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Title: Hypertensive Disorders in Pregnancy and Preterm Delivery and Subsequent Stroke in Asian Women: A Retrospective Cohort Study

Short title: Hypertensive disorders in pregnancy and stroke

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Abstract

Background and Purpose – Few studies exist concerning the risk of stroke associated with hypertensive disorders in pregnancy (HDP) in Asian women. This study investigates whether preterm delivery further complicates this risk in women with HDP in Taiwan.

Methods - Based on universal insurance claims data, 1,092 pregnant women newly diagnosed with HDP from 2000–2004 and aged 15–40 years were identified as the HDP cohort. Then, 4,715 randomly selected persons without HDP frequency matched with the index year were designated as the non-HDP controls. Both cohorts were followed until the end of 2008 to measure the incidence of stroke.

Results - The HDP cohort had a higher incidence of stroke than the non-HDP cohort (30.1 vs. 12.8 per 10,000 person-years), with an overall adjusted hazard ratio (HR) of 2.04 (95% CI = 1.18–3.51) for stroke. Preterm delivery increased the risk of stroke to 3.22-fold (95% CI = 1.48-6.99) (*P* for trend=0.002). The age-specific V-shaped risk association showed that the highest risk of stroke was noted among subjects 15–18 years old in the HDP group (HR = 13.4, 95% CI = 1.54–116.7) and followed by women aged 35 years old and older (HR = 5.56, 95% CI = 1.47–21.0).

Conclusion – Pregnant women with HDP have an increased risk of subsequent stroke. Preterm delivery and older ages increase the risk of subsequent stroke. Adolescents

with HDP also have an elevated risk of stroke. Early identification of women with HDP is needed for prevention.

Keywords: follow-up study, gestational hypertension, preeclampsia, preterm delivery, stroke

Introduction

Gestational hypertension and preeclampsia are hypertensive disorders during pregnancy (HDP).[1-2] Gestational hypertension refers to the onset of hypertension without proteinuria after 20 weeks of gestation, while preeclampsia is characterized by the onset of hypertension and proteinuria after 20 weeks of gestation. Gestational hypertension occurs in approximately 6% of pregnancies and evolves into preeclampsia in 10%—20% of cases.[3-4] Preeclampsia is a prevalent life-threatening disorder affecting pregnant women and their fetuses.[5-6] The incidence of preeclampsia range from 3%—14% of pregnancies worldwide and 5%—8% in the United States.[1, 7] HDP and cardiovascular diseases share many risk factors, including pre-existing hypertension, diabetes, obesity, renal disease, collagen vascular disease, anti-phospholipid syndrome, advanced age, and endothelial dysfunction.[5, 8-12] Such cardiovascular risks that appear during pregnancy may have subsequent health consequences, including stroke.[13-16]

Both case-control and cohort studies have reported an association between HDP and later cardiovascular disease.[13-19] However, studies on the association between HDP and the risk of subsequent stroke are limited in Asian populations. In this work, a retrospective cohort study was performed using a set of population-based universal insurance data to investigate the incidence of stroke after delivery among women with

HDPs, with emphasis on the age-specific risk and the interaction with preterm delivery.

Methods and Materials

Data sources

This study used data from reimbursement claims of the universal National Health Insurance program, which was launched in March 1995, by incorporating 13 insurance programs in Taiwan. This insurance program provides health care to 99% of the population.[20] The National Health Research Institute (NHRI) has been responsible for managing the insurance data. The claims data of 1 million randomly selected subjects from 23 million insured individuals registered from 1996–2008 were obtained from the NHRI. With approval from the NHRI, the scrambled identification of insured individuals and contracted institutions to linked files were used, including the registry of medical facilities, details of inpatient orders, ambulatory care, as well as dental services and prescriptions. The diagnoses were coded using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). [21]

Study sample

From the claims data, we used special delivery codes in the claims file specifically designed by the insurance system to identify the date of delivery of pregnant women. Patients with HDP (ICD-9-CM 642) were then identified from the group of women having their first pregnancies (primigravid) included in the database from January 1, 2000 through December 31, 2004; these women were designated as the HDP cohort. For each HDP case identified, four primigravid women without the

history of HDP were randomly selected, frequency matched in the same year, and were designated as the non-HDP controls. In all, 174 subjects were excluded; these were the ones with histories of stroke or hypertension (ICD-9-CM 401-405 or A-code A260 and A269) diagnosed before the index date (the date the subject being selected into the study) or with missing information (age or sex). Then, 1,092 women were selected as the HDP cohort and 4,715 women as the non-HDP cohort.

