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Cognitive decline and polypharmacy in an elderly population.

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COGNITIVE DECLINE AND POLYPHARMACY IN AN ELDERLY POPULATION

By

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DEDICATION

To my parents Jorge and Ximena, and my sister, Fabiola who have always been there to give me support and encouragement in the different challenges I take in my life.

ABSTRACT

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Aging is associated with increased risk of chronic disease, comorbidities, and greater medication use. Polypharmacy, the concomitant use of 5 or more medications, has been associated with adverse health effects, and potentially cognitive decline. The proposed hypothesis is that polypharmacy increases the risk of cognitive decline in elderly people.

Using longitudinal data from 572 participants from the New Mexico Aging Process Study cohort, the impact of polypharmacy on the Mini Mental State Examination (MMSE) scores and Mild Cognitive Impairment (MCI) was studied. The statistical analyses were performed using mixed linear regression multivariable models and generalized estimating equations, adjusting for important covariates.

Polypharmacy was associated with a 0.11±0.09 decrease in MMSE scores (p-value=0.23) and an increased risk of MCI (odds ratio=1.95, 95% CI 0.40-9.43). The results suggest that polypharmacy may increase the rate of cognitive decline in elderly people. Larger studies in other populations are needed to support this hypothesis.

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INTRODUCTION

AGING

The Department of Health & Human Services estimates that by 2030 there will be 72.1 million individuals 65 years of age or older in the United States, an estimate that is more than twice the number of older people in 2000.[1] According to the last US Census, there are 672,095 persons 60 and older in the Commonwealth of Kentucky, and it is expected that by 2030 this number will increase to 1,287,999, or 26% of the population.[2]

Furthermore the life expectancy for the general US population born during 2008 was 78.1 years, and 75.6 and 80.5 years for males and females respectively.[3] In addition, from this same analysis, it was established that the life expectancy for 65 year old people in US for 2008 was 18.78 years; in other words, we can expect that a person 65 years of age in 2008 will live until about 85 years of age.[3] There are also differences in life expectancy by race; the life expectancies for Hispanics are 80.9 years, 78.37 years for non- Hispanic whites, 74.03 years for blacks, and 73.70 years for non-Hispanic blacks.[3]

There are several anatomical and physiological changes associated with aging that increase the probability of adverse reactions to commonly used drugs. Some of these changes include a decrease in saliva production, atrophy of gastric mucosa and muscularis mucosae, decrease in stomach acid production, decrease in liver size and blood flow, decrease in creatinine clearance and glomerular filtration rate, changes in the body fat composition, among others.[4] These changes and the increased need of

treatments due to the presence of chronic diseases, may increase the risk of experiencing adverse drug reactions (ADR), drug-drug interactions and drug-disease interactions, particularly due to the physiological changes related with age, such as changes in absorption, distribution, metabolism and excretion of the drugs.[5]

When adverse drug reactions occur in older people, they are more likely to be severe and less likely to be recognized or reported by the patient. In addition it has been described that the incidence of adverse drug reactions correlates with age, and can cause death in 18% of older hospitalized patients.[5] Furthermore, considering all the factors that are most consistently associated with ADR, polypharmacy is considered the most important.[5]

POLYPHARMACY AND POTENTIALLY INAPPROPRIATE PRESCRIBING

Polypharmacy has been defined in several different ways, but the most common definition is the simultaneous use of five or more medications.[6-8] Literature described that the prevalence of polypharmacy is between 5% to 78%, wherein the variation depends on the definition used and the sample studied.[6] Kaufman et al (2002) analyzed the data from The Slone Survey between 1998 and 1999, describing that 57% of American women aged 65 years or older took at least five medications, and 12% took at least 10 medications.[9] Nobili et al. studied the prevalence of polypharmacy in the Lombardy Region of Italy among 1,915,579 people aged 65 years or older (1,767,239 included in the analysis) living in that region, and found that 88% of the elderly population received at least one drug prescription, and 46% received five or more drugs.[10]

Over time, several criteria have been developed to evaluate the appropriateness of prescribing in elderly people. One of those criteria, and the most widely used are the Beers Criteria, which defines Potentially Inappropriate Medication (PIM) as those medications that are thought to offer inadequate benefits or to pose so much risk to older persons that they are rarely appropriate to prescribe.[11] Beers Criteria are explicit criteria used to determine inappropriate medication use, originally applied in nursing homes for quality assurance, health service research and clinical practice guidelines.[11] Since 1991, several updates and modifications of the original Beers criteria have been published, including the last update of 2012.[12]

This last update was performed by the American Geriatric Society by a panel of 11 experts in the field, who reviewed and graded different evidence to develop the final criteria. The final criteria comprises 3 categories: PIM and classes to avoid in older adults, PIM and classes to avoid in older adults with certain diseases and syndromes that the drugs listed can exacerbate, and finally medication to be used with caution in older adults.[12] This update was designed to be used in all ambulatory and institutional settings of care for populations aged 65 and older in the United States.[12]

In addition to Beers Criteria, a new screening tool has been developed and is called STOPP (Screening Tool of Older Person's Potentially Inappropriate Prescriptions). In this case, a panel of experts analyzed 68 potentially inappropriate prescribing practices in older people, from which they included 65 in the final STOPP.[13] STOPP criteria include different instances such as drug-drug and drug-disease interactions, drugs which adversely affect older patients at risk of falls and duplicate drug prescriptions.[13]

In a study comparing both methods for defining PIM, Gallagher et al. conclude that STOPP identified significantly more PIMs than Beers criteria (2003 version) in acutely ill older patients. However, they made strong emphasis in that Beers criteria may not be suitable to be used outside the US, mostly because many of the drugs present in the Beers' criteria are rarely used in Western Europe.[13]

Among the drugs that have been associated with adverse events, cognitive decline and loss of independence are the anticholinergics.[14] This association is supported by the ample evidence showing that drugs with anticholinergic properties are especially likely to cause adverse events leading to cognitive impairment, cognitive decline, delirium, falls and loss of independence.[14, 15] Anticholinergics may affect the brain by blocking the neurotransmitter acetylcholine, and older people are more susceptible to these effects due to the age-related changes. The changes that are mostly related with the increased susceptibility to anticholinergics are a decrease in cholinergic neurons or receptors in the brain, a reduction in hepatic and renal clearance of drugs, and an increase in blood barrier permeability, especially during acute diseases.[14]

One way to evaluate the potential risk at which the patients are exposed when using anticholinergics is using the Anticholinergic Cognitive Burden (ACB), which is a scale designed to identify the severity of any anticholinergic effect on cognition. In this case, anticholinergic drugs are scored according to the anticholinergic effect, thus drugs with established clinically relevant cognitive effects are scored with 2 or 3, and those with serum anticholinergic activity or *in vitro* affinity for muscarinic receptors but with not known clinically relevant cognitive effect are scored with one.[14] Another tool to evaluate the risk associated with the use of anticholinergics is the Anticholinergic Risk

Scale (ARS), which is a tool designed to estimate the extent to which an individual patient may be at risk of anticholinergic adverse effects that can lead to some kind of cognitive dysfunction. In this scale, medications are divided in three categories, moderate anticholinergic potential (1 point), strong anticholinergic potential (2 points), and very strong anticholinergic potential (3 points).[14, 15]

