the prescription for those medications in October 2015. Among the twenty agents designated as PIMs for the elderly in the DUR system, amitriptyline and amantadine were the only strong anticholinergics currently included.

In the future, the following researches will be needed: First, in all studies from chapter Ⅲ to chapter Ⅴ, the recipients of Medical aid were in the highest risk of using excessive anticholinergic agents. More research will be required to identify the causes of these excessive use in that group and how to reduce them. Second, the use of weak anticholinergics in this study was found not to increase the risk of AD. However as the volume of those prescription was very high in the older adults, more rigorous studies should be conducted whether it could affect the course of AD. In patients with severe dementia admitted to a nursing home, psychotropic

anticholinergics may be overdosed to control the excess mental behaviors. In order to confirm this, follow-up studies such as separate analysis of inpatients and outpatients, and subgroup studies according to severity of Alzheimer's disease will be necessary.

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국문 초록

서론

개인과 사회에 미치는 부담이 매우 큰 알츠하이머 질환은 특정 약물의 사용과도 관련되어 있다. 항콜린성이 강한 약물은 인지기능을 악화시킬 수 있어 치매가 있는 노인을 비롯하여 모든 노인에게 피해야 하는 부적절한 약물로 분류된다.

노인에서 항콜린제의 사용 실태에 대한 일부 연구가 있으나 대규모 연구는 거의 없고, 항콜린부담을 실제 처방량으로 노출을 정량화한 연구는 매우 제한적이다. 항콜린성이 강한 약물 (강한 항콜린제)은 특히 인지기능이 저하되어 있는 노인이나 치매 환자에서 매우 주의를 요하는데, 실제 적절하게 사용되는 지를 적절히 평가한 연구 역시 매우 드물다. 부적절한 항콜린제의 사용이 인지기능을 악화시킴은 알려져 있으나, 치매의 발생에도 영향을 미치는지를 연구하기 위해서는 잘 고안된 전향적 추적조사가 필요한데, 충분한 표본을 대상으로 노출을 정량화하여 장기추적한 연구는 없으며 기존의 몇몇 연구들에서도 상반된 결과를 보여주고 있다.

본 연구는 항콜린성 약물의 노출과 알츠하이머 치매와의 관련성에 관한 연구로, 연구 목적은 다음과 같다.

(1) 항콜린성 약물의 표준화처방량을 산출하여 약물 사용기간, 누적처방기간과 같이 흔히 사용되는 정량적 측정지표와의 상관성을 확인한다. 실제 사용한 약물의 용량 단위까지 정확히 산정하여 표준화한 표준화처방량을 노출지표로 하여 한국 노인에서 항콜린성 약물의 처방 양상을 자세히 살펴본다.

(2) 부적절한 항콜린제의 사용을 피해야 하는 알츠하이머 환자에서 항콜린제의 처방 양상을 비유병군과의 비교를 통해 확인한다. 알츠하이머 질환 외에도 항콜린성 약물의 사용에 영향을 미치는 요인을 확인한다.

(3) 전향적 코호트연구를 통해 항콜린성 약물 사용이 알츠하이머 질환의 발생 위험을 높이는지를 확인하고 노출추적기간 및 연령대에 따른 차이를 조사한다.

연구 방법

(1) Beers Criteria 와 Anticholinergic Cognitive Burden (ACB) scale 을 이용하여 강한 항콜린제와 약한 항콜린제의 목록을 선정하였다. 의약품 허가정보 등을 기반으로 하여 항콜린제별 노인적정용량을 설정한 후 2012 년 국민건강보험공단 노인코호트 DB 의 상세 진료처방내역과 mapping 하여 모든 항콜린제의 연간 표준화처방용량을 계산하였다. 처방내역의 투여일자를 이용하여 항콜린제별 처방일수와 누적처방일수를 계산하고 표준화처방용량과의 상관성을 상관분석과 회귀분석으로 확인하였다.