Socio-demographic variables and co-morbidities

The socio-demographic variables used in this study included sex, age, occupation, urbanization of the residential area, and monthly income used for premium estimation. The age of each study subject was measured by the difference between the index date and the date of birth. In accordance with the National Statistics of Regional Standard Classification, all insured persons were grouped into three urbanization levels based on population densities (low, moderate, and high).

Moreover, the baseline co-morbidity history for each subject was also identified, including diabetes (ICD-9-CM 250 or A-code A181), hyperlipidemia (ICD-9-CM 272.9 or A-code A189), coronary artery disease (CAD, CD-9-CM 410-413, 414.0, 414.8, 414.9 or A-code A270 and A279), preterm delivery (ICD-9-CM 644), lupus (ICD-9-CM 710.0), and thrombophilia (ICD-9-CM 286.9).

Statistical analysis

The study subjects with and without HDP were linked to the registry for inpatient and outpatient claims data to identify those who developed stroke (ICD-9-CM 430-437, 674.0 or A-code A290-294 and A299). Each subject was either followed from the index date until December 31, 2008 or was censored. The follow-up time, in person-years, was calculated for each subject until the diagnosis of stroke or censored due to death, withdrawal from the insurance system, or loss to follow-up.

The distributions of categorical socio-demographic variables and co-morbidities were compared between HDP and non-HDP cohorts, and the differences were examined using a Chi-square test. Likewise, the incidence densities by socio-demographic variables were calculated for each cohort. The HDP to non-HDP rate ratio for stroke with a 95% confidence interval (CI) for each variable was calculated. We used logistic regression analysis to measure odds ratio (OR) and the corresponding 95% CI for evaluating the association between each comorbidity and HDP.

Cox's proportion hazard regression was used to assess the effects of HDP on the risk of stroke, adjusting for variables that were significantly related to HDP as observed through the Chi-square analyses. The hazard ratios (HRs) and 95% CIs were calculated using the model. Cox's proportion hazard regression was also used to examine the interaction between HDP and preterm delivery associated with stroke. On

the other hand, Kaplan-Meier analysis and the log-rank test were used to estimate the stroke-free proportions for the risk of developing stroke in the HDP and non-HDP cohorts.

All analyses were performed using SAS statistical software (version 9.1 for Windows; SAS Institute, Inc., Cary, NC, USA), Kaplan-Meier analysis and the log-rank test were performed by R (version 2.11.1 R Foundation for Statistical Computing, Vienna, Austria). The results were considered statistically significant when two-tailed *P* values were less than 0.05.

Results

Characteristics of the study subjects and incidence of stroke

This study consisted of 1,092 HDP cases and 4,715 non-HDP pregnant women after excluding ineligible subjects. The HDP cohort was older than the non-HDP group (29.5 ± 4.82 years vs. 27.8 ± 4.95 years, $P<0.001$) (data not shown). Most subjects were 25 to 29 years old (38.2% in non-HDP, 34.8% in HDP, $P=0.048$). The degrees of urbanization were similar in both groups (Chi-square $P=0.70$). The mean follow-up periods in our study were 6.64 ± 1.57 years in the HDP cohort and 6.40 ± 1.57 years in the non-HDP cohort (data not shown).

Table 1 presents the incidence densities in both cohorts and HDP-to-non-HDP rate ratios of stroke by socio-demographic status. Occupations and urbanization of residential areas of study subjects were not significantly different between the two groups. A V-shape relationship was observed for the incidence of stroke across the age groups in both HDP and non-HDP cohorts. The lowest incidence was 6.2 per 10,000 person-years in women 19–24 years of age in the non-HDP cohort, and 20.6 per 10,000 person-years in those 25–29 years of age in the HDP cohort. Exceptionally higher incidence of 103.1 per 10,000 person-years was noted for HDP patients 15–18 years of age. Overall, the stroke incidence was 2.35-fold higher in the HDP than in the non-HDP cohort (30.1 vs. 12.8 per 10,000 person-years) with an adjusted hazard ratio

(HR) of 2.04 (95% CI = 1.18–3.51) (data not shown).