Pasina et al. performed a study among elderly patients admitted in an Italian internal medicine or geriatric ward analyzing the use of drugs with anticholinergic properties and the cognitive and functional performance. In this study, cognitive performance was measured using short blessed test (SBT, higher scores indicate worse cognition) and functional performance was evaluated using Barthel Index (BI, higher scores indicate better functional performance, 100 being the maximum). The authors concluded that patients receiving drugs with anticholinergic properties have a mean SBT score of 8.9 (95% CI 8.4-9.3) which was significantly different from the mean SBT of 7.8 (95% CI 7.2-8.4;p=0.006) obtained by the patients not receiving drugs with anticholinergic properties.[14] Furthermore, Pasina et al. described that the patients treated with anticholinergic drugs have a mean BI of 82.4 (95% CI 80.8-84.0), which is 5 points lower than the 87.8 points (95%CI 85.9-89.7;*p*=<0.0001) obtained by the patients receiving no anticholinergic medication.[14]

In a follow-up study performed in Finland by Jyrkkä et al., a population of 294 elderly people was followed between 2004 and 2007, recording the use of medications and the cognitive function of participants.[16] Regarding polypharmacy, they observed that from 294 participants, 154 (52.4%) were using at least 6 medications concomitantly in 2004, and that by 2007 the number of participants using 6 or more medications

increased to 192 (65.3%). Furthermore, the authors observed that excessive polypharmacy, defined as the concomitant use of 10 or more medications, was associated with a decline in the cognitive capacity measured by MMSE (mini-mental state examination) compared with the non-polypharmacy group.[16] In particular, they observed that from the 154 with polypharmacy (5 or more concomitant medications), 60 (38.96%) had impaired cognition at baseline, and at follow up, from the 192 participants with polypharmacy, 87 (45.31%) were found to have impaired cognition.[16] In particular, they observed that the group with excessive polypharmacy had lower MMSE scores at baseline compared with the non-polypharmacy group ($p=0.020$) and that this difference remained significant over the three-year follow up ($p<0.001$).[16]

COGNITIVE IMPAIRMENT

It has been estimated that without changes in mortality or new effective prevention strategies or curative treatments, the number of affected people with dementia will double every 20 years reaching 81.1 million people by 2040.[17] Mild cognitive impairment (MCI) or Cognitive Impairment non dementia (CIND)[18] is a syndrome defined as cognitive decline greater than that expected for an individual's age and education level but that does not interfere notably with activities of daily life.[19] In addition, it differs from dementia, in that the cognitive impairment in dementia is more severe and widespread and has a substantial effect on daily function.[19] However, it has been described that a percentage of the cases of MCI evolve to dementia or Alzheimer's Disease (AD) [19, 20], which emphasizes the importance of studying MCI.

In general terms, Gauthier et al. described in 2006 that previous studies described a prevalence of MCI in the general elderly population between 3% and 19%, with an

incidence of 8-58 per 1000 per year, and a risk of developing dementia of 11-33% over 2 years.[19]

In a more recent study, Plassman et al. used the data from the "Aging, Demographics and Memory Study (ADAMS study)", which is a longitudinal study that includes individuals from all regions in the US, to estimate the incidence of CIND and the progression of CIND to dementia during the follow up period.[18] The researchers found that the amount of participants who evolved to dementia from CIND was less than 50%.[18] Their results indicated that the incidence of CIND is 60 cases per 1,000 person-years.[18]

Factors that affect cognition are depicted below in a directed acyclic graph (Figure 1). In the studies performed regarding MCI, it has been found that higher age, history of a diagnosis of hypertension, ethnicity and lower education are significant risk factors in the development of the condition.[17, 21] In a study performed in elderly women in which lifestyle factors and comorbidities were evaluated regarding the development of cognitive impairment, results concluded that lifestyle risk factors, comorbid disorders and genetic factors contribute to the development of age-related cognitive impairment.[22] In particular, Rasmusssen et al. noticed that obesity and depression were significantly associated with cognitive impairment, with OR values of 1.54 (95% CI=1.00-2.36) and 3 (95% CI=1.28-7.06), respectively.[22]

Deficits in executive function, as compared to other cognitive domains, have been associated with decrease status and decrease ability for older individuals to carry out activities of daily living.[23] Thus, cognitive impairment and dementia are strong predictors of incident disability.[24] Among other factors that can be associated with

cognitive impairment, it has been described that higher years of education may have a protective effect on cognitive decline.[17] Related with education, it has been described that lower SES is associated with higher risk of MCI or CIND. Sattler et al. studied the differential effect of cognitive leisure activities, education and socioeconomic status on the development of MCI and Alzheimer's disease using a cohort recruited for the ILSE (German acronym for Interdisciplinary Longitudinal Study of Adult Development) study, which is comprised by people born between 1930 and 1932, and doing 12 years of follow up.[25] Their results show that high SES was associated with a 69% reduced risk of developing MCI/AD compared with low SES (OR=0.31, 95%CI 0.14-0.73, $p<0.01$).[25]

Smoking and alcohol consumption have also been found to be associated with cognitive impairment, however, these associations are still ambiguous.[26] Okusaga et al. studied the possible connection between cardiovascular risk factors, such as smoking, and cognitive function. Their results shown that being a smoker was significantly associated with worse cognitive performance on all the cognitive function tests performed (MMSE, Trail making test, digit symbol substitution, among others) except for the verbal fluency test.[27] Furthermore, Huang et al. studied the association of cognitive impairment with different habits such as smoking in a population of Chinese 90 years and older. However, their results show that current smoking habits had a significant OR for cognitive impairment only among men (2.1, 95% CI=1.2-4.0).[28] Supporting the lack of association between smoking and cognitive impairment in women, Rasmussen et al., who studied cognitive impairment among elderly women, found that smoking was not significantly associated with cognitive impairment.[22]

It has been described that heavy drinking may induce cerebral blood flow reduction, brain shrinkage, neuron apoptosis, and synapse loss, all of which may lead to evident cognitive decline.[29] However, research has also shown that light moderate alcohol use may reduce the risk for cognitive impairment.[29] Rasmussen et al. found that consumption of alcohol, particularly medium to moderate consumption, was associated with a decreased risk of cognitive impairment ($p=0.01$) and that the relation between amounts of alcohol consumed and risk for cognitive impairment produced a U-shaped curve. Xu et al. found that moderate drinkers, defined as those who had consumed no more than two drinks a day for at least 6 months, had the smallest decrease of MMSE score (2.9 ± 4.0) and heavy drinkers, defined as those who consumed more than two drinks a day for more than 6 months, had the largest decrease in MMSE score (8.6 ± 6.6) during a 2 year follow up study.[29]

It has also been described that an increased number of comorbidities is associated with increased risk of cognitive impairment. Gallucci et al. in a longitudinal study following the elderly population of the municipality of Treviso, Italy, found that an increased Charlson Comorbidity index was associated with a decline in cognitive function (univariate analysis with a p-value $=0.008$)[30] However, additional research has shown that specific diseases are independently associated with cognitive impairment. Among these diseases are hypertension [26, 31], depression [31, 32] and diabetes.[26]

