SURVIVAL ANALYSIS FOR THE ASSOCIATION BETWEEN ANTI-HYPERTENSIVE MEDICATION AND TIME TO DEMENTIA WITH COMPETING RISK

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DEDICATION

This study is wholeheartedly dedicated to those who have offered me support and inspiration. To my teachers who have opened my eyes to see the beautiful research world; to my family who have supported me to achieve my life goal; to my classmates who shared their words of discussion; to my Church family who have provided me with spiritual encouragement. The fruit of this study is not only a paper, but also a better me, whom I dedicate to Jesus Christ, my forever Lord of life.

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Xinhua Flora Hu

SURVIVAL ANALYSIS FOR THE ASSOCIATION BETWEEN ANTI-HYPERTENSIVE MEDICATION AND TIME TO DEMENTIA WITH COMPETING RISK

Background: High blood pressure (HBP) is a common risk factor for dementia in elder population. Anti-hypertensive medications have been reported to associate with lower incidence rate of dementia in elder African Americans. The Apolipoprotein E (ApoE) ε4 allele has been shown to be associated with both increased dementia and hypertension risk. However, previous studies had not examined the association between anti-hypertensive medications by ApoE status accounting for the competing risk from death.

Methods: This is a prospective observational cohort study in 1236 community-dwelling hypertensive African Americans aged 65 years and older without dementia at baseline, with follow-up cognitive assessment and clinical evaluation for dementia diagnosis. Dementia-free mortality was considered as the competing risk. Of these, 707 participants were genotyped for ApoE status. Anti-hypertensive medication use was obtained from prescription records in the electronic medical records of the Indiana Network for Patient Care (INPC). Cox proportional cause-specific hazard (CSH) regression models were applied to assess the association between anti-hypertensive medication use and CSHs for dementia and death in ApoE ε4 carriers and non-carriers separately.

Key results: In ApoE ε4 carriers, participants using anti-hypertensive medications had lower CSH of dementia compared to those not on anti-hypertensive

medications before adjusting for blood pressure (BP) (hazard ratio (HR), 0.365; 95% CI, 0.170 – 0.785; $p = 0.0099$). The HR was no longer significant once BP control was adjusted (HR, 0.784; 95% CI, 0.197 – 3.123; $p = 0.7303$). Anti-hypertensive medications were not associated with dementia rate in non-carriers. In ApoE ε4 non-carriers, participants on anti-hypertensive treatment showed significantly lower CSH of death compared to those not on mediations adjusting for covariates and BP control (HR, 0.237; 95% CI, 0.149 – 0.375; $p < 0.0001$). There was no significant association between anti-hypertensive medication use and death in ApoE ε4 carriers.

Conclusions: Anti-hypertensive medication was associated with lower dementia rate in ApoE ε4 carriers and that rate was primarily mediated through BP control. In non-carriers, anti-hypertensive medication was significantly associated with lower mortality rate and this association appears to be independent of BP control.

Sujuan Gao, Ph.D., Chair

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LIST OF ABBREVIATIONS

AD	Alzheimer's disease
ANOVA	Analysis of variance
ApoE	Apolipoprotein E
BP	Blood pressure
CI	Confidence interval
CIF	Cumulative incidence function
CSH	Case-specific hazard
HR	Hazard ratio
DBP	Diastolic blood pressure
HBP	High blood pressure
SBP	Systolic blood pressure

Chapter One

Introduction

Dementia is a progressive degenerative brain condition with impairment in at least two neuropsychiatric or cognitive domains which are not explained by non-degenerative or primary psychiatric disorders [1]. Dementia is not a single disease, but a syndrome; its symptoms, including memory loss, difficulty in planning and organizing, etc., are common to several brain disease. Risk factors for dementia includes age, family history, gender (female), smoking, high blood pressure (HBP), and diabetes [2].

A common risk factor for dementia is hypertension, which is one of the most prevalent chronic diseases in older adults in the United States [3-5]. The age-adjusted prevalence of hypertension was 29% in 2011-2012 in U.S. adults, among which 76% were taking medication to lower their blood pressure (BP), and 52% had their BP controlled to below 140/90 mm Hg [6]. A recent meta-analysis of prospective studies showed both systolic blood pressure (SBP) and diastolic blood pressure (DBP) were positively correlated with the risk of dementia in the population aged ≥ 65 years in a dose-response fashion [7].

Hypertension prevalence is particularly high in African Americans [8]. The previous studies showed that anti-hypertensive medications were significantly associated with lower risk of incident dementia in older hypertensive African Americans through better BP control [9, 10].

Apolipoprotein E ε4 (ApoE ε4) gene is a major genetic risk factor for late-onset AD [11, 12] and hypertension [13, 14]. Hypertension and ApoE ε4 genotypes showed a synergistic effect on the acceleration of cognitive decline [15-18] and AD [19]. ApoE ε4

carriers who had HBP but not using anti-hypertensive medications had been shown to have elevated risk of AD dementia [20]. In previous studies including both ApoE ε4 carriers and non-carriers, the significant association between anti-hypertensive medication and dementia rate was no longer significant after adjusting for ApoE ε4 genotypes suggesting a potential role for ApoE in the relationship between anti-hypertensive medication and dementia rate [9, 10].

Death is an inevitable factor in cohort studies of elderly participants [21]. Since the study design uses periodic evaluation to determine dementia status, the occurrence of death precludes the determination of dementia status [22]. Loss to follow-up due to death would be non-ignorable when the exposure variable of interest, anti-hypertensive medication use in my research, may be associated with mortality. Including death into survival analysis as a competing risk reduces potential bias in the risk estimate of dementia [23, 24]. Cox proportional cause-specific hazard (CSH) regression model is appropriate for causal analysis in the presence of competing risks [25].