The Kaplan-Meier survival analysis showed that the stroke-free rate was 2.2% less in the HDP women than in the non-HDP women (Log-rank *P*=0.001) (Figure 1). Most events actually occurred within 4—8 years of follow-up. Furthermore, the incidence of stroke during puerperium (from delivery to 6 weeks postpartum) was 4.33-fold higher in the HDP than in the non-HDP cohorts (142.0 vs. 32.8 per 10,000 person-years) (data not shown). However, the risk shown in the univariate Cox's proportional regression analysis was not significant (HR = 4.32, 95% CI = 0.27–69.1).

Comorbidities in study subjects

Table 2 shows the prevalence of selected morbidities in the study subjects. Patients with HDP were more likely to have diabetes (2.8% vs. 0.8%, *P*<0.0001), hyperlipidemia (1.5% vs. 0.5%, p = 0.0006), placental abruption (1.9% vs. 0.8%, *P*=0.0009), preterm delivery (31.0% vs. 24.1%, *P*<0.0001), lupus (1.4% vs. 0.3%, *P*<0.0001), and thrombophilia (0.18% vs.0.15%, *P*=0.79). The logistic regression analysis showed that diabetes mellitus, hyperlipidemia, preterm delivery, placental abruption, and lupus were significantly associated with HDP. The multivariable regression model measured OR associated with preterm delivery was 1.41 (95% CI = 1.22-1.63).

Table 3 shows the values of co-morbidity–adjusted age-specific risk of stroke in

both groups that have been measured using the Cox's proportional regression analysis. Compared with subjects 19–24 years of age in the non-HDP group, the V-shape HRs of stroke increased with age in both groups. However, exceptionally higher risk with a large CI range was noted for HDP patients 15–18 years of age (HR = 13.4, 95% CI = 1.54–116.7), and followed by women aged 35–40 years old (HR = 5.56, 95% CI = 1.47–21.0). .

Interaction between HDP and preterm delivery

Figure 2 presents the Kaplan-Meier curves for the interaction between HDP and preterm delivery in relation to the occurrence of stroke. Women with HDP and preterm delivery were the most likely to experience a stroke, followed by women with HDP but not preterm delivery; in comparison, women with normal pregnancy were least likely to experience stroke (Log-rank *P*=0.0016). Compared with normal pregnancy, the interaction analysis shows that the risk of stroke was greater for women with only HDP than those with only preterm delivery, and the highest for those with both HDP and preterm delivery (*P* for trend=0.002 Table 4). Women with both HDP and preterm delivery had an adjusted HR of 3.22 (95% CI = 1.48–6.99).

Discussion

The pathogenesis of preeclampsia likely involves both maternal and fetal factors.[21,22] Abnormal placental vasculature developed in early pregnancy may lead to reduced maternal uteroplacental perfusion. The released anti-angiogenic factors in the maternal circulation could alter maternal systemic endothelial function, leading to hypertension and other related manifestations.[23-24] Gestational hypertension may have the same pathophysiological change as preeclampsia. These factors may partly explain the association between HDP and stroke. HDP is in the cardiovascular risk profile, which may lead to atherosclerosis and act as a clinical marker for poor cardiovascular health.

A strong association between HDP and subsequent stroke was found; in addition, preterm delivery enhanced the risk. This finding is in accordance with other studies. A Norwegian follow-up study found that women with histories of preeclampsia and preterm delivery had a 5.08-fold higher risk of cerebrovascular mortality than women who were free of preeclampsia and went to term.[14] Wilson et al. have demonstrated a 3.6-fold elevated risk of mortality from cerebrovascular disease in women with preeclampsia.[16] In a case-controlled study, Brown et al. have reported that women with preeclampsia had a relative risk of 1.63 for developing ischemic stroke.[17] The results of the meta-analysis conducted by Bellamy et al. demonstrated that the relative

risk of future stroke for preeclampsia is 1.81 (95% CI, 1.54 to 2.67).[13] Another meta-analysis by McDonald et al. have shown that women with a history of preeclampsia have an increased risk of subsequent stroke (RR, 2.03; 95% CI, 1.54 to 2.67).[15]