Regarding the association between hypertension and cognitive decline, cross-sectional studies have reached divergent results, while most longitudinal studies performed have demonstrated a significant association between hypertension and cognitive decline.[26]

Depression, as mentioned before, has also been independently associated with mild cognitive impairment and dementia. Several studies have shown that subjects with depression had higher risk of cognitive decline or of developing any dementia.[31-33] One of this studies (Scuteri et al), was a cross-sectional study of 6180 Italian elderly patients admitted to a hospital network. They found that patients with depression have an OR of 2.70 (95% CI 2.33-3.13, p-value= 0.002) for cognitive impairment compared with not depressed patients, and that patients with depression and hypertension have an OR of 2.69 (95% CI 2.21-3.29, p-value= 0.001) of having cognitive impairment compared with normotensive non depressed patients.[31] On the other hand, Scuteri et al., also found that patients with depression and with depression and hypertension have an OR of 2.71 (95% CI 2.34-3.13, p-value= 0.001) and 1.95 (95% CI 1.59-2.40, p-value= 0.001) of having a lower functional independence regarding the non-depressed patients and those normotensive and non-depressed patients.[31]

A diagnosis of diabetes mellitus has also been independently associated with increased risk of cognitive impairment.[26] Recent studies have demonstrated that longer duration of diabetes, lack of anti-diabetic medication, and higher number of hypoglycemic episodes were associated with an increased risk of cognitive decline.[26]

Physical activity has been associated as a protective factor against cognitive impairment in elderly.[26] Hung et al., who studied the impact of lifestyle habits on cognitive function of Chinese people 90 years and older, found that current exercise was a protective factor against cognitive impairment (unadjusted OR 0.337, 95%CI 0.180-0.675 for men).[28] Rassmussen et al. found that among women exercise has a dose-

dependent and inverse relationship with cognitive impairment, with an OR for the group that exercises of 0.54 (95% CI=0.37-0.81) regarding the group that doesn't.[22]

Another association that is worth analyzing is the one between Body Mass Index (BMI) and cognitive impairment.[30] One of this studies showed that women with a BMI of 27.5 or greater have an OR of 1.54 (95%CI=1.00-2.36, p=0.04) of having cognitive impairment that women with lower BMI.[22] Furthermore, Galluci et al. found that higher BMI acts as a protective factor against cognitive impairment, however, they also found that the interaction between BMI with age was significant, and that the positive effect of the high BMI decreased as the age of the individual increased.[30]

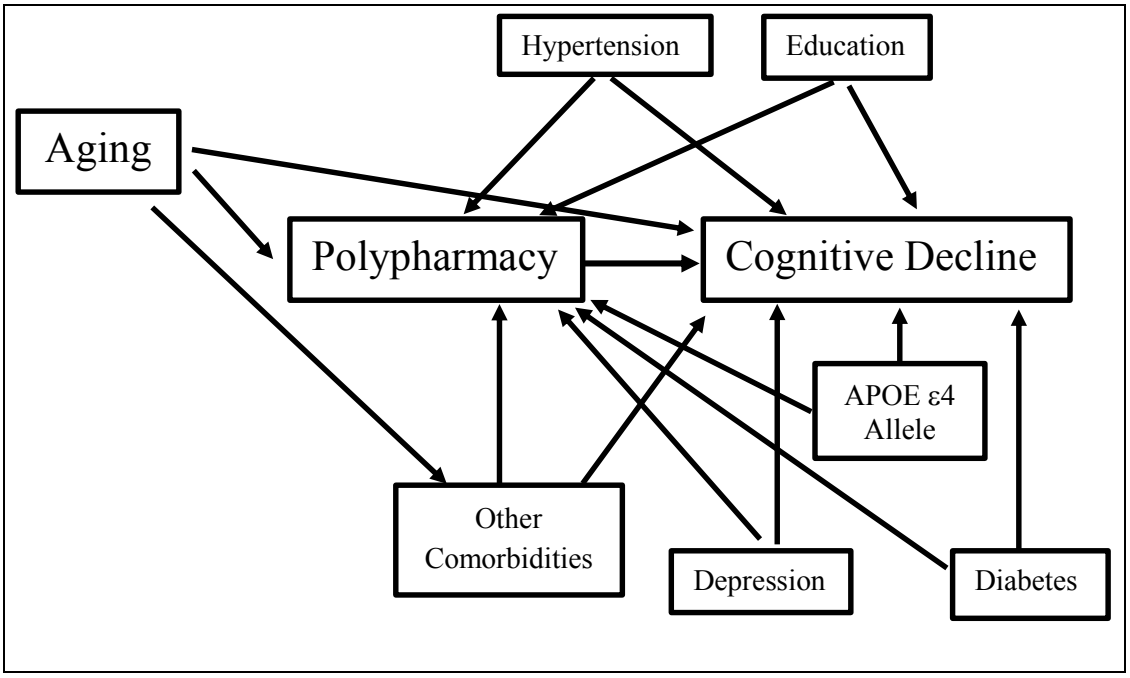
Finally, Apolipoprotein E (APOE) is a glycoprotein involved in the transport of cholesterol and lipids through cell membranes, and it is thought to be involved in cell growth and neuronal regeneration in the brain.[34, 35] The APOE genotype has 3 polymorphisms determined by 3 alleles, ε2, ε3 (the most common and the one considered as the normal polymorphism) and ε4.[34-38] From these 3 polymorphisms, the presence of allele ε4 has been associated with a higher risk of mortality, cardiovascular disease, AD, dementia and cognitive decline, among other adverse effects.[37, 39, 40] On the other hand, allele ε2 has been associated with decreased risk of mortality, dementia and levels of cholesterol.[40, 41]

All the age-related changes mentioned above, as well as the use of different and multiple inappropriate drugs in elderly patients, can affect the cognitive status of an elderly person in the different cognitive domains also affecting the functional independence of that person.[24].

The loss of functionality and cognitive decline will come with an increase in the cost of living and healthcare for this population. According to the published data it is estimated that by 2030, the population 65 and older will represent 20% of the US population and 50% of healthcare costs. [7]

Considering the dearth of scientific studies analyzing the effects of polypharmacy and potentially inappropriate medications on cognitive decline, and particularly in the American population, this study seeks to use previously collected data to further investigate the effects of these exposures and other possible factors on cognitive status changes.