(2) 2012 년 노인코호트의 70 세 이상 388,629 명을 대상으로 항콜린제의 표준화처방량에 따른 노인의 특성, 항콜린제별 처방량, 강한 항콜린제의 동시처방일 비율, 강한 항콜린제 사용 환자의 주요동반질환, 연령대별 처방양상 등을 확인하였다. 또한 과도한 항콜린제의 사용을 연간 90 dose/year 로 정의하고 인구학적 변수, 다약제복용, 인지기능에 영향을 미치는 항콜린제 이외의 약물의 처방, 주요

만성질환, 강한 항콜린제의 주요 적응증 질환 등을 포함하여 다변량 로지스틱회귀분석을 수행함으로써 과도한 항콜린제 사용의 예측요인을 확인하였다.

(3) 2012 년 알츠하이머 유병자와 비유병자를 정의하고, 알츠하이머 유병자군과 비유병자군 간에 항콜린제 처방 양상을 비교하였다. 기본 인구학적 변수, 주요 만성질환 등을 포함한 다변량 로지스틱 회귀분석을 통해 알츠하이머 질환이 강한 항콜린성 약물의 과도한 사용을 예측하는지를 확인하였다. 또한 강한 항콜린제 적응증 질환의 유병 수준을 통제하여 분석을 수행함으로써 알츠하이머 유병 상태가 강한 항콜린제 처방을 줄이는 것과 관련이 있는지를 확인하였다.

(4) 2002-2013 년 국민건강보험 노인코호트 DB 를 이용한 코호트연구를 통해 항콜린제의 사용이 알츠하이머 질환의 발생 위험을 높이는지를 확인하였다. 2002-2004 년까지 모든 정신계 질환 및 알츠하이머 질환 진단을 한번도 받지 않은 사람으로서 2005 년 건강보험자격을 유지하고 있는 342,522 명을 대상으로 2013 년까지 추적조사를 통해 항콜린제의 노출량과 알츠하이머의 발병을 확인하였다. 알츠하이머 발병일, 마지막 진료일, 사망일 중 가장 빠른 일자를 추적종료시점으로 하여, 2002 년부터 추적종료시점까지의 항콜린제 연간 평균 노출량을 구하고, 노출에 따른 알츠하이머 발생의 위험을 비례위험회귀모형을 이용하여 분석하였다. 노출은 연평균 강한 항콜린제의 표준화사용량에 따라 0-9, 10-49, 50-119, ≥ 120 dose/year 로 구분하였다. 기본 인구학적 변수, study entry 이전 2004 년의 주요 성인질환 및 강한 항콜린제의 주요 적응증 질환의 병력, 항콜린제 외 인지기능에 부정적인 영향을 미칠 수 있는 기타 약물의 처방량 등을 공변량으로

하여 보정하였다. 노출기간 및 대상자의 연령에 따라 알츠하이머 질환의 발생에 대한 강한 항콜린제의 영향이 달라지는지를 확인하기 위해 노출추적기간 (longer: 9-12 년 vs. shorter: 3-8 년)과 2002 년 노출추적시작 시점에서의 연령 (younger elderly: 65 세 미만, older elderly: 65 세 이상)을 기준으로 네 개의 군으로 층화하여 각 하위군에 관해서도 동일한 분석을 수행하였다.

(5) 부가적인 연구로, 첫번째, 2005-2006 년 국가건강검진을 수검한 노인만을 대상으로 국가건강검진자료를 통해서 얻은 혈압, 혈당 등의 주요건강지표와 흡연 등의 생활습관 변수를 추가적으로 통제한 후 분석을 수행하였다. 둘째, prodromal effect 에 의한 비뚤림 가능성을 최대한 배제하기 위해 항콜린제 노출변수의 정의를 다양하게 설정하여 추가적인 연구를 수행하였다. 즉, 추적종료시점 이전 1 년간 및 2 년간 강한 항콜린제의 사용을 제외하고 분석을 수행하거나, 추적종료시점 이전 1 년 간의 전체 강한 항콜린제의 사용량 및 노출추적 전기간의 항우울제의 사용을 배제하고 노출을 평가하거나, 개별 약물군별로 노출량을 측정한 후 알츠하이머 질환의 발병과의 관련성을 확인하였다.

연구 결과

(1) 항콜린제의 표준화처방량과 처방기간, 누적처방기간과의 상관성을 확인하였을 때, 약한 항콜린제, 강한 항콜린제, 전체 항콜린제 모두에서 누적처방기간과의 상관성은 83-87% 정도로 높은 상관관계를 보여주었다. 표준화처방량과 처방기간과의 상관성은 이보다 약 10% 낮은 수준이었다.