Hypertensive disorders during pregnancy are complicated by placental abruption, preterm delivery, or fetal death.[25-29] In our analysis, HDP (independent of diabetes and hyperlipidemia) was an important risk factor associated with stroke. Previous data analysis showed that women with gestational hypertension had slightly increased risk of developing stroke, consistent with other studies.[13, 16] Thus, in our study, the reported association was likely diluted by gestational hypertension. However, gestational hypertension is as important as preeclampsia as a factor that can induce subsequent stroke.[18] The present study further demonstrated that preterm delivery further increased the HR of stroke to 3.22 for women with HDP. The association between stroke and preterm delivery alone was not significant in the multivariable analysis. However, the preterm delivery did increase the stroke risk for 126% in women with HDP. This finding is consistent with previous studies, which also demonstrated that preterm delivery further increase the risk of stroke in women with HDP.[14, 18] Based on the results of the Denmark registry–based study, women with preeclampsia and preterm delivery are at an elevated risk of higher subsequent

cardiovascular disorders, such as hypertension, ischemic heart disease and congestive heart failure, and type 2 diabetes mellitus.[18] However, placental abruption, a risk factor of preterm delivery,[27] was not a significant risk factor for stroke in our analysis (data not shown).

Pregnant adolescents and older women with HDP had a higher HR of future stroke than women aged 25–29 years. Adolescent pregnancy has not yet been proven as a risk factor for HDP.[7] Because the sample size of teen pregnancy was small in this study, a high incidence of subsequent stroke in teens with HDP may be due to chance. To the best of our knowledge, this is the first report of this type, although it warrants a further study. It is well known that adolescents have increased risk for adverse pregnancy outcomes, such as low-birth-weight babies and infant deaths and premature death in their later life.[30-31] Biological immaturity and socioeconomic factors might account for the poorer outcome among pregnant adolescents.

This study has several limitations. Adolescent pregnancy is relatively rare in Taiwan, and their sample size in the HDP group was small. With a large confidence interval of HR due to only a single stroke case identified, random error should be considered for the highest stroke incidence among all age groups. However, adolescent pregnancy in the non-HDP group also had increased risk of stroke with a greater sample size. The multivariate analysis demonstrated that this V-shaped

age-specific association did not occur by chance. Second, the NHRI database provided limited information on socio-demographic characteristics, with information unavailable on marital status, educational level, body mass index, smoking habit, and laboratory data. These variables could not be adjusted in the analysis. However, we were able to use occupation, income, and residential area for adjustment. These socioeconomic characteristics had no significant association. Third, some information on chronic conditions, such as hyperlipidemia, was unavailable for few individuals. However, this situation happened in both groups. Fourth, matched cohort study design may benefit this study with convenience and efficiency, but there is a possibility of over estimation of association between HDP and stroke. To reduce this possibility, we excluded women with pre-existing hypertension prior to the pregnancy. Finally, stroke and other diseases were identified by ICD-9-CM codes. However, patients with stroke in Taiwan are generally cared for at larger hospitals with adequate diagnosis and majority of pregnant women receive adequate prenatal cares. These codes were reviewed and validated by auditors of medical records for the insurance system to insure the accuracy of the claims.

Summary

In conclusion, our study results can be generalized to apply to pregnant women in Taiwan for the association between HDP and stroke because we used a representative

population data. Pregnant women with HDP have about a two-fold increased risk for future stroke. The risk increases further for women with both HDP and preterm delivery. This potential interaction is worthwhile in considering prevention strategies. Moreover, adolescents with HDP may have a higher risk of subsequent stroke than older pregnant women with HDP. This association remains unclear. Further prospective studies regarding pregnancy disorders in teen mothers are needed.

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Disclosures

None.

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Legends

Figure 1. The stroke-free proportions estimated for the hypertensive disorders in pregnancy (HDP) and non-HDP cohorts using the Kaplan-Meier method.