The current study performed survival analysis to estimate the association between anti-hypertensive medication and time-to-dementia, with death as a competing risk, in hypertensive ApoE ε4 carriers and non-carriers, respectively. In this competing risk setting, time to incident dementia and time to death without dementia are two competing survival outcomes, *i.e.* participants reach the endpoint for either of the two outcomes.

Chapter Two

Methods

The current study is a secondary data analysis using data collected as part of the Indianapolis-Ibadan Dementia Project [9].

Study population

The Indianapolis-Ibadan Dement Project was a prospective cohort study. This analysis uses the cohort from the African Americans in Indianapolis, U.S.A. In 1992, 2212 of the community-dwellings no younger than 65 years of age were recruited and enrolled. All participants underwent regular follow-up cognitive assessment and clinical evaluations by psychiatrists and neuropsychologists. Details of the cohorts have been described in the previous studies [9, 10]. Total of 1236 elder participants were included in this study. The study used a two-stage design, including a screening evaluation every 2 – 3 years followed by a more comprehensive home-based clinical evaluation of participants selected by stratified random sampling based on screening results. The diagnostic criteria for dementia is from both the Diagnostic and Statistical Manual of mental Disorders, Revised Third Edition (DSM-III-R) and the International Classification of Diseases, 10^{th} Revision (ICD-10) [9, 10].

Study endpoints

Baseline for each participant in this study was defined as the date of enrollment in the study. The primary study endpoint was the date of a dementia diagnosis for participants with incident dementia. The study endpoint of the competing risk was the

date of death for participants who had not been diagnosed dementia. The date of last IIDP evaluation was used for censoring.

Anti-hypertensive Medications

The prescription for anti-hypertensive medication on each participant were recorded during the period of study from his/her enrollment. The details for collecting prescription data were described in previous studies [9, 10]. Anti-hypertensive medications were categorized into classes of drugs used, as shown in previous study [9]. In the current study, I did not include the category of anti-hypertensive medication in the statistical model.

Blood pressure measures

All consenting participants were measured for BP records, starting from the second follow-up evaluation in 1997 for those enrolled in the 1992 cohort; Seated SBP and DBP were measured three times from the left arm by trained interviewers with Omron digital input/output units (Omron Healthcare Inc., Bannockburn, IL) at approximately 15-min intervals [9]. The average of the three measures were recorded for statistical analysis. An indicator variable was derived to indicate suboptimally treated BP (> 140 mmHg systolic or > 90 mmHg diastolic).

ApoE genotype

ApoE genotypes were determined by gene amplification and cleavage with Hhal, with the DNA samples which had been extracted under standard procedures from fresh

blood spots collected on filter paper, from the consent participants who enrolled in 2001 or before [9, 26].

Statistical Analyses

I compared participants' characteristics by dividing participants into three mutually exclusive groups: those who developed dementia, those who died, and participants censored for both events. One-way analysis of variance (ANOVA) and Fisher's exact tests were used for continuous variables and categorical variables, respectively, to compare the characteristics of participants among the three groups. I next categorized the participants into two groups: one is consisted of participants were prescribed anti-hypertensive therapy and the other is consisted of participants who were not. Similarly, one-way ANOVA and Fisher's exact tests were used for the comparison of the participant characteristics between the two groups.

I plotted cumulative incidence function (CIF) curves of dementia and of death, and then performed Gray's test to compare the CIFs over time between those received and those did not receive the anti-hypertensive medication. Gray's tests were performed in ApoE ε4 carrier and non-carrier participants, respectively.

I next plotted CIF curves of dementia and of death, performed Gray's test to compare the CIFs over time among the participants with well controlled BP, suboptimally treated BP, and missing value of BP, respectively.

Cox proportional cause-specific hazard (CSH) regression models were used to determine the association between anti-hypertensive medications and the hazard of dementia in ApoE ε4 carriers and non-carriers, respectively. Covariates include baseline

age, education, gender, and comorbid medical conditions. A second set of models included suboptimal BP control to determine whether association between medication use and dementia was mediated through BP control.

p-values smaller than 0.05 were considered statistically significant.

All statistical analyses were performed using the Statistical Analysis System (SAS) [Release Version 9.4, SAS Institute Inc, Cary, NC, US].

Ethics

Informed consents were collected from all study participants. The study was approved by the Indiana University-Purdue University institutional review board (IRB).

Chapter Three

Results

Comparisons of Participant Characteristics

Of the 1236 hypertensive participants who had not been diagnosed dementia at baseline, 114 (9%) developed dementia, 511 (41%) died without dementia, and 611 (49%) were censored for both events. In Table 1, I compared the demographic characteristics, ApoE genotypes, BP measures, and comorbid conditions of the participants who ended with dementia, death, and censored, respectively. The participants who developed dementia were significantly older at baseline (76.9 ± 6.9 years old) and at endpoint (84.8 ± 6.8 years old), comparing to the other two groups. There were significant differences on the years of education among the three groups, where the group developed dementia showed the fewest years of education (8.8 ± 3.3). Males are more likely to die rather than to develop dementia or to be censored, compared to females. The participants who developed dementia are more likely to contain ApoE ε4 allele (46.3%), comparing to the other two groups (p-value = 0.1012). Those died without dementia showed the lowest ratio of receiving anti-hypertensive medication (60.7%) and of chronic renal disease comorbid (1.8%); those developed dementia showed the highest ratio of heart comorbid condition (49.1%). The participants being censored showed the highest ratio of cancer comorbid condition (47.8%). No significant differences had been detected among the groups with respect to the remaining variables in Table 1.