(2) 2012 년 노인 코호트 대상자에서 강한 항콜린제의 연간 표준화처방용량은 65.6 dose 였다. 50% 이상의 노인은 15 dose/year 미만의 적은 양의 항콜린제를 처방받았으나, 180 dose/year 에 해당하는 매우 높은 양의 강한 항콜린제에 노출된 노인도 10% 가까이 되었다. 강한 항콜린제 중에서는 chlorpheniramine 과 amitriptyline 의 처방 비중이 과반을 차지하였다. 의료급여 대상자인 경우, 다약제 복용인 노인이 경우, 약한 항콜린제의 처방량이 많을수록, 그리고 항콜린제 외에 인지기능을 손상시킬 수 있는 약제의 사용빈도가 높을수록 과도한 양의 강한 항콜린제에 노출될 가능성이 높았다. 파킨슨질환과 우울증이 강한 항콜린제의 과도한 사용의 가장 큰 예측인자였으며, 그 외에도 비뇨기계질환, 전정기관 이상 등으로 인한 어지럼증, 호흡기질환의 순으로 강한 항콜린제의 과도한 처방과 관련성이 있었다.

(3) 알츠하이머 유병군과 비유병군에서 항콜린제의 처방양상을 비교하였을 때, 강한 항콜린제의 연간 처방량은 유병군과 비유병군에서 각각 63.1 dose, 90.2 dose 로 알츠하이머군에서 높았으며, 약한 항콜린제의 처방량 역시 알츠하이머 유병군에서 높았다. 알츠하이머 비유병군에서는 항히스타민제의 처방량이 매우 높았으며 (33.6 dose/year) 그 다음으로 항우울제의 처방량이 높은데 비해 (17.3 dose/year), 유병군에서는 항우울제의 처방량이 가장 많았고 (30.0 dose/year) 이보다 약간 적은 비율로 항히스타민제 의 처방량이 높았다 (28.5 dose/year). 개별 약물별로 비교하였을 때에는 알츠하이머 비유병군에서는 chlorpheniramine (39.8%)과 amitriptyline

(21.8%)의 비중이 높았으며, 유병군에서는 amitriptyline (20.4%)과 chlorpheniramine (19.6 %)이 유사한 비율로 가장 높았다.

(4) 전체 노인 대상자에서 연령, 성별, 소득수준 등의 인구학적 변수를 보정한 후 알츠하이머 유병자에서 강한 항콜린제의 과도한 사용의 위험은 비유병군에 비해 36% 높았다. 알츠하이머 질환의 유병 자체가 과도한 처방의 감소와 관련이 있는지를 확인하기 위해 기본 인구학적 변수 이외에 주요 만성질환 및 우울증, 파킨슨병, 비뇨기계 질환 등 강한 항콜린제의 주요적응증 질환을 포괄적으로 보정한 후 알츠하이머 유병군에서의 강한 항콜린제의 과도한 사용의 위험비를 확인하였을 때, 알츠하이머 유병군에서 강한 항콜린제의 과도한 사용의 odds 는 비유병군에 비해 12% 낮았다.

(5) 12 년간의 경시적 코호트연구를 통해 강한 항콜린제의 과도한 사용이 알츠하이머 질환의 발병위험을 높이는 지를 확인하였다. 노출추적기간과 추적조사시작시점에서의 연령을 기준으로 네 개의 하위군으로 층화분석을 수행하였을 때 전체 대상자의 76.3%에 해당하는 '장기간 (9-12 년) 노출 추적 대상자'에서 강한 항콜린제 노출에 따른 알츠하이머 질환의 발생 위험비 (95% 신뢰구간)는 대조군에 비해 50-119 dose/year 군과 ≥ 120 dose/year 군에서 각각 1.22 (1.17-1.28), 1.41 (1.33-1.49)로 높았다. 또한 장기간 노출이 추적된 대상자 중에서도 2002년 노출평가 시작 시점에의 연령이 65세 미만이었던 젊은 노인층 (younger elderly)에서 강한 항콜린제 사용과 알츠하이머 질환의 발병과의 관련성이 가장 높아, 대조군에 비해 50-119 dose/year 및 ≥ 120 dose/year 노출군에서 알츠하이머 질환의

발생 위험비 (95% 신뢰구간)는 각각 1.49 (1.34-1.67), 1.78 (1.57-2.03)이었다.