Figure 1: Directed acyclic graph (DAG) based on the information obtained from the literature



METHODS

I. Population

The population studied is a subset of the New Mexico Aging Process Study (NMAPS), which was initiated in 1979 as a longitudinal study of nutrition and aging. The study annually monitored the nutritional status of participants through measurements of dietary intake, biochemical parameters, anthropometry, body composition and cognitive and functional status.[42]

The inclusion criteria for the NMAPS was that the study subjects must be 60 or older, free of major medical conditions, and living independently[43]. This population was defined as "healthy" because the participants did not present clinical conditions and were not taking prescription medication with 2 exceptions, specifically thyroid replacement therapy and antihypertensive medication to control systolic blood pressure initially <180 mm Hg or diastolic pressure <100 mm Hg.[44] These inclusion criteria were only applied to the subjects when entering the study, and NMAPS participant were not required to maintain good health to continue in the study. Exclusion criteria include serious clinical conditions, such as recent myocardial infarction, significant peripheral vascular disease, insulin-dependent diabetes, hepatic disease, history of cancer requiring surgery, radiotherapy or chemotherapy in the past 10 years and untreated hypertension.[45]

NMAPS was initiated with the recruitment of 303 volunteers to participate in a study examining the relationship between nutrition and immune function, and this subsequently evolved into a multidisciplinary, longitudinal study examining the impact of

nutrition on resultant changes in body composition and organ function in relation to the aging process and health status of the elderly.[44] During the study, new recruits replaced those who may have died or dropped from the study.[45]

NMAPS subjects were seen annually at which time they underwent assessment for cognitive, sensory and physical function (including blood sampling), health habits and attitudes, morbidity, falls, dietary intake, physical activity, body composition and nutritional status.[45] Information on health status and comorbidities were ascertained by physical examination (including pulse, blood pressure, height and weight measurements[45]) and medication use.[46] Cognitive function was assessed using Mini mental state examination (MMSE), the geriatric depression scale (GDS), Wais R digit span, Fuld object memory evaluation, Color trails 1 and 2 and clock drawing[45]. Apolipoprotein E genotype was assessed using restriction fragment length polymorphism analysis of polymerase chain reaction products.[47]

Since 1980 approximately 40 subjects developed Alzheimer's disease or other dementia and follow up was discontinued because it was no longer possible to obtain competent informed consent.[45] The average dropout rate was 4.2% per year.[45]

In order to fulfill the objectives of the present study, data were utilized from participants who had cognitive evaluations, particularly, those participants for who the MMSE scores were available. Data from participants whose information regarding education was missing were excluded from the analysis. The same was done for those participants for whom the information regarding polypharmacy was missing. Thus, the final sample consisted of 572 participants, and 2955 observations.

II. Exposure variable(s) assessment and definition

Polypharmacy was defined as the concomitant use of 5 or more medications. The evaluation consists of the simple count of prescribed and over the counter (OTC) medications. Medications were self-reported during each year the participant was interviewed. Therefore an individual may be classified as having polypharmacy some years but not others in this longitudinal dataset.

III. Outcome variable(s) assessment and definition

The changes in cognitive function were evaluated using the Mini Mental State Examination. The MMSE is a short test that evaluates the different domains of cognition and is a simplified, scored form of the cognitive mental status examination [38]. The MMSE includes 11 questions, and requires 5 to 10 minutes to administer [48]. It was designed to concentrate only on the cognitive aspects of mental function, excluding questions concerning mood, abnormal mental experiences and the form of thinking [48].

Between the years of 1989 and 1993, the standardized version of the MMSE was applied, however between 1994 and 2003 a modified MMSE was applied in NMAPS. Therefore, data were cleaned and recoded where necessary to conform to the standardized Mini-Mental State Evaluation [48].

Literature described a cutoff score between 22 and 25 for people with more than 8 years of education to define cognitive impairment. [49, 50] For this reason, the cutoff score to define MCI in the present study was a MMSE score ≤ 23 points.

IV. Covariate assessment and definitions

The covariates that were analyzed to minimize confounding include sex, ethnicity, marital status, housing, working status, education level, Charlson Comorbidity Index,

presence of hypertension, presence of diabetes, presence of depression, presence of APOE ε4 allele and BMI. These were selected because have been previously associated with cognitive decline, mild cognitive impairment and/or polypharmacy. [16, 25, 30, 33]

The Charlson Comorbidity Index[51] was used to categorized the health status of the patients. The data were categorized as follows:

- Charlson comorbidity Index=0
- Charlson comorbidity Index=1
- Charlson comorbidity index ≥2

This categorization was made based on the sample distribution, and considering that the number of participants with a Charlson index score of 2 or more was small, they were all grouped in one category.

In addition to the above, as a second covariate to evaluate health status, we used living situation, which was defined as a dichotomous variable in which the participant was or was not institutionalized.

Education was analyzed as a categorical covariate. The participants were asked for their highest level of education. The data were divided in the following categories:

- 12 or less years of education
- between 12 and 16 years of education
- more than 16 years of education

The presence or absence of Apolipoprotein E ε4 allele in the participants was also included as a covariate, because as mentioned before, it has been associated with higher risk of AD and cognitive decline. The covariate was analyzed as a dichotomous variable, considering the presence or absence of at least one ε4 allele

Hypertension and diabetes were treated as a dichotomous variable, evaluating the presence or absence of the diagnosis. Diagnosis data was obtained from participant's self-report and physical examination.[46]

Depression was assessed in two ways. The GDS was applied during the NMAPS; in this case the variable was defined as dichotomous where if the GDS score was greater or equal than 5 the participant was considered depressed. The second was using the presence or absence of a depression diagnosis according to the medical history obtained by interviewing the participant.

It has been described that greater involvement in physical, intellectual and social activities have a protective role in the development of MCI.[52] In order to evaluate the participation of the study subjects in these activities, the working status covariate was used. This was defined as a dichotomous variable in which the participant was employed or doing volunteer jobs at the moment of the interview or not.

The NMAPS categorized marital status as married, divorced, widowed or never married. However the number of subjects in all the categories except "married" was small, therefore, all the categories that implied that the participant was alone (i.e., divorced, widowed or never married) were merged together in one category. Therefore, marital status was analyzed as a dichotomous covariate.

Body mass index (BMI) was categorized as follows, according to the categories defined by the World Health Organization (WHO):

- BMI < 25 (normal weight)
- 25≤BMI<30 (overweight)
- BMI≥ 30 (obese)

V. Statistical Analyses

To compare the unadjusted differences between groups of participants with and without polypharmacy, T-tests were applied for continuous variables and χ^2 for categorical variables. When a cell count is smaller than 5, Fisher's exact test was applied.

The data from the study are longitudinal, and therefore data were collected over a span of several years for each participant (range: 1 to more than 10 years). To account for the correlation of measurements across time within each subject, a random effects mixed model was used, with a random effect for subject. This mixed linear model was used to evaluate the hypothesis described above as well as include the mentioned covariates as fixed factors or effects.

In order to define which covariates should be included in the model, a model was run including all the covariates and removing one at a time and if the change in the estimate for polypharmacy was greater than a 10% then the covariate was included in the final model.

The covariates diabetes, depression and housing were not included in the covariate assessment process because the sample sizes were not adequate.

The mixed effects model was implemented using the SAS Proc Mixed procedure, which can perform linear regression for longitudinal data using both fixed and random effects. MMSE scores were modeled as a function of presence or absence of polypharmacy as well as covariates including age at baseline, years since baseline, and other covariates as determined by the covariate selection process above.