In Table 2, I compared the demographic characteristics, the status of BP control, and the endpoints between the participants who received anti-hypertensive treatment and

who did not. Compared to those in the absence of anti-hypertensive treatment, the participants on anti-hypertensive medication showed bigger ratio of females (78.9% *vs.* 65.7%), greater burden of heart comorbid condition (49.3% *vs.* 30.2%), chronic renal disease (8.0% *vs.* 4.0%), diabetes (41.9% *vs.* 26.9%), atrial fibrillation (12.2% *vs.* 5.7%), and cancer (50% *vs.* 27.1%). The participants receiving anti-hypertensive treatment showed higher ratio of developing dementia (10.0% *vs.* 7.6%) or being censored (52.0% *vs.* 44.5%), but less likely to die (38.0% *vs.* 47.9%). The participants on anti-hypertensive medication showed better controlled BP than those not on anti-hypertensive medication (63.4% *vs.* 48.2%). The mean age at endpoint in those on anti-hypertensive medication were older than those not on anti-hypertensive medication (82.2 ± 6.4 *vs.* 79.2 ± 6.7 years).

Comparison of CIFs of Dementia and of Death over Time between the Participants with and without Anti-hypertensive Medication, in ApoE ε4 Carriers and Non-carriers

I used nonparametric model to compute the CIFs of dementia and of death over time. In ApoE ε4 carriers, the CIF curves of dementia over time apparently separated from about 5 years till the end of follow-up period between the participants with and without anti-hypertensive medication. Those received anti-hypertensive therapy showed smaller CIFs of dementia over time comparing to those did not receive (Fig.1A, $p = 0.1401$). The CIFs of death over time did not separate between those on anti-hypertensive medication and those not on anti-hypertensive medication (Fig.1B, $p = 0.4346$). In ApoE ε4 non-carriers, the CIF curves of dementia over time did not show unambiguous change attributed to the anti-hypertensive treatment (Fig.1C, $p = 0.2748$). The CIF of death over

time in those received anti-hypertensive therapy significantly decreased comparing to those did not receive therapy at any time point during follow-up (Fig.1D, $p < 0.0001$). Briefly, anti-hypertensive therapy apparently decreased the risk of dementia, not of death, in ApoE ε4 carriers. In ApoE ε4 non-carriers, anti-hypertensive therapy significantly decreased the risk of death, not of dementia. These results suggested the associations between anti-hypertensive medication and time-to-dementia or time-to-death could be very different between in ApoE ε4 carriers and in non-carriers.

Comparison of CIFs of Dementia and Death over Time among Participants with Different BP Control Status

I computed and compared the CIFs of dementia and of death among the participants with distinct BP control levels (Fig. 2). The CIF of dementia over time in those with good BP control were apparently lower than of those with suboptimally treated BP (Fig.2A, $p = 0.0962$). The CIF of death over time in the participants with good BP control significantly decreased compared to those with suboptimally treated BP (Fig.2B, $p < 0.0001$). The above results suggested the association between BP control and the risk of dementia or of death.

Interestingly, the participants with missing value of BP showed the highest values of CIFs of dementia and of death, comparing to the other two groups (Fig.2A – 2B). This result indicated the observations of BP were missing not at random (MNAR). How to model the missing data mechanism is a problem related to my study; however, it is beyond the scope of this Master thesis and I will leave it for future research.

The Association between Anti-hypertensive Medication and the CSH of Dementia and of Death in ApoE ε4 Carriers

In Table 3, I present results from Cox proportional CSH regression models, which were applied on ApoE ε4 carriers and non-carriers, respectively. My primary interest is the association between anti-hypertensive medication and the CSH of dementia. I also assessed the association between anti-hypertensive medication and the CSH of death, which acted as the competing risk for dementia. BP control status, demographic characteristics, and comorbid medical conditions were covariates in my statistical models.

ApoE ε4 carriers prescribed with any anti-hypertensive medication were found to have a significantly decrease of CSH of dementia (Table 3, HR, 0.365; 95% CI, 0.170 – 0.785; $p = 0.0099$) compared to the carriers not on anti-hypertensive medication, adjusting for all covariates except BP control. After adjusting for BP control, the significance of the HR of dementia disappeared (Table 3, HR, 0.784; 95% CI, 0.197 – 3.123; $p = 0.7303$). Suboptimally treated BP is likely to be a risk factor for the CSH of dementia, since the *p*-value was at the edge significance (Table 3, HR, 2.485; 95% CI, 0.983 – 6.283; $p = 0.0545$). The above results demonstrated that anti-hypertensive medication was associated with the CSH of dementia in hypertensive elders, reducing the rate of the incidence of dementia by better control the BP level in ApoE ε4 carriers (Fig. 3A).

I also checked the association between anti-hypertensive medication and the CSH of death. The results were shown in Table 4. ApoE ε4 carriers with anti-hypertensive medication did not show significant change of CSH of death, adjusting for all covariates

except BP control (Table 4, HR, 0.923; 95% CI, 0.579 – 1.472; $p = 0.7365$). The HR was not significantly different after adjusting for BP control (Table 4, HR, 0.617; 95% CI, 0.318 – 1.196; $p = 0.1529$). Suboptimally treated BP showed no association with the CSH of death (Table 4, HR, 1.519; 95% CI, 0.926 – 2.491; $p = 0.0975$). These HR estimates did not suggest the role of BP control in the occurrence of death in ApoE ε4 carriers. The rate (CSH) of death in ApoE ε4 carriers were not significantly associated with anti-hypertensive medication (Fig. 3A).

The Association between Anti-hypertensive Medication and the CSH of Dementia and of Death in ApoE ε4 Non-Carriers

ApoE ε4 non-carriers who had received anti-hypertensive treatment were found to have no apparent change of CSH of dementia (Table 3, HR, 1.311; 95% CI, 0.558 – 3.342; $p = 0.9124$) compared to the non-carriers not on anti-hypertensive medication, adjusting for all covariates except BP control. This HR did not change apparently after adjusting for BP control (Table 3, HR, 1.037; 95% CI, 0.265 – 4.060; $p = 0.9588$). The above results showed that anti-hypertensive medication was not associated with the incident rate (estimated by CSH) of dementia in ApoE ε4 non-carriers (Fig. 3B).