(6) Prodromal bias 를 가능한 배제한 후의 결과를 확인하기 위해 추적종료시점 이전의 최근 1 년 및 2 년의 강한 항콜린제를 제외하거나 추적 전 기간 동안의 항우울제 처방량 및 최근 1 년간의 강한 항콜린제 사용을 모두 제외한 후 알츠하이머 질환의 발생 위험을 확인하였을 때 장기간 추적조사 그리고/또는 젊은 고령층에서 강한 항콜린제 노출과 알츠하이머 발병과의 관련성이 약해졌으나 여전히 유의하며 유사한 양상으로 나타났다. 또한 두 군간에 처방량의 분포가 가장 유사한 항히스타민제만의 영향을 조사하였을 때에도 ≥ 120 dose/year 에서 '장기간 노출추적, 젊은 고령층'에서 알츠하이머 발병의 위험은 유의하게 높게 나타났다.

결론

상당수의 노인에서 부적절한 항콜린제가 과도하게 사용되고 있으며, 알츠하이머 환자는 알츠하이머 비유병자에 비해 더 많은 양의 강한 항콜린제를 처방받고 있었다. 강한 항콜린성을 갖는 항우울제와 항히스타민제의 처방량은 전체 노인과 알츠하이머 환자 모두에서 높았으므로 이들 약물의 사용을 줄이기 위한 노력이 우선되어야 하고, 알츠하이머 질환에서의 부적절한 항콜린제 사용양상은 비유병자와 달라 알츠하이머 유병자에서 부적절한 항콜린제의 사용을 줄이기 위한 방안은 비유병자와는 달라야 할 것으로 생각된다.

항콜린성이 강한 약물에 장기간 과도하게 노출되면 알츠하이머 질환의 진행 뿐 아니라 발생위험을 증가시킬 수 있으며 그 위험은 예방의 효용이 큰

젊은 노인층에서 더욱 큰 것으로 나타났다. 이는 부적절한 항콜린제의 사용을 줄였을 때 알츠하이머 질환의 발생의 예방 또는 지연에 기여할 수 있음을 시사한다.

주요어: 항콜린제, 알츠하이머 질환, 치매, 국민건강보험 노인코호트, 노인, Beers 기준, 항콜린성 인지부담 척도

학번: 2013-31220

APPENDIX

Appendix 1. Adequate daily dose for the elderly of anticholinergic agents

Generic name	Dosage (mg)	Generic name	Dosage (mg)	Generic name	Dosage (mg)
Alprazolam	2	Cyproheptadine Orotate	4	Metoprolol Succinate	48
Alverine Citrate	120	Dexbrompheniramine Maleate	6	Molindone HCl	15
Amantadine HCl	100	Dexchlorpheniramine Maleate	6	Morphine Sulfate Hydrate	20
Amantadine Sulfate	100	Diazepam	4	Nifedipine	30
Amitriptyline HCl	10	Dicyclomine HCl	30	Nortriptyline HCl	30
Amitriptyline HCl S.R. Gr.	10	Dimenhydrinate	150	Olanzapine	5
Amoxapine	25	Diphenhydramine HCl	75	Oxcarbazepine	600
Atenolol	50	Diphenhydramine Citrate	38	Oxybutynin HCl	5
Belladonna Total Alkaloid	200	Dipyridamole	75	Paroxetine Hydrochloride Hydrate	10
Belladonna Ext.	32	Disopyramide Phosphate	75	Perphenazine	12
Belladonna Leaf Ext.	1	Doxepin HCl	25	Pethidine HCl	150
Belladonna Tinc. D4	225	Doxylamine Succinate	25	Pimozide	2
Belladonna Alkaloid	1	Fentanyl Citrate Micronized	400	Prednisone	5