Generalized estimating equations (GEE) were applied using the SAS Genmod procedure, which allows regression of dichotomous outcomes for repeated measures, considering the correlation of multiple observations within subjects.[53]

VI. Power calculations

The power to detect an association between polypharmacy and MCI was 62.74%, considering the following:

- Cohort study design
- Total sample population of 572 for the analysis of polypharmacy
- Alpha level of 0.05
- An exposure to polypharmacy of 39.5%
- A risk of MCI of 3.98% among those exposed to polypharmacy; and
- A risk of MCI of 8.96% among those unexposed to polypharmacy

The power to detect a difference of 1 point in the means between the MMSE scores at the first and last evaluation is >99%, and to detect a difference of 0.5 points is 91.04%, taking into consideration the following:

- Sample size of 572 individuals
- Variance for MMSE score at baseline of 4.75
- Variance of MMSE score at endpoint of 8.35

The power calculations were conducted using OpenEpi software.[54]

RESULTS

I. Population characteristics

Most of the study subjects were female (63.6%), white (88.5%), and married (66.6%) (Table 1). In addition, 47.2% of the study population had between 12 and 16 years of education and 36.2% had more than 16 years of education.

The average number of medications for the population was 2.4 at first evaluation and 4.1 at the last evaluation; however the number of medications ranged from 0 to 16 and the prevalence of polypharmacy at baseline and endpoint was 14% and 40%, respectively. The overall prevalence of MCI in the study population was 4.6% and 7% at baseline and endpoint, respectively (Table 2).

From a comorbidity perspective, the majority of the sample studied was non-diabetic, normotensive, non-depressed (although the GDS scores indicated that most of the sample have depressive symptoms), had normal weight and a Charlson comorbidity index of 0, which indicated that the majority of participants of this study were generally healthy (Table 2).

Participants with polypharmacy were mostly women with normal weight, had between 12 and 16 years of education and had a Charlson comorbidity index higher than 0. Furthermore, the majority of the participants with polypharmacy were not diagnosed with depression nor hypertension (Table 3).

In the same way, participants with MCI represent a small percentage of the sample, and they were mostly females with normal BMI, had more than 12 years of

education, did not have hypertension, and had a Charlson comorbidity index equal or higher than 2 (Table 4).

II. Covariate assessment results

The results of the covariate assessment indicated that sex, presence or absence of APOE ε4 allele, BMI, presence or absence of hypertension, and Charlson index were confounding covariates, and therefore, should be included in the multivariable models.

III. Unadjusted analyses

The bivariate analysis shows that the group with polypharmacy had a significantly higher MMSE score than those with no polypharmacy at baseline and at the final evaluation. There was no significant difference in the change of the MMSE score between those with polypharmacy and those without it (Table 5).

The association between MCI and polypharmacy was significant both at baseline and the endpoint evaluation; however when looking at the sample distribution, MCI was more common among those with no polypharmacy than among those with polypharmacy (Table 5).

Furthermore, the analysis of the MMSE scores among those who changed polypharmacy status from non-polypharmacy to polypharmacy, compared with those who didn´t change polypharmacy status was significant, showing a higher MMSE score for those who changed status to polypharmacy (Table 6).

IV. Adjusted Analyses

When the mixed multivariable-adjusted model was run, polypharmacy was associated with a decreased MMSE score, although the association was not statistically

significant. Age at baseline was associated with a significant decrease in the MMSE score by 0.047 points per each additional year of age. Furthermore, a higher Charlson comorbidity index was significantly associated with a lower MMSE score, while the presence of hypertension was significantly associated with a higher MMSE score (Table 7).

Consistent results were observed when the outcome was replaced by the change in the MMSE score (MMSE at final evaluation – MMSE at baseline). Age and a higher Charlson comorbidity index were significantly associated with a higher decline in the score and hypertension was associated with a lower decline in the MMSE score. (Table 8)

In the analysis of MCI as an outcome, the direction of the estimates were consistent with the MMSE analysis (Table 9).

DISCUSSION

The analysis performed showed a high prevalence of polypharmacy in a relatively healthy population, but a low prevalence of mild cognitive impairment. Polypharmacy was associated with lower MMSE scores in this population, and although the association was not statistically significant, the direction of effect suggests that polypharmacy could be an important factor in cognitive decline. Other notable findings include the effects of male gender, Charlson comorbidity index greater than 0 and the presence of APOE ε4 allele on cognitive decline, even though only Charlson comorbidity index reach statistical significance. Furthermore, hypertension was significantly associated with higher MMSE scores. These results were consistent with the analyses done for both MCI and for change in MMSE score over time.

The prevalence of polypharmacy increased over the follow-up period, and this was positively associated with an increase in the MCI rates, although the association did not reach statistical significance. However, a very low proportion of the sample did have both polypharmacy and MCI (0 and 1.57% at baseline and endpoint, respectively), which is reflected in the power to detect this association (62.74%), leaving a 37.26% chance of a type II error, if there is truly an association. Similarly, the MMSE scores were significantly higher in participants with polypharmacy than participants without polypharmacy both at baseline and at the endpoint evaluation (p-value= 0.009 and 0.0002 respectively). A reason for this may be that participants with polypharmacy have higher basal and final MMSE scores than participants without polypharmacy, however patients

with polypharmacy have a more pronounced decreased in the MMSE score over the follow up period than participants without polypharmacy.

When comparing the results from the unadjusted versus the adjusted analysis, it is possible to observe that the association between polypharmacy and MMSE scores are in the opposite direction; while the unadjusted cross-sectional analyses both at baseline and at the final exam indicated that patients with polypharmacy have higher MMSE scores, the adjusted longitudinal analysis shows that polypharmacy is associated with a decrease in MMSE scores over time This demonstrates the importance of considering a baseline MMSE score in order to evaluate the effect of an specific exposure, in this case polypharmacy, on the outcome of interest, in this case MMSE score, MMSE score change and MCI.

The observed prevalence of MCI in the studied population was about 7% at the last evaluation performed, lower than the prevalence described by the literature which can be up to 20%.[19] The low prevalence of MCI in this sample could be explained by the fact that higher education has been described as a protective factor for MCI and cognitive decline in elderly people[17, 25], and the sampled population was highly educated, with more than 80% of the sample having more than 12 years of education and 36.19% having more than 16 years of education.

The results obtained by the present study are consistent with those obtained by Jyrkka et al, whose study reported that polypharmacy and male sex are associated with a lower MMSE score[16]. Furthermore, the present study showed that a CCI equal or higher than 2 is significantly associated with lower MMSE scores and cognitive impairment, which is consistent with the results obtained from Scuteri et al, whose findings indicate

that the number and severity of comorbidities are negatively associated with cognitive impairment.[31]

In the present study hypertension was found to be associated with significantly higher MMSE scores and smaller changes in MMSE scores, while previous studies have found that hypertension has a negative impact on cognitive performance.[27, 31] However, it has been described that the treatment of hypertension can act as a protective factor for cognitive decline and MCI/dementia. In a review done by Duron and Hanon (2008), it was described that even though hypertension has been positively correlated with cognitive decline and dementia, treated hypertensive subjects have a decreased in cognitive decline compared with those untreated.[55] This is potentially consistent with the results obtained from the multivariable regression models, wherein it was observed that hypertension was significantly associated with increasing MMSE scores and significantly decreasing MCI. If the 'non-hypertensive' group in this study actually includes some individuals with undiagnosed hypertension, our study results would be consistent with those summarized by Duron and Hanon.