Figure 2. Kaplan-Meier model for measuring the stroke-free proportions in subjects with and without hypertensive disorders in pregnancy (HDP) and preterm delivery (PRE).

Table 1. Comparisons of the incidence densities of stroke between cohorts with and without hypertensive disorders during pregnancy by socio-demographic factors

Variables	Non-HDP				HDP				Rate ratio	Crude HR (95% CI)
	N	Cases	PY	Rate†	N	Cases	PY	Rate†		
All	4715	40	31286	12.8	1092	21	6988	30.1	2.35	2.37 (1.40–4.02)**
Age (in years)										
15–18	170	3	1160	25.9	14	1	97	103.1	3.99	3.29 (1.01–12.7)*
19–24	1206	5	8101	6.2	188	4	1227	32.6	5.28	1.00 (reference)
25–29	1801	13	11858	11.0	380	5	2428	20.6	1.88	1.31 (0.59–2.91)
30–34	1134	13	7485	17.4	359	7	2276	30.8	1.77	2.12 (0.97–4.66)
35–40	404	6	2683	22.4	151	4	961	41.6	1.86	2.84 (1.15–6.99)*
Urbanization										
Low	493	3	3295	9.1	106	4	675	59.3	6.51	1.00 (reference)
Moderate	962	7	6402	10.9	231	6	1490	40.3	3.68	0.98 (0.39–2.46)
High	3236	30	21425	14.0	751	11	4798	22.9	1.64	0.93 (0.42–2.08)
Occupation										
White collar	3274	29	21377	13.6	739	13	4687	27.7	2.04	1.00 (reference)
Blue collar	785	6	5401	11.1	205	7	1356	51.6	4.65	1.19 (0.64–2.21)
Unemployed‡	683	5	4509	11.1	148	1	946	10.6	0.95	0.68 (0.29–1.61)
Income										
<15,000	1549	9	10286	8.7	332	6	2174	27.6	3.15	1.00 (reference)
15,000–29,999	2414	23	16009	14.4	590	12	3722	32.2	2.24	1.47 (0.80–2.70)
≥30,000	7452	8	4991	16.0	170	3	1091	27.5	1.72	1.51 (0.69–3.28)

HDP, hypertensive disorders in pregnancy; PY, person-years.

*P<0.05, **P< 0.01

† Per 10,000 person-year

‡ Unemployed: retired, low income

Table 2. Odds ratio and 95% confidence interval of selected co-morbidities associated with HDP measured using logistic regression analyses

Variables	HDP cases Yes/No	Model 1 OR (95% CI)	Model 2 OR (95% CI)
Diabetes			
No	1062/4676	1.00 (reference)	1.00 (reference)
Yes	30/39	3.39 (2.09-5.47)***	2.74 (1.67-4.50)***
Hyperlipidemia			
No	1076/4691	1.00 (reference)	1.00 (reference)
Yes	16/24	2.91 (1.54-5.49)**	2.29 (1.20-4.35)*
CAD			
No	1068/4623	1.00 (reference)	1.00 (reference)
Yes	24/92	1.13 (0.72-1.78)	0.96 (0.60-1.53)
Preterm delivery			
No	753/3581	1.00 (reference)	1.00 (reference)
Yes	339/1134	1.42 (1.23-1.64)***	1.41 (1.22-1.63)***
Abruption			
No	1071/4677	1.00 (reference)	1.00 (reference)
Yes	21/38	2.41 (1.41-4.13)**	2.27 (1.32-3.91)**
Lupus			
No	1077/4701	1.00 (reference)	1.00 (reference)
Yes	15/14	4.68 (2.25-9.72)***	4.26 (2.02-8.95)**
Thrombophilia			
No	1090/4708	1.00 (reference)	1.00 (reference)
Yes	2/7	1.23 (0.26-5.95)	1.32 (0.27-6.42)

CAD, coronary artery disease; HDP, hypertensive disorders in pregnancy; OR, odds ratio; CI,confidence interval.

Model 1: Unadjusted

Model 2: Adjusted for age and urbanization level

*P<0.05, **P<0.01, ***P<0.0001

Table 3. Cox's proportional hazard regression analyses for age-specific risk of stroke in non-HDP and HDP cohorts.