ApoE ε4 non-carriers receiving anti-hypertensive treatment were found to have a significantly decrease of CSH of death compared to those did not receive anti-hypertensive medication, adjusting for all covariates except BP control (Table 4, HR, 0.448; 95% CI, 0.309 – 0.649; $p < 0.0001$). The HR of death retained after adjusting for BP control (Table 4, HR, 0.237; 95% CI, 0.149 – 0.375; $p < 0.0001$). Suboptimally treated BP was not shown to be a risk factor for death (Table 4, HR, 1.351; 95% CI,

0.889 – 2.053; $p = 0.1586$). I concluded from the above estimates that anti-hypertensive medication was significantly associated with the CSH of death without the involvement of BP control (Fig. 3B).

Chapter Four

Discussion

In 2017, nearly 50 million people suffered dementia worldwide. This number is expected to increase to 75 million by 2030, mainly attributed to population aging [27]. Without available disease-modifying treatments for dementia currently, the high prevalence of dementia will increase health care burden by increasing the costs of caring people for dementia [28]. Prevention and management of dementia have become the priority for public health in many countries [27]. For this purpose, I need to identify risk factors for dementia and to investigate the potential association between the medication interventions and the hazard of dementia. The current study assessed the association between anti-hypertensive medication use and the hazard of dementia in hypertensive elders separately for ApoE ε4 carriers and non-carriers.

The association between anti-hypertensive medication and dementia rate differed by ApoE ε4 carrier status. For ApoE ε4 carriers, anti-hypertensive medication use was significantly associated with reduced dementia rate and the reduced rate appeared to be mediated via BP control. However, there was no significant association between anti-hypertensive medication use and dementia rate in the non-carriers.

The association between anti-hypertensive medication and death also differed by ApoE ε4 status. In non-carriers, those on medication had significantly reduced rate of death compared to those not on medication (HR, 0.448; 95% CI, 0.309 – 0.649; $p < 0.0001$) and this rate remained after adjusting for BP control (HR, 0.237; 95% CI, 0.149 – 0.375; $p < 0.0001$). In ApoE ε4 carriers, there was no significant association between medication and the rate of death. These results suggest that the associations between anti-

hypertensive medication and the rate of dementia or of death are different between ApoE ε4 carriers and non-carriers.

This differences in the estimated associations may indicate potential difference in the underlying mechanisms of the development of dementia and mortality risk between ApoE ε4 carriers and non-carriers. Further biomedical researches could help explore the related mechanisms.

My currents results are consistent with previous findings of the association between anti-hypertensive medication use and dementia: the odds of incident dementia significantly reduced by 38% (odds ratio, 0.62; 95% CI, 0.45 – 0.84) and the rate of incident dementia significantly reduced by 43% (HR, 0.57; 95% CI 0.37–0.88) in the participants received anti-hypertensive medications, comparing to those did not receive [9, 10]. However, in these earlier studies, the researchers had not included death, the competing risk for dementia in the elders, into the statistical model to assess the risk of incident dementia [9]. This weakness was overcome in the present study with competing-risk survival analytical model as the statistical method. I also assessed the association between anti-hypertensive medication and rate of death. Furthermore, I performed investigation in ApoE ε4 carriers and non-carriers separately. These analyses are the strength of my current study, providing detailed information for the investigation.

In the current study, medication data were limited to the names of the medicine reported by participants. I don't have the information on the dosage, frequency, and duration of the medication use. I am in the lack of longitudinal BP information. The baseline covariates were not balanced between the participants received anti-hypertensive treatment and those did not. These are the major weakness of the present study.

Chapter Five

Conclusion

In conclusion, I found that the association between anti-hypertensive medication and dementia risk differed by ApoE ε4 carrier status after accounting for the competing risk due to death. In ApoE ε4 carriers, anti-hypertensive medication use was significantly associated with reduced dementia risk and the reduced risk appeared to be mediated via BP control. However, there was no significant association between anti-hypertensive medication use and dementia risk in non-carriers. In non-carriers, anti-hypertensive medication was significantly associated with lower mortality risk and this association appears to be independent of BP control. Further research is needed to confirm my findings in other populations.

Table 1. Characteristics of Participants by Endpoint Status

Characteristics	Demented (alive or died)		Died without dementia		Loss of follow-up		*P* value
	N	Mean ± SD or no. (%)	N	Mean ± SD or no. (%)	N	Mean ± SD or no. (%)	
Baseline:							
Mean age (SD), years	114	76.9 ± 6.9	511	74.9 ± 6.6	611	74.4 ± 5.5	0.0004**
Male, no. (%)	114	26 (22.8%)	511	161 (31.5%)	611	129 (21.1%)	0.0003**
Years of education (SD)	114	8.8 ± 3.3	510	9.5 ± 2.9	610	10.5 ± 2.7	< 0.0001***
Stroke, no. (%)	114	7 (6.1%)	511	26 (5.1%)	611	37 (6.1%)	0.7565
Heart comorbid condition, no. (%)	114	56 (49.1%)	511	232 (45.4%)	611	241 (39.4%)	0.0471 *
Chronic renal disease, no. (%)	114	10 (8.8%)	511	9 (1.8%)	611	63 (10.3%)	< 0.0001***
Diabetes – type 1 or 2, no. (%)	114	41 (36.0%)	511	195 (38.2%)	611	219 (35.8%)	0.7250
Atrial fibrillation, no. (%)	114	10 (8.8%)	511	63 (12.3%)	611	51 (8.4%)	0.0792
Chronic obstructive pulmonary disease, no. (%)	114	5 (4.4%)	511	39 (7.6%)	611	52 (8.5%)	0.3422
Cancer, no. (%)	114	41 (36.0%)	511	189 (37.0%)	611	292 (47.8%)	0.0005**
ApoE ε4 carriers, no. (%)	82	38 (46.3%)	217	78 (36.0%)	408	138 (33.8%)	0.1012
Baseline systolic blood pressure (SD), mmHg #	74	152.5 ± 26.0	312	145.6 ± 23.0	454	146.0 ± 21.8	0.0540
Baseline diastolic blood pressure (SD), mmHg #	74	78.1 ± 14.9	312	77.3 ± 12.3	454	78.1 ± 12.2	0.6752
Treatment (prescribed antihypertensive), no. (%)	114	82 (71.9%)	511	310 (60.7%)	611	424 (69.4%)	0.0035**
Follow-up:							
Mean systolic blood pressure (SD), mmHg #	74	150.0 ± 21.5	312	144.8 ± 21.0	454	145.6 ± 19.2	0.1333
Mean diastolic blood pressure (SD), mmHg #	74	76.6 ± 12.0	312	76.0 ± 10.9	454	76.2 ± 10.2	0.9018
Blood pressure suboptimally treated, no. (%) ##	74	35 (47.3%)	312	130 (41.7%)	454	174 (38.3%)	0.2894
Mean age at endpoint (SD), years	114	84.8 ± 6.8	511	79.2 ± 6.6	611	82.1 ± 6.1	< 0.0001***