From the results obtained it is possible to suggest that polypharmacy is a risk factor for cognitive decline and MCI; however further research regarding the drugs used by older people is necessary to establish whether the number of drugs the risk factor or if it is a specific drug or group of drugs the responsible for the cognitive impairment. In this regard, it has been described that anticholinergic drugs and other drugs categorized as PIM are highly associated with cognitive impairment, whereas other categories of drugs have not shown an association. [56] In this regard, it is important that future research take into consideration that drugs can have a negative or positive impact on the cognitive

performance of a subject by direct or indirect pathways, or not have any impact at all, which makes even more important not to study the drug use in this population only by the number of drugs used, but also by the type of drugs. This approach may be potentially helpful in the clarification of confusing results, such as the ones obtained by the unadjusted analysis. Furthermore, it is important to take into account that patients without polypharmacy may have undiagnosed and/or untreated diseases that are negatively impacting their cognitive performance.

In addition to the above, the impact of polypharmacy in an elderly patient will vary depending on the his/her physical condition, particularly because it is known that the process of absorption, distribution, metabolism and excretion, undergo modifications associated with aging, and this can complicate the ability of elderly people to clear the drugs they are receiving, with a different degree in each patient. However, the more drugs the patient is receiving, the more likely it is to observe an adverse drug event, such as cognitive impairment. [6, 7, 9] This, is another important reason why future research should involves specific drug analysis, such as PIM, or ACB, into its aims.

One of the strengths of the present study, is that due to the high homogeneity of the studied population, the internal validity of the study is high, decreasing the chances of bias or systematic error.[57] Another strength of the study, was the availability of data from a longitudinal study with a long time span, which allows to evaluate the evolution of the cognitive performance of the study subjects. Finally, the fact that the data available comprised data on APOE genotypes for most of the subjects as well as other covariates such as hypertension, BMI and education level, allowed the incorporation and analysis of

these covariates, minimizing confounding and allowing comparison with other studies that were also able to adjust for these factors.

Part of the homogeneity of the population is the health status of the studied sample, where the prevalence of diabetes in the studied sample (0.53%) was much lower than the 26.9% prevalence described for Americans older than 65 years old.[58] Furthermore, the prevalence of hypertension in the studied sample was of 34.45% while the prevalence of hypertension described for Americans 65 or older is 71.6%.[59] The prevalence of obesity observed was of 10.53% which is lower than the 35% of adults 65 or older described for US population[60]. All this information demonstrates that the sampled population was unusually healthy compared with the general American population.

In this same regard, according to the U.S. Department of Health and Human Services Administration of Aging, the percentage of older people that completed high school rose from 28% to 71% between 1970 and 2003. Approximately 83% of the sample studied had completed a high school education, and taking into consideration that the recruitment process was between 1979 and 2003, it is possible to establish the this sample was highly educated compared with the general American population.

An analysis of the association between potentially inappropriate medication and cognitive decline was attempted, with an attempt to define the number of PIM according to 2012 Beers criteria for each participant in order to obtain a number of PIM and use it as an exposure instead of polypharmacy. However, after thorough analysis of the data available, the way the drugs were coded did not allow for a drug-specific analysis, which is needed for a proper analysis of Potentially Inappropriate Medication or for

Anticholinergic Cognitive Burden scale. Drugs were coded using the AHFS pharmacologic therapeutic classification, which was developed by the American Society of Health System Pharmacists to improve the organization of drug formularies in institutional or governmental settings. The code allows a hierarchic classification in 4 tier categories considering the pharmacological, therapeutical or chemical properties of the compound[61]. One of the disadvantages of this classification system is that some drugs can have multiple classes, which represent a problem when trying to analyze specific drugs. In addition to the multiple classes per drug, the NMAPS used just the first 3 tiers to code the name of the drugs, so instead of obtaining a drug name, the code only gives a classification, for example antibacterials, bile acid sequestrants or antiarrhythmic agents. Therefore, the coding of the data did not allow for a deeper analysis of the drugs prescribed to the participants, which would have help to give some light regarding the utilization pattern of drugs among elderly population in America.

A better classification system to use for coding drug names is the Anatomical Therapeutic Chemical (ATC) classification system. This code was developed by the WHO Collaborating Centre For Drug Statistics Methodology to be use in drug utilization statistics[62]. For this reason, this code is the appropriate one to develop drug utilization studies.

Among the limitations of the study, it is possible to point out that the population studied was predominantly white, female, and well educated, which makes this population very homogeneous and not necessarily generalizable to other populations in the U.S. or around the world.

MMSE was designed as a screening tool and therefore is a brief and fast tool to evaluate patients, which makes it a very good tool to apply in a research study; however it does not gives you a definitive diagnosis, which should be achieved by the application of several specific tests and the analysis of a trained professional. Nevertheless, this does not invalidate the results of the study, MMSE is still a validated tool to detect alterations in cognitive performance, but it stresses the fact that for a deeper analysis of how drugs affect cognition, it would be important to perform a more specific study of cognitive function, for which obtaining specific diagnoses, differentiating the types of cognitive impairments or types of dementia may shed light on how to face the problems of patients suffering from these diseases.

As mentioned before, polypharmacy also may have an impact on the ability to perform activities of daily living, which leads to a loss of independence. For this reason it is important that future research not only study cognitive decline as an outcome, but also analyze how the exposure to drugs, measured as polypharmacy, PIM or other, affects the ability of elderly people to function as independent individuals. Additionally, the study of changes in the different cognitive domains due to aging, and how drug utilization affects them is still a pending subject, which would help improve drug safety and quality of life in the growing older population.

It is also important for future research to consider the use of validated and standardized tools when measuring cognitive and functional performance of elder individuals, rather than creating novel tools which lack validation in this population. Validated tools will give better quality results. Finally, in order to obtain comparable and

generalizable results, future studies must carefully plan the recruitment strategies to obtain a representative sample of older people.

CONCLUSION

The results obtained from the present study suggest that polypharmacy, Charlson comorbidity index, and the presence of APOE ε4 allele negatively affect the performance of older adults on the MMSE. Further studies are needed in order to establish the mechanism in which polypharmacy affects cognition, including the analysis of the impact of PIM and anticholinergic drugs on cognitive performance of older people. Additionally, the role of hypertension and anti-hypertensive treatment in cognitive performance should be further studied, considering that studies suggest that antihypertensive treatment could be an important tool to prevent cognitive decline. Finally, the present study further stresses the need of future characterization of the elderly population, from a demographic and health perspective, making special emphasis in the causes of dependence and decrease on quality of life, such as cognitive impairment.