Generic name	Dosage (mg)	Generic name	Dosage (mg)	Generic name	Dosage (mg)
Benztropine Mesylate	1	Fesoterodine Fumarate	4	Prochlorperazine Malate	5
Brompheniramine Maleate	4	Flavoxate HCl	300	Prochlorperazine	20
Bupropion HCl	300	Fluvoxamine Maleate	100	Promethazine HCl	25
Captopril	50	Furosemide	20	Quinidine Sulfate Hydrate	600
Carbamazepine	200	Haloperidol	2	Ranitidine Bismuth Citrate	800
Carbinoxamine Maleate	12	Hydralazine HCl	30	Ranitidine HCl	300
Chlorpheniramine Maleate	4	Hydrocortisone	10	Risperidone	2
DL-Chlorpheniramine Maleate	4	Hydroxyzine HCl	30	Scopolamine Butylbromide	30
D-Chlorpheniramine Maleate	90	Hyoscyamine Sulfate Hydrate	1	Scopolamine HBr	30
Chlorpromazine HCl	30	Imipramine HCl	25	Scopolamine	2
Chlorthalidone	25	Isosorbide Dinitrate	15	Solifenacin Succinate	5
Cimetidine	800	Isosorbide Dinitrate Coated Gr.	40	Solifenacin Fumarate	5
Clemastine Fumarate	1	Isosorbide-5-Mononitrate	40	Solifenacin Tartrate	5
Clidinium Bromide	8	Isosorbide-5-Mononitrate S.R. Gr.	40	Thioridazine HCl	75

Generic name	Dosage (mg)	Generic name	Dosage (mg)	Generic name	Dosage (mg)
Clomipramine HCl	25	Isosorbide-5-Mononitrate Montan Glycol Wax Mixture 40%	100	Tolterodine L-Tartrate	2
Clozapine	150	Isosorbide Solution	70	Trazodone HCl	150
Codeine Phosphate Hydrate	60	Loperamide HCl	6	Trifluoperazine HCl	5
Colchicine	1	Loperamide Oxide Hydrate	2	Trihexyphenidyl HCl	5
Cyclobenzaprine HCl	15	Loxapine Succinate	60	Triprolidine HCl Hydrate	8
Cyproheptadine HCl Hydrate	4	Meclizine HCl Hydrate	25	Trospium Chloride	40

Appendix 2. Other non-anticholinergic agents impairing cognitive function (Referenced by Beers Criteria)

Amisulpride	Flurazepam	Paliperidone
Aripiprazole	Flutoprazepam	Pinazepam
Blonanserin	Haloxazolam	Quazepam
Bromazepam	Lafutidine	Quetiapine
Bromperidol	Levomepromazine	Roxatidine
Brotizolam	Lithium	Sulpiride
Chlordiazepoxide	Loprazolam	Temazepam
Chlorprothixene	Lorazepam	Thiothixene
Clobazam	Melperone	Tiapride
Clonazepam	Mesoridazine	Tofisopam
Clorazepate	Mexazolam	Triazolam
Estazolam	Midazolam	Ziprasidone
Ethyl Loflazepate	Mosapramine	Zolpidem
Famotidine	Nemonapride	Zopiclone
Fludiazepam	Niperotidine	Zotepine
Fluocinolone	Nizatidine	Zuclopenthixol
Flupentixol	Nordazepam	

Appendix 3. The ICD codes which were used to define each disease (group)

Disease	ICD code
Diabetes mellitus	'E10' 'E11' 'E12' 'E13' 'E14'
Hypertension	'I10'
Myocardial infarction	'I21' 'I22' 'I25'
Cardiovascular diseases	'G45' 'G46' 'H34' 'I60' 'I61' 'I62' 'I63' 'I64' 'I65' 'I66' 'I67' 'I68' 'I69'
Dizziness	'H81' 'H93' 'R42'
Sleep disorder	'G47' 'F51'
Genitourinary diseases	'N30' 'N31' 'N32' 'N39' 'N40' 'R32' 'R35'
Epilepsy	'G40' 'G41'
Parkinson's diseases	'G20' 'G21' 'G22' 'G23'
Neuralgia	'G53' 'M45' 'M46' 'M47' 'M48' 'M49'
Respiratory diseases	'J06' 'J00' 'J10' 'J20' 'J30' 'J45'
Skin diseases	'L20' 'L21' 'L23' 'L24' 'L30' 'L50'