 # Average blood pressure measure per person from repeated blood pressure measurements
Defined as all blood pressure measurements > 140 mmHg systolic or > 90 mmHg diastolic pressure during follow-up
**p < 0.05 **p < 0.01 ***p < 0.001*

Table 2. Characteristics of Participants by Anti-hypertensive Treatment Status

Characteristics	Not prescribed antihypertensive		Prescribed antihypertensive		*P* value
	N	Mean ± SD or no. (%)	N	Mean ± SD or no. (%)	
Baseline:					
Mean age (SD), years	420	75.3 ± 6.3	816	74.6 ± 6.0	0.0539
Male, no. (%)	420	144 (34.3%)	816	172 (21.1%)	< 0.0001***
Years of education (SD)	418	9.8 ± 3.1	816	10.0 ± 2.9	0.4308
Stroke, no. (%)	420	19 (4.5%)	816	51 (6.2%)	0.2433
Heart comorbid condition, no. (%)	420	127 (30.2%)	816	402 (49.3%)	< 0.0001***
Chronic renal disease, no. (%)	420	17 (4.0%)	816	65 (8.0%)	0.0079**
Diabetes – type 1 or 2, no. (%)	420	113 (26.9%)	816	342 (41.9%)	< 0.0001***
Atrial fibrillation, no. (%)	420	24 (5.7%)	816	100 (12.2%)	0.0002**
Chronic obstructive pulmonary disease, no. (%)	420	25 (6.0%)	816	71 (8.7%)	0.0930
Cancer, no. (%)	420	114 (27.1%)	816	408 (50%)	< 0.0001***
ApoE ε4 carriers, no. (%)	190	69 (36.3%)	517	185 (35.8%)	0.9296
Follow-up:					
Demented (either died later or alive)	420	32 (7.6%)	816	82 (10.0%)	0.0035**
Died without dementia	420	201 (47.9%)	816	310 (38.0%)	
Loss of follow-up (alive without dementia)	420	187 (44.5%)	816	424 (52.0%)	
Blood pressure suboptimally treated, no. (%) #	162	84 (51.8%)	678	255 (37.6%)	0.0013**
Mean age at endpoint (SD), years	420	79.2 ± 6.7	816	82.2 ± 6.4	< 0.0001***

 # Defined as all blood pressure measurements > 140 mmHg systolic or > 90 mmHg diastolic pressure during follow-up
**p < 0.05 **p < 0.01 ***p < 0.001*

Table 3. Results of Cox PH Regression Model of Time-to-Dementia

Variable	ApoE ε4 Carriers (HR (95%CI), *p*)	Non-carriers (HR (95%CI), *p*)	
Age at baseline	1.157 (1.092 – 1.225), <.0001 ***	1.121 (1.067 - 1.178), <.0001 ***	**Models without adjusting for BP control**
Years of education	0.917 (0.817 - 1.028), 0.1367	0.844 (0.762 – 0.934), 0.0011 **	
Prescribed any anti-hypertensive medication (vs. Not prescribed anti-hypertensive medication)	0.365 (0.170 – 0.785), 0.0099 **	1.311 (0.558 – 3.342), 0.9124	
Male (vs. Female)	0.417 (0.149 - 1.242), 0.1163	1.671 (0.776 – 3.596), 0.1892	
Heart comorbid condition	0.890 (0.414 - 1.910), 0.7643	0.988 (0.491 - 1.988), 0.9729	
Chronic renal disease	3.441 (1.135 - 10.434), 0.0290 *	0.810 (0.240 – 2.739), 0.7350	
Stroke	2.197 (0.588 – 8.199), 0.2417	1.696 (0.502 – 5.732), 0.3954	
Atrial fibrillation	0.553 (0.119 – 2.568), 0.4499	0.766 (0.315 – 1.865), 0.5573	
Chronic obstructive pulmonary disease	1.505 (0.480 – 4.722), 0.4834	N/A	
Cancer	0.980 (0.471 - 2.042), 0.9577	0.386 (0.198 – 0.752), 0.0052 **	
Diabetes – type 1 or 2	0.505 (0.237 - 1.074), 0.0759	0.914 (0.429 - 1.948), 0.8167	
Age at baseline	1.211 (1.117 – 1.314), <.0001 ***	1.1434 (1.070 - 1.222), <.0001 ***	**Models with adjusting for BP control**
Years of education	0.937 (0.798 - 1.101), 0.4284	0.787 (0.684 – 0.904), 0.0008 **	
Prescribed any anti-hypertensive medication (vs. Not prescribed anti-hypertensive medication)	0.784 (0.197 – 3.123), 0.7303	1.037 (0.265 – 4.060), 0.9588	
Male (vs. Female)	0.854 (0.243 – 3.000), 0.8052	1.471 (0.525 – 4.122), 0.4624	
Heart comorbid condition	0.615 (0.218 - 1.734), 0.3578	2.201 (0.883 – 5.486), 0.0905	
Chronic renal disease	2.070 (0.513 – 8.351), 0.3068	1.272 (0.355 – 4.556), 0.7121	
Stroke	0.755 (0.092 – 6.211), 0.7937	1.975 (0.414 – 9.433), 0.3935	
Atrial fibrillation	0.558 (0.069 – 4.537), 0.5857	0.692 (0.241 – 1.986), 0.4940	
Chronic obstructive pulmonary disease	1.334 (0.344 – 5.174), 0.6771	N/A	
Cancer	1.018 (0.364 - 2.851), 0.9722	0.493 (0.220 – 1.106), 0.0861	
Diabetes – type 1 or 2	0.684 (0.257 - 1.819), 0.4469	0.338 (0.113 - 1.016), 0.0534	
Blood pressure suboptimally treated	2.485 (0.983 – 6.283), 0.0545	2.346 (1.015 – 5.418), 0.0460 *	

* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$

Table 4. Results of Cox PH Regression Model of Time-to-Death

Variable	ApoE ε4 Carriers (HR (95%CI), *p*)	Non-carriers (HR (95%CI), *p*)	
Age at baseline	1.083 (1.045 – 1.123), <.0001 ***	1.100 (1.070 – 1.130), <.0001 ***	**Models without adjusting for BP control**
Years of education	0.984 (0.918 – 1.056), 0.6550	0.919 (0.869 – 0.972), 0.0032 **	
Prescribed any anti-hypertensive medication (vs. Not prescribed anti-hypertensive medication)	0.923 (0.579 – 1.472), 0.7365	0.448 (0.309 – 0.649), <.0001 ***	
Male (vs. Female)	1.313 (0.803 – 2.148), 0.2781	2.123 (1.449 – 3.110), 0.0001 ***	
Heart comorbid condition	0.935 (0.602 – 1.450), 0.7627	1.249 (0.864 – 1.807), 0.2374	
Chronic renal disease	0.300 (0.072 – 1.248), 0.0978	0.215 (0.079 – 0.589), 0.0028 **	
Stroke	0.762 (0.298 – 1.943), 0.5688	1.317 (0.657 – 2.640), 0.4379	
Atrial fibrillation	1.190 (0.555 – 2.553), 0.6548	0.770 (0.453 – 1.307), 0.3323	
Chronic obstructive pulmonary disease	0.960 (0.456 – 2.023), 0.9146	N/A	
Cancer	0.729 (0.469 – 1.133), 0.1596	1.031 (0.739 – 1.439), 0.8574	
Diabetes – type 1 or 2	0.789 (0.507 – 1.230), 0.2960	1.668 (1.158 – 2.404), 0.0061 **	
Age at baseline	1.102 (1.055 – 1.152), <.0001 ***	1.077 (1.043 – 1.112), <.0001 ***	**Models with adjusting for BP control**
Years of education	1.061 (0.972 – 1.158), 0.1846	0.926 (0.862 – 0.993), 0.0317 *	
Prescribed any anti-hypertensive medication (vs. Not prescribed anti-hypertensive medication)	0.617 (0.318 – 1.196), 0.1529	0.237 (0.149 – 0.375), <.0001 ***	
Male (vs. Female)	1.294 (0.704 – 2.378), 0.4062	1.851 (1.184 – 2.893), 0.0069 **	
Heart comorbid condition	0.887 (0.511 – 1.539), 0.6696	1.656 (1.063 – 2.579), 0.0256	
Chronic renal disease	0.321 (0.076 – 1.353), 0.1215	0.222 (0.070 – 0.711), 0.0112 *	
Stroke	0.339 (0.080 – 1.425), 0.1397	0.812 (0.318 – 2.077), 0.6639	
Atrial fibrillation	1.489 (0.663 – 3.346), 0.3347	0.796 (0.449 – 1.410), 0.4344	
Chronic obstructive pulmonary disease	0.940 (0.403 – 2.190), 0.8856	N/A	
Cancer	0.737 (0.439 – 1.238), 0.2489	1.161 (0.792 – 1.702), 0.4457	
Diabetes – type 1 or 2	0.939 (0.558 – 1.578), 0.8119	1.440 (0.931 – 2.229), 0.1016	
Blood pressure suboptimally treated	1.519 (0.926 – 2.491), 0.0975	1.351 (0.889 – 2.053), 0.1586	

* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$

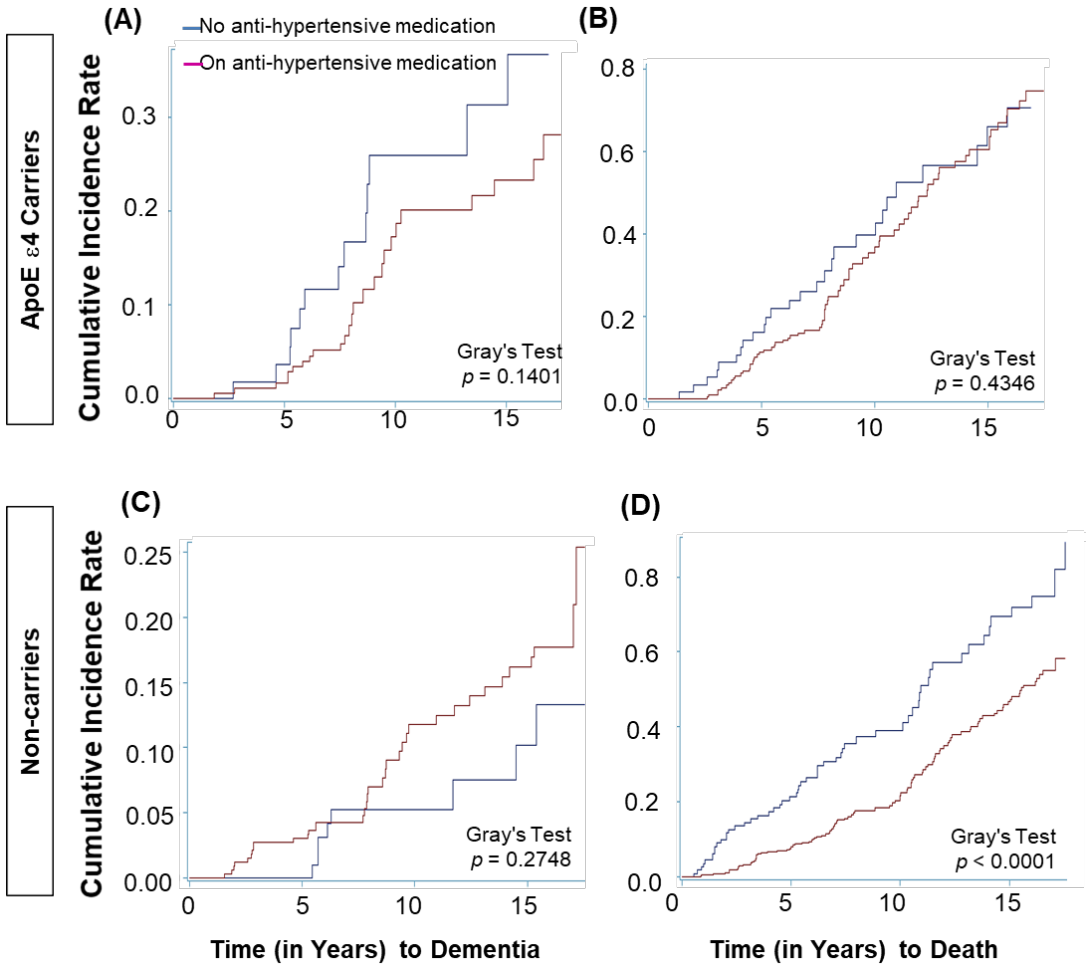

Figure 1. Cumulative Incidence Functions of Dementia and of Death over Time for ApoE ε4 Carriers and Non-carriers, by Anti-hypertensive Medication Status

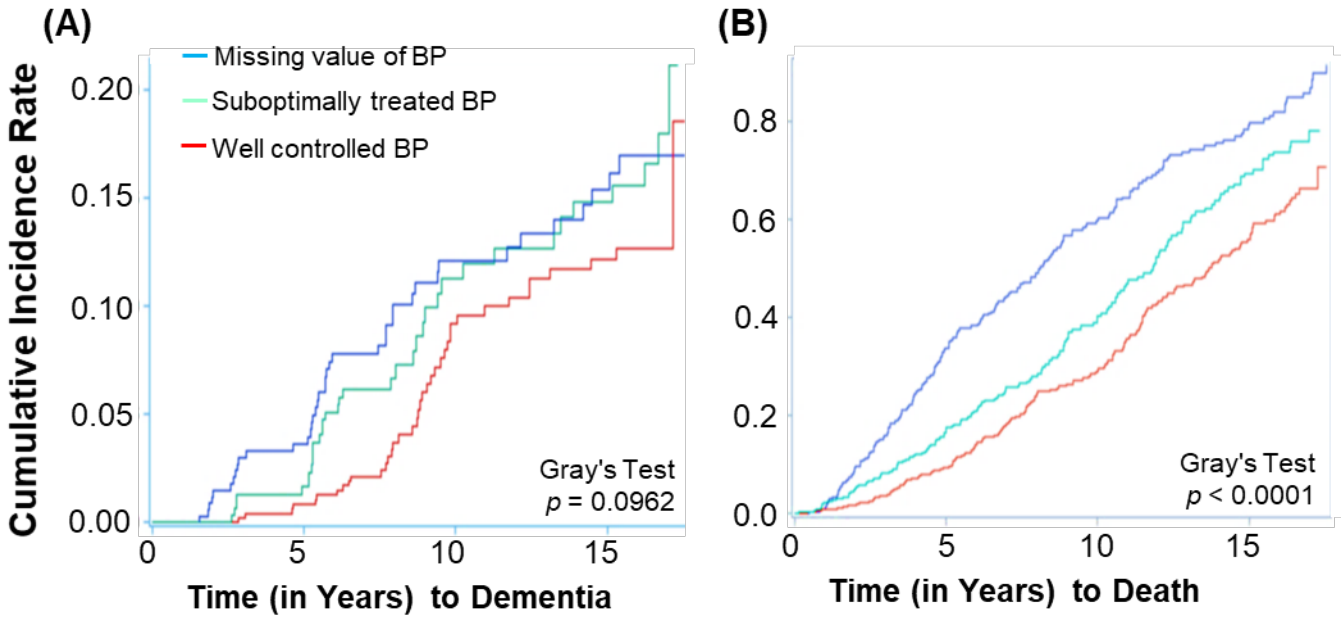

Figure 2. Cumulative Incidence Functions of Dementia and of Death over Time for Participants by BP Status