Variables	Non-HDP	HDP
Age (in years)	HR (95%CI)	HR (95%CI)
15–18	4.31 (1.03–18.1)*	13.4 (1.54–116.7)*
19–24	1.00 (reference)	4.24 (1.12–16.0)*
25–29	1.73 (0.62–4.88)	3.06 (0.88–10.6)
30–34	2.75 (0.97–7.76)	4.53 (1.43–14.4)*
35–40	3.06 (0.92–10.2)	5.56 (1.47–21.0)*

HDP, hypertensive disorders in pregnancy.

Note: Adjusted for urbanization level, diabetes mellitus, hyperlipidemia, coronary artery disease, preterm delivery, abruption, lupus, and thrombophilia

*$P<0.05$

Table 4. Interaction between HDP and preterm delivery associated with stroke in Cox's model controlling for socio-demographic factors and other co-morbidities

Variables		Model 1	Model 2
		HR (95% CI)	HR (95% CI)
HDP	Preterm delivery		
No	No	1.00 (reference)	1.00 (reference)
No	Yes	1.55 (0.80–3.00)	1.51 (0.77–2.93)
Yes	No	2.19 (1.11–4.33)*	1.96 (0.98–3.91)
Yes	Yes	3.79 (1.78–0.87)**	3.22 (1.48–6.99)**
	P for trend	0.0002	0.002

HDP, hypertensive disorders in pregnancy.

Model 1: Unadjusted

Model 2: Adjusted for age, urbanization level, diabetes mellitus, hyperlipidemia, coronary artery disease, abruption, lupus, and thrombophilia

