Online Supplemental Material for the following article

TITLE: Potential health impact and cost-effectiveness of drug therapy for prehypertension

Study population:

Before starting this study, we search the published or unpublished articles from PubMed and Clinical trial.gov as well as the Chinese Clinical Trial Register (ChiCTR). Until now, there are seven randomised control clinical trials which aim to testify the effect from antihypertensive treatment (TROPHY Study, PHARAO study, PREVER study, CHINOM study, NCT01816698). However, only two studies have finished and published their results. The patents' characteristics are shown in **Table A1**. There are still three additional RCTs indicated as PREVER study, CHINOM study or registered as NCT01816698, which are currently recruiting participants or just finished. The inclusion and exclusion criteria are listed **Table A2**. Similar to the finished and ongoing clinical trials (**Table A1 and A2**), our simulated cohort did not include individuals with prior CVD. This also kept the predictive validity of the multivariate risk equations used in our model. Our study focused on individuals with high-range prehypertension (130-139/85-89 mmHg), as there was limited evidence of treatment effect available beyond this range (e.g, 120-130/80-85 mmHg). The characteristics of this population in our study were from Nanjing Community Cardiovascular Risk Survey study and were comparable with two previous nationally representative sample of Chinese residents [1, 2]. But they would vary in sensitivity analyses. The details of the study design had been previously reported[3].

Model structure:

In the Markov model, the cohort members with prehypertension progress through the model on four different disease path. Disease paths and disease states in each path are described below (**Figure A1- Figure A5**). On the prehypertension path, a person with prehypertension can undergo hypertension or have stroke, CHD, HF directly and either die or survive. Similarly, a patient with hypertension may undergo stroke, CHD, HF and either die or survive, but they cannot move back to prehypertension (**Figure A1**). On the HF path, patients can either survive or die from a heart failure suffered within a period (**Figure A3**). On the CHD and stroke, they have a very similar pathway as HF (**Figure A4 and Figure A5**).

Transition probability

For the estimation of primary CVD event rate, we firstly estimate the incidence of CHD, stroke and HF by their corresponding and validated risk equations using the individual data from Nanjing Community Cardiovascular Risk Survey study. The distribution for each risk factors among participants with prehypertension and hypertension can be found in **Table A3** and **Table A4**. Second, we average the incidence by each age groups. Third, the exponential interpolation was employed to smooth the age-specific annual rates for persons older than 75 years. Finally, based on the derived exponential function (shown on **Figure A6 and Figure A7**), we can derive the average age-specific annual rates from 30 to 100 years, but these rates will be enlarged or reduced by 25% during sensitivity analysis.

By the above method, our model does not have to dynamically calculate the CHD, stroke and HF incidence in every cycle. This will simplify our model and reduce the computational burden.

We will not use the above procedure to estimate the incident hypertension among prehypertensive participants as we want to explore the impact from those factors related to hypertension development in our following sensitive analysis. After calculating the event rate, we will convert them into transition probability. The relationship between the event rate (r) and the transition probability (ρ) for time period t is given by: $\rho = 1 - e^{-rt}$.

Cost:

In order to derive the cost of antihypertensive treatment and CVD events in China, we search them from two Chinese literature databases (CQVIP, Wanfan data) , China Health Statistics Yearbook report and PubMed as well. The quality of the article varied largely. however, we will primarily choose those performed at country level and then province level. Among those selected paper, clinical trials data will be first option and then observational studies. All study should not only report the average total cost but also the breakdown cost for each treatment (eg, drug cost, salary costs of primary healthcare providers).

For the cost of antihypertensive cost, the average cost per patient of $114.4 in urban control group was used [4]. For the cost of first-ever stroke, it will be calculated by adding the costs of hospitalized patients with stroke(RMB:12768.46) [5] and average annual cost for post stroke(RMB: 8219.72)[6].

For the cost of first-ever CHD, we choose the same method as Yanfei Wu' study[7], which assumed 50% surgery and 50% nonsurgery treatment from China Health Statistics Yearbook 2013(RMB:16802.4 for nonsurgery treatment, RMB:34835.7 for surgery treatment). For the cost of first-ever HF, RMB 7147.9 was also extracted from China Health Statistics Yearbook 2013 and the cost of post HF, it is estimated that RMB1837 will be used in Yu SB' study [8].

Regarding the range of the cost, as quite few studies reported the standard deviation and the distribution of the costs is more likely to be skewed, so we will use the 1/3 of the average cost as the minimum value, and 3 times as the maximum. This large variation will include most of the scenarios after crossed checking with those not selected studies. For those survivors after first-ever CHD event, we assumed to be 10% of that of year 1 for survivors afterwards.

Model validation

Our model was firstly validated by comparing model-projected life expectancies with actual China life tables in 2013[9]. We then computed the predicted 5-year CHD, stroke and HF incidences and mortality rates from our base-case model and compared them with incidence rates reported from published studies.