TABLES

Table 1: Demographic characteristics of studied population at baseline

Variable	N	%
Age		
≤ 70 years old	152	30.71
71-80 years old	229	46.26
More than 80 years old	114	23.03
Missing	77	
Sex		
Men	208	36.36
Women	364	63.64
Education		
more than 16 years	207	36.19
12-16 years	270	47.20
12 or less years	95	16.61
Ethnicity		
White	314	88.45
Hispanic	29	8.17
Black	2	0.56
Other	10	2.82
Missing	217	
Marital		
Married	381	66.61
Divorced	44	7.69
Separated	4	0.70
Single/Never married	19	3.32
Widowed	124	21.68
Housing		
Independent	563	98.43
Institution	9	1.57
Currently working		
Yes	472	82.52
No	100	17.48
Apoe4		
Yes	331	64.90
No	179	35.10
Missing	62	

Table 2: Health characteristics of the population studied

	First Evaluation		Last Evaluation	
Age (Mean ±SD)	74.75±6.93		79.78±6.63	
Range	[60-96]		[65-99]	
N	495		494	
Nº of Meds (Mean ±SD)	2.43±2.29		4.10±2.88	
Range	[0-16]		[0-15]	
N	572		572	
Polypharmacy (N, %)				
No polypharmacy	491	85.84	346	60.49
Polypharmacy	81	14.16	226	39.51
MMSE_Score(Mean ±SD)	28.40±2.18		28.14±2.89	
Range	[12-30]		[3-30]	
N	572		572	
MCI (N, %)				
Present	26	4.55	40	6.99
Absent	546	95.45	532	93.01
BMI (Mean ±SD)	25.23±3.84		25.02±4.07	
Range	[17.15-40.18]		[15.05-41.82]	
N	539		513	
Normal	279	51.76	279	54.39
Overweight	203	37.66	180	35.09
Obese	57	10.58	54	10.53
Missing	33		59	
Depression (N, %)				
+ GDS	477	88.83	441	81.82
- GDS	60	11.17	98	18.18
Missing	35		33	
+ Diagnosis	24	4.20	31	5.42
- Diagnosis	548	95.80	541	94.58
Diabetes (N, %)			569	
+ Diagnosis	1	0.18	3	0.53
-Diagnosis	567	99.82	566	99.47
Missing	4		3	

Hypertension (N, %)				
+ Diagnosis	161	28.35	196	34.45
- Diagnosis	407	71.65	373	65.55
Missing	4		3	
Charlson Comorbidity Index (N, %)				
0	349	60.56	256	44.99
1	88	15.49	129	22.67
≥2	136	23.94	184	32.34
Missing	4		3	

Table 3: Description of population by polypharmacy status at the last evaluation

	No Polypharmacy		Polypharmacy		χ^2
	N	%	N	%	p-value
Sex					
Male	139	40.17	69	30.53	0.02
Female	207	59.83	157	69.47	
Education					
more than 16 years	127	36.71	80	35.4	0.59
12-16 years	158	45.66	112	49.56	
12 or less years	61	17.63	34	15.04	
Body Mass Index					
Normal (<25)	176	57.52	103	49.76	0.14
Overweight (25-30)	103	33.66	77	37.20	
Obese (>30)	27	8.82	27	13.04	
Diabetes					
+ Diagnosis	2	0.58	1	0.45	0.78 *
- Diagnosis	343	99.42	223	99.55	
Depression					
+ Diagnosis	12	3.47	19	8.41	0.01
- Diagnosis	334	96.53	207	91.59	
+GDS	268	82.97	173	80.09	0.40
- GDS	55	17.03	43	13.31	
Missing	33				
Hypertension					
+ Diagnosis	78	22.61	118	52.68	<0.0001
- Diagnosis	267	77.39	106	47.32	
Missing	3				

* Fisher's exact test

Table 4: Description of population by MCI status at the last evaluation

	No MCI		MCI		χ^2
	N	%	N	%	p-value
Sex					0.12
Male	183	35.5	19	47.5	
Female	343	64.5	21	52.2	
Education					0.62
more than 16 years	191	35.9	16	40	
12-16 years	254	47.7	16	40	
12 or less years	87	16.4	8	20	
Body Mass Index					0.002*
Normal (<25)	251	52.4	28	82.4	
Overweight (25-30)	176	36.7	4	11.8	
Obese (>30)	52	10.9	2	5.9	
Diabetes					0.8*
+ Diagnosis	3	0.6	0	0	
- Diagnosis	527	99.4	39	100	
Depression					0.6
+ Diagnosis	29	5.5	2	5	
- Diagnosis	503	94.5	38	95	
					0.16*
+GDS	408	81.3	33	89.2	
- GDS	94	18.7	4	10.8	
Missing	33				
Hypertension					0.02
+ Diagnosis	189	35.7	7	17.9	
- Diagnosis	341	64.3	32	82.1	
Missing	3				
Charlson Comorbidity Index					0.07
0	245	46.2	11	28.2	
1	119	22.5	10	25.6	
≥2	166	31.3	18	46.2	
Missing	3				

* Fisher's exact test

Table 5: Unadjusted associations between polypharmacy and measures of cognitive decline.

	No Polypharmacy[a]	Polypharmacy[a]	P-value
MMSE Score			
Baseline[b]	28.33±2.26	28.85±1.53	0.009
Final[c]	27.80±3.22	28.66±2.19	0.0002
MMSE Score delta[d]	-0.35±3.27	-0.08±0.40	0.28
MCI (baseline)			0.017[e]
Absent	465	81	
Present	26	0	
MCI (final)			0.02
Absent	315	217	
Present	31	9	

[a] Polypharmacy is defined as the concomitant use of 5 or more medications
[b] at the moment the first MMSE performed.
[c] at the moment of the last MMSE performed.
[d] Change in MMSE score from baseline to final evaluation.
[e] Fisher's exact test

Table 6: Unadjusted associations between change in polypharmacy status and MMSE score.

Variable	No Change in Polypharmacy Status[a]	Change in Polypharmacy Status[b]	p-value
MMSE Score (final)	27.97±3.06	28.60±2.32	0.0079
MMSE Score delta	-0.31±3.09	-0.06±2.63	0.32

[a] No change in polypharmacy status includes those participants who did not change their polypharmacy status during the follow up and those who changed from polypharmacy to no polypharmacy.
[b] Change in polypharmacy status only includes those participants who changed from no polypharmacy to polypharmacy.

Table 7: Mixed multivariable linear model results examining the effect of polypharmacy on MMSE score. *N=439*

Covariates	**β**	**SE[a]**	**P-value**
Polypharmacy	-0.11	0.092	0.23
Gender			
Male	-0.15	0.10	0.14
Female	0		
Age at baseline	-0.045	0.0079	<0.0001
Charlson comorbidity index			
≥2	-0.22	0.11	0.043
1	-0.065	0.13	0.62
0	0		
ApoE4 allele	-0.17	0.10	0.099
BMI			
Obese	0.048	0.15	0.76
Overweight	0.16	0.096	0.096
Normal	0		
Hypertension	0.22	0.10	0.033
Years since baseline	-0.024	0.016	0.13
MMSE score at baseline	0.34	0.027	<0.0001

[a] SE=Standard error

Table 8: Mixed multivariable linear model results examining the effect of polypharmacy on the change in MMSE score. *N=439*