*P <0.05, **P <0.01

Figure 1

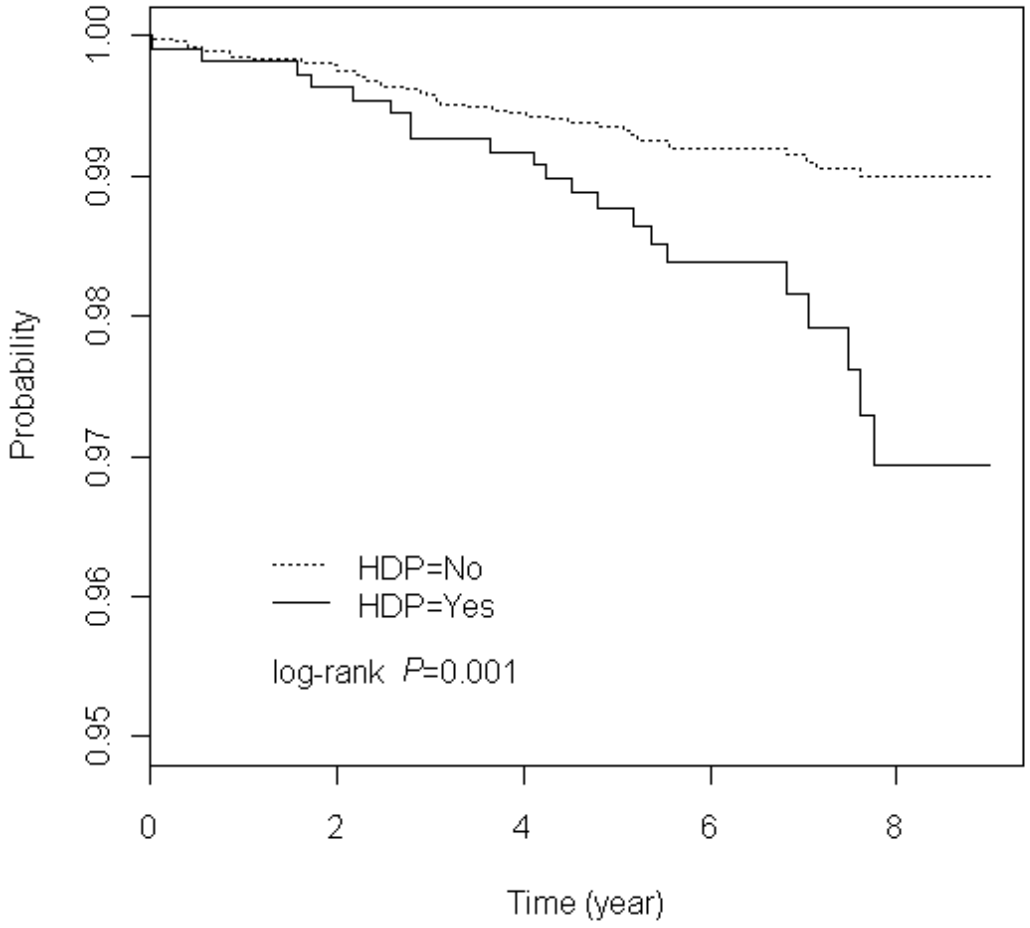
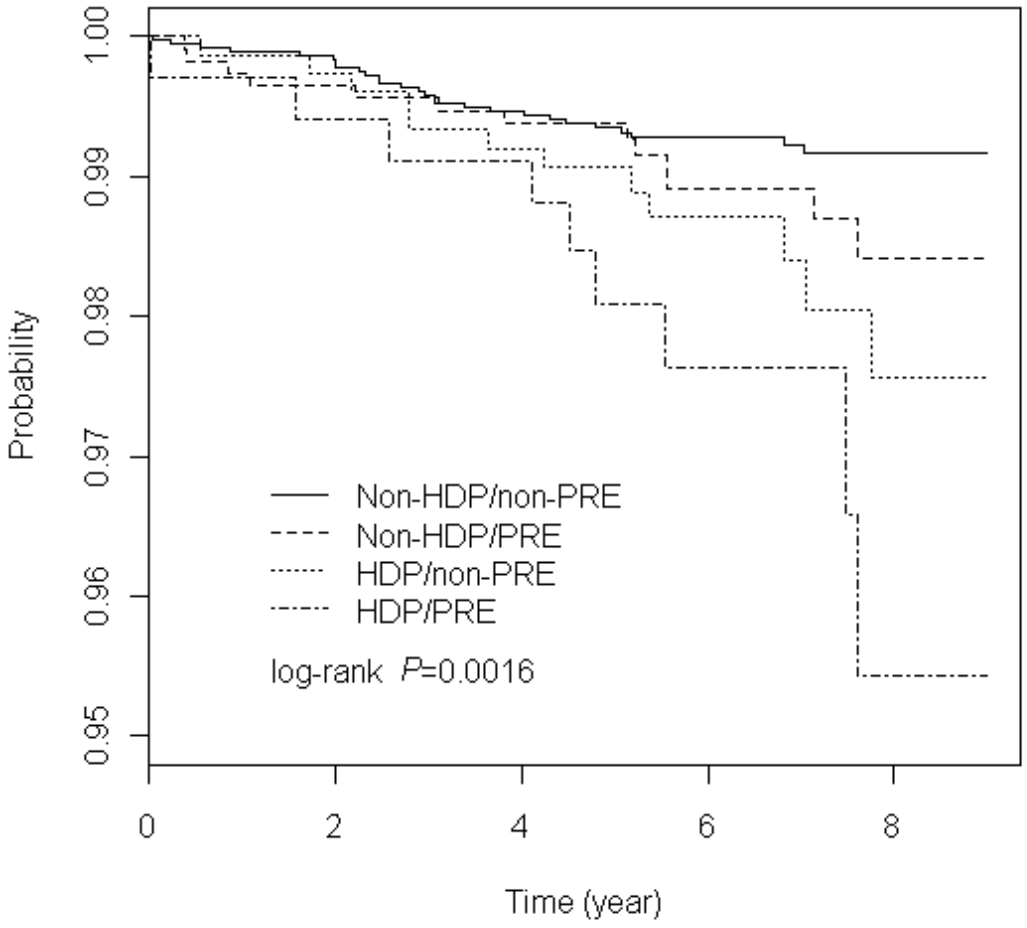

Probability
1.00
0.99
0.98
0.97
0.96
0.95
0
2
4
6
8
Time (year)
HDP=No
HDP=Yes
log-rank P=0.001

Figure 2


Probability
1.00
0.99
0.98
0.97
0.96
0.95
0
2
4
6
8
Time (year)
Non-HDP/non-PRE
Non-HDP/PRE
HDP/non-PRE
HDP/PRE
log-rank P=0.0016