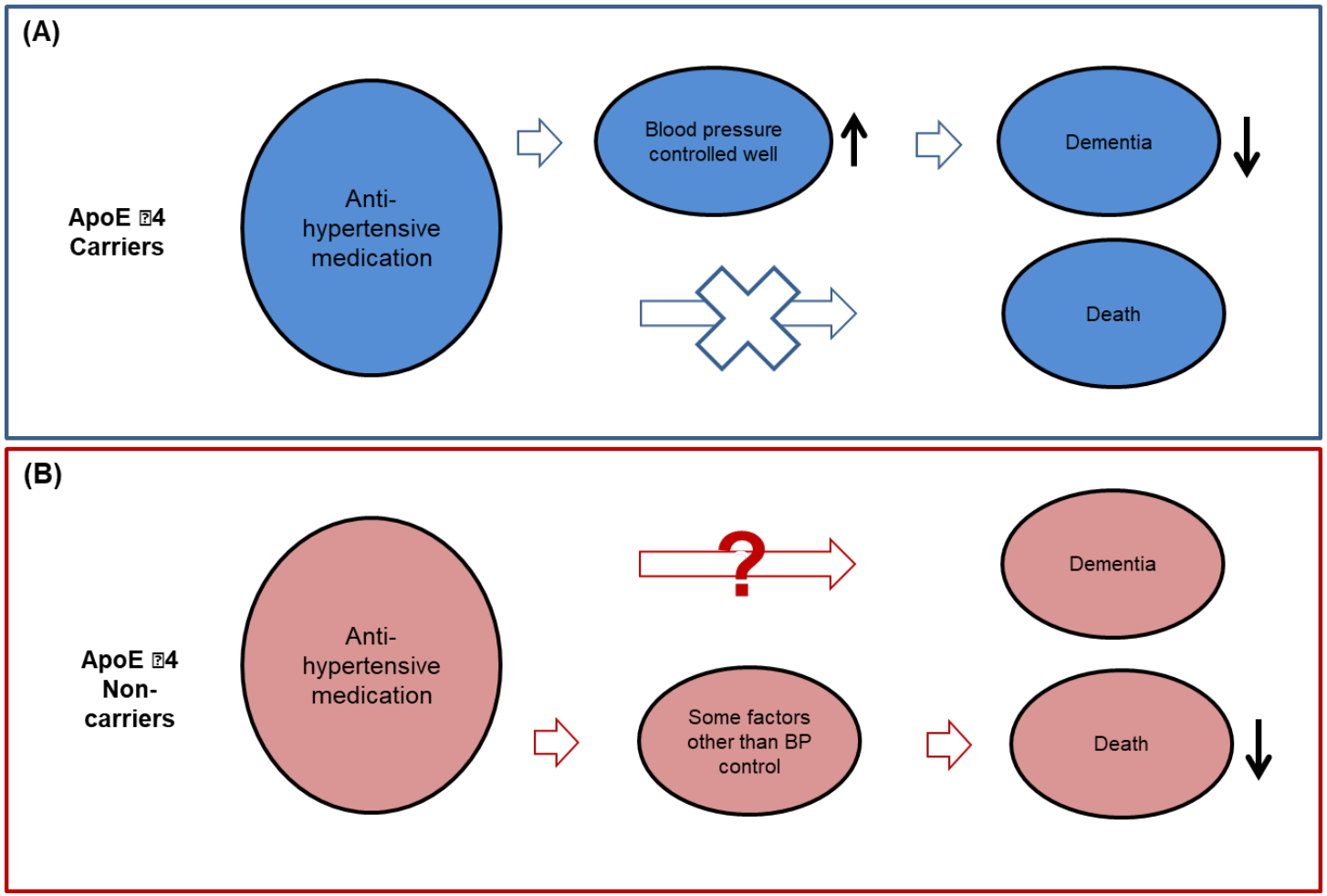

Figure 3. Scheme of the Association between Anti-hypertensive Medication and the Occurrence of Dementia and of Death in ApoE ε4 Carriers and Non-carriers

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Curriculum Vitae

Xinhua Flora Hu

- **Professional Experiences**

Biostatistician summer intern, Vertex Pharmaceutical, Boston MA, 2018

- duties
- Integrate clinical data from distinct studies to establish a novel ADAM Dataset
- Perform statistical programming for data analysis

Biostatistician research assistant, Dept. of Biostatistics, IUPUI, Indianapolis, IN, 2017

- duties
- Establish Dataset and perform statistical programming for data analysis

Associate director, R &D, Jiangsu Biolink Diagnostics. Co., China, 2012 - 2016

- duties
- Manage the clinical laboratory

Post-doctoral fellow, Stark Neuroscience Institute, IUPUI, Indianapolis, 2008 - 2012

- duties
- Design and perform the bioresearch projects

• Education

- Fudan University, Shanghai, China, 1997, BS in Biochemistry
- Institute of Neuroscience, Chinese Academy of Sciences, Shanghai, China, 2004, Ph.D in Neuroscience
- Spinal Cord and Brain Injury Research Center, University of Kentucky, U.S.A., 2008, Postdoctoral scholar, research field: gene therapy
- Spinal Cord and Brain Injury Research Group, Indiana University, U.S.A., 2011, Postdoctoral fellow, research field: chemical therapy
- Department of Biostatistics, Indiana University, U.S.A., present, graduate student, expected degree: MS. in biostatistics

• Awards and Fellowships

- The Taizhou Talent Award: Taizhou, Jiangsu, China, 2012
- University Fellowship: IUPUI, U.S.A., 2009 – 2011
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• Publications

1. **Hu X**, Jin L, Feng L. Erk1/2 but not PI3K pathway is required for neurotrophin 3-induced oligodendrocyte differentiation of post-natal neural stem cells. J. Neurochem. 2004 Sep;90(6):1339-47

2. Jin L, **Hu X**, Feng L. NT3 inhibits FGF2-induced neural progenitor cell proliferation via the PI3K/GSK3 pathway. J Neurochem. 2005 Jun; 93(5):1251-61

3. **Hu X**, Chen E, Xu, XM. A novel effect of the chemical compound xxxx in the replacement of the oligodendrocytes during spinal cord injury (*in preparation)*

4. Wu W, **Hu X, …..** Gao S, Xu, XM. Activity-modulated corticospinal tract plasticity improves forelimb function after spinal cord injury (*in preparation*)