Covariates	**β**	**SE[a]**	**P-value**
Polypharmacy	-0.12	0.092	0.20
Gender			
Male	-0.14	0.10	0.17
Female	0		
Age at baseline	-0.047	0.0079	<0.0001
Charlson Comorbidity Index			
≥2	-0.23	0.10	0.031
1	-0.065	0.13	0.62
0	0		
ApoE ε4 allele	-0.17	0.10	0.093
BMI			
Obese	0.046	0.15	0.77
Overweight	0.16	0.096	0.10
Normal	0		
Hypertension	0.22	0.10	0.031
Years since baseline	-0.024	0.016	0.14
MMSE score at baseline	-0.67	0.027	<0.0001

[a] SE=Standard error

Table 9: Multivariable GEE model results examining the effect of polypharmacy on probability of MCI. *N=439*

Covariates	**OR[a]**	**95% Confidence Limit**
Polypharmacy	1.94	(0.40, 9.43)
Sex		
Male	2.50	(0.52, 12.12)
Female (Reference)	1.0	(1.0, 1.0)
Age at baseline	1.11	(0.98, 1.25)
Charlson Comorbidity Index		
≥2	1.4	(0.21, 9.26)
1	0.90	(0.05, 3.32)
0 (Reference)	1.0	(1.0, 1.0)
ApoE ε4 allele	2.18	(0.48, 9.96)
BMI		
Obese	0.78	(0.08, 7.29)
Overweight	0.21	(0.04, 1.09)
Normal (Reference)	1.0	(1.0, 1.0)
Hypertension	0.12	(0.02, 0.65)
Years Since baseline	1.27	(0.91, 1.78)
First MMSE score	-0.40	(0.30, 0.52)

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CURRICULUM VITAE

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Education

University of Louisville, Louisville, KY **2012-present**

- MS in Epidemiology student at the School of Public Health and Information Sciences
    - GPA 3.815
    - Thesis: Cognitive decline and polypharmacy in an elderly population.

Universidad de Chile, Santiago, Chile **2007-2008**

- Professional Degree as Pharmaceutical Chemist, Universidad de Chile, *magna cum laude*
    - Thesis: "Evaluation of the prescription quality and its relation with the functionality in hospitalized elderly people".

Universidad de Chile, Santiago, Chile **2002-2006**

- Bachelor Degree in Pharmaceutical Sciences, Universidad de Chile

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Research Experience

University of Louisville, Louisville, KY **December 2012-September 2013**

Research Assistant for the National Children's Study

- Data Management, preparing databases on collected data

- Develop new methodologies to do a more efficient and more accurate data collection
- Translation of documents associated with the study

Universidad de Chile, Santiago, Chile **May 2005-August 2005**

Research Assistant for Toxicology,

- Develop the laboratory activities for Toxicology class. Practical experience related with inhibition of acetylcholine in the presence of parathion.

Teaching Experience

Harnecker Carey IP, Santiago, Chile **June-December 2011**

In-house Thesis Advisor

- Javiera Péndola Retamal
  - "Prosecution status analysis of the patent applications for a particular Harnecker-Carey's client, Carey y Cia's Intellectual property Area"

Universidad de Chile, Santiago, Chile **March -June 2008**

Teaching assistant for Clinical Pharmacology

- Guide students through clinical activities
- Evaluate oral presentations and written tests

Universidad de Chile, Santiago, Chile **March 2005-June 2006**

Teacher's assistant for Cellular Biology and Genetics,

- Prepare laboratory activities.
- Guide students through laboratory activities
- Evaluate written tests.

Work Experience

Harnecker Carey IP, Santiago, Chile **June 2008-July 2012**

Patent Specialist

- Analyze patent applications and prepare strategies to help pharmaceutical and food industries applicants to achieve the grant of said application.
- Occasional drafting of patent applications for local applicants and/or inventors in the field of life science.

- Occasional counsel on regulatory matters.

Universidad de Chile, Santiago, Chile **August 2007-December 2008**

Pharmacy Intern

- Performed Medication reconciliation and Independence/functionality evaluation at arrival of patients.
- Intensive pharmacotherapy follow up of elderly hospitalized patients and their progress during hospitalization, including functionality/independence evaluation during the hospitalization, and upon discharge.

University of California San Diego, San Diego, CA **March –June 2007**

Pharmacy Intern

- Pharmacy intern at the Internal Medicine and Abdominal Transplant Departments.
- Perform Medication reconciliation of hospitalized patients as well as outpatients.
- Pharmacotherapy follow up of patients during hospitalization, performing the proper interventions whit the medical team when necessary.
- Pharmacotherapy counseling and education for discharged patients and outpatients from transplant clinic.

Farmacias Cruz Verde, Santiago, Chile **December 2006-January 2007**

Professional Internship in retail/community pharmacy

- Patient counseling and education.
- Keeping up to date product stocks.
- Maintaining Control substance book updated.

Conference Presentations

National Children's Study Expanded Steering Committee Meeting, Washington, D.C.

Poster Presentation 2013

- "National Children's Study: Provider-Based Sampling: Recruitment Outcomes in Jefferson County" **Ximena Oyarzún Gonzalez,** Tiffany Robinson, Sharon Nuss, Bruce Gale, Irma Ramos, Jeffrey King, Deborah Winders Davis, David Tollerud,
- "National Children's Study Provider-Based Sampling: Healthcare Provider Influence and Recruitment Outcomes in Jefferson County", **Ximena Oyarzún Gonzalez,** Tiffany Robinson, Sharon Nuss, Bruce Gale, Irma Ramos, Jeffrey King, Deborah Winders Davis, David Tollerud

ISPOR 2nd Latin American Conference, Río de Janeiro, Brail

Podium Presentation 2009

- "Prescription of potentially inappropriate drugs in elderly hospitalized patients", Jirón M., Escobar L., Orellana S., Jara P., **Oyarzún X**., Arriagada L., Griñen H.
- Awarded as ISPOR best podium presentation

ISPOR 2nd Latin American Conference, Río de Janeiro, Brasil.

Poster Presentation 2009

- "Use of potentially inappropriate drugs in elderly patients hospitalized in an internal medicine unit at a university hospital", Escobar L., Jirón M., Orellana S., **Oyarzún X**., Arriagada L., Ruíz I., Martínez G., Dechent C., Carrasco VH., Biere A.

XII National Congress of Geriatrics and Gerontology, Santiago, Chile

Podium Presentation 2008

- "Characterization of the patients discharged from an Acute Geriatric Patients Unit". **Oyarzún X**., Jirón M., Escobar L.

XII National Congress of Geriatrics and Gerontology, Santiago, Chile

Poster Presentation 2008

- "Functionality evaluation and Prescription quality in elderly patients hospitalized in an Acute Geriatrics Patients Unit" **Oyarzún X.**, Jirón M., Escobar L., Martínez G., Dechent C.

Professional Memberships

- Society for Epidemiologic Research

Additional Skills

Languages

Fluent in written and spoken Spanish (native) and English (110/120 points in TOEFL, November 2013)

Computational

Proficient in: Microsoft Office (Word, Excel, Outlook, PowerPoint), pubmed.com, Cochrane database, Workspace, esp@cenet, Patentscope. Basic Knowledge of Microsoft Access and SAS

Activities

- Member of Scout Group. Started from young age and became a Scout leader in 2003. Leading the girls' group and teaching them responsibility and team work. (1992-2004)

- Member of School Volleyball Team (1995-2000)

References

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