Tables A1 Finished studies

	TROPHY Study[10]	PHARAO study[11]:
Author	Stevo Julius et al	Stephan Lu¨ ders et al
Inclusion criteria	1:Subjects between the ages of 30 and 65 (inclusive) 2: have an average clinic BP in the high normal range of < 130-139/85-89 mmHg or 130-139/< 89 mm Hg	1,Age more than 50 years 2. had high-normal office BP in accordance with the definition of JNC7/ESH
Exclusion criteria	1: Have proteinuria >1 + (by dipstick method) 2: have a stroke, myocardial infarction (MI), transient ischemic attack (TIA), the presence of any clinically significant evidence of atherosclerosis or hypertensive target organ involvement or any significant medical condition that may compromise participation in this study.	1, Age less than 50 or greater than 85 years, 2, Prior use of antihypertensive medication 3, Blood pressure >=140/90 4, heart failure (NYHA grade II–IV), 5, unstable angina pectoris, 6. kidney disease (creatinine clearance <30 ml/min), 7, progressive potentiallyfatal disease (life expectancy <1 year), 8, Alcohol and drug addiction, 9, angiooedema or allergy to ramipril
Drug	Candesartan/placebo	Ramipril/placebo
N	391/381	505/503
Mean age	48.6/48.3	62.2/62.3
Sex, % male	59.1%/60.1%	49.7%/47.1%
BMI (kg/m^2)	29.9/30.0	27.1/26.6
Baseline SBP(mm Hg)	133.9/134.1	134.4/134.4
Baseline DBP(mm Hg)	84.8/84.8	83.6/83.6
Total Cholestrol (mg/dl)	202.9/205.7	NR
Triglycerides (mg/dl)	145.8/159.8	NR
HDLCholestrol (mg/dl)	48.9/49.2	NR
Glucose	95.5/95.9	NR
Serum Creatinine	0.84/0.85 ((mg/dl))	NR
Hx Diabetes	NR	14.3%/12.5%
Smoker	NR	12.1%/16.7%
Previous CAD	NR	6.7%/6.2%
Hyerlipidamia	NR	50.7%/50.3%
Myocardial infarction	NR	1.0%/0.8%
Renal insufficiency	NR	0.6%/1.4%
Peripheral arterial occlusive disease	NR	1.6%/1.4%
Chronic obstructive pulmonary disease	NR	3.4%/2.6%
Regular alcohol intake	NR	46.9%/44.1%

Tables A2 ongoing studies

	PREVER study[12]	CHINOM study[13]	NCT01816698[7]
Investigator	Flávio D Fuchs	Lisheng Liu	Zhiming Zhu
Drug	Chlorthalidone 12.5 mg plus amiloride 2.5 mg / placebo	Telmisartan / Indapamide / reserpine compound or placebo	Taurine granule / placebo
Inclusion criteria	1, 30 to 70 years of age 2, office average blood pressure: 120-139/80-89, if DM: systolic BP 120-130mmHg	1. Age: 45-79(male) or 50-79 (female) years old; 2. Blood pressure: 130≤SBP<140mmHg and/or 85≤DBP<90mmHg; 3. At least one of other cardiovascular risk factors; Cardiovascular risk factors: 1.Waist Circumference (WC): Male≥85cm , female≥80cm or overweight（BMI >25kg/m2） 2. TC≥220mg/dL or TG≥150mg/dL or HDL-C<40mg/dL 3. Glucose Level: 6.1≤FPG<7.0mmol/L and/or 7.8≤OGTT 2hPG<11.1mmol/L 4. Current smoker 5. Cardiac insufficiency (NYHA II) 6. Proteinurea or microalbuminuria 7. Family history of early onset of cardiovascular diseases 8. Family history of hypertension or diabetes 9. Age> 65 years old	Blood pressure: 120mmHg≤SBP<140mmHg.
Exclusion criteria	1,low life expectancy 2,other indications for the use of diuretics, such as cardiovascular disease 3,intolerance to the study drugs 4, pregnancy	1. Diabetes mellitus（FPG≥7.0mmol/L and/or OGTT 2hPG≥11.1mmol/L） 2. Hypertensive patients（SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg） 3. Patients participating in any other studies within three months or concomitantly 4. Presence of renal dysfunction, Cr >133 mmol/L, or BUN > 14.2mmol/L 5. Presence of hepatic dysfunction (AST and/or ALT is 3 times higher than normal limit) 6. Hypersensitivity to agents used in this study 7. Stroke or myocardial infarction within 6 months of the enrollment. 8. Balloon dilatation of coronary arteries or bypass operation within 2 months prior to the study 9. Presence of malignant tumors or other serious diseases 10.Pregnant or lactating women; women in reproductive age not using recognized contraceptive methos 11. Gout or serum uric acid higher than 8.0mg/dL 12. Incapacity or unwillingness to sigh the informed consent 13. Incapacity for follow up 14. Other reasons that on the discretion of the investigators that not appropriate to participate into the study	1. Diabetes 2. Hypertension: SBP≥140mmHg, or DBP≥90mmHg. 3. known allergy to trial drugs 4. Myocardial infarction or cerebrovascular accident in the year preceding the trial 5. Clinical Congestive Heart Failure 6. Secondary hypertension 7. Pregnancy or lactating women 8. Malignant tumor 9. Gastroesophageal reflux or gastroduodenal ulcer 10. History of hepatitis or cirrhosis 11. History of kidney disease 12. Body weight< 35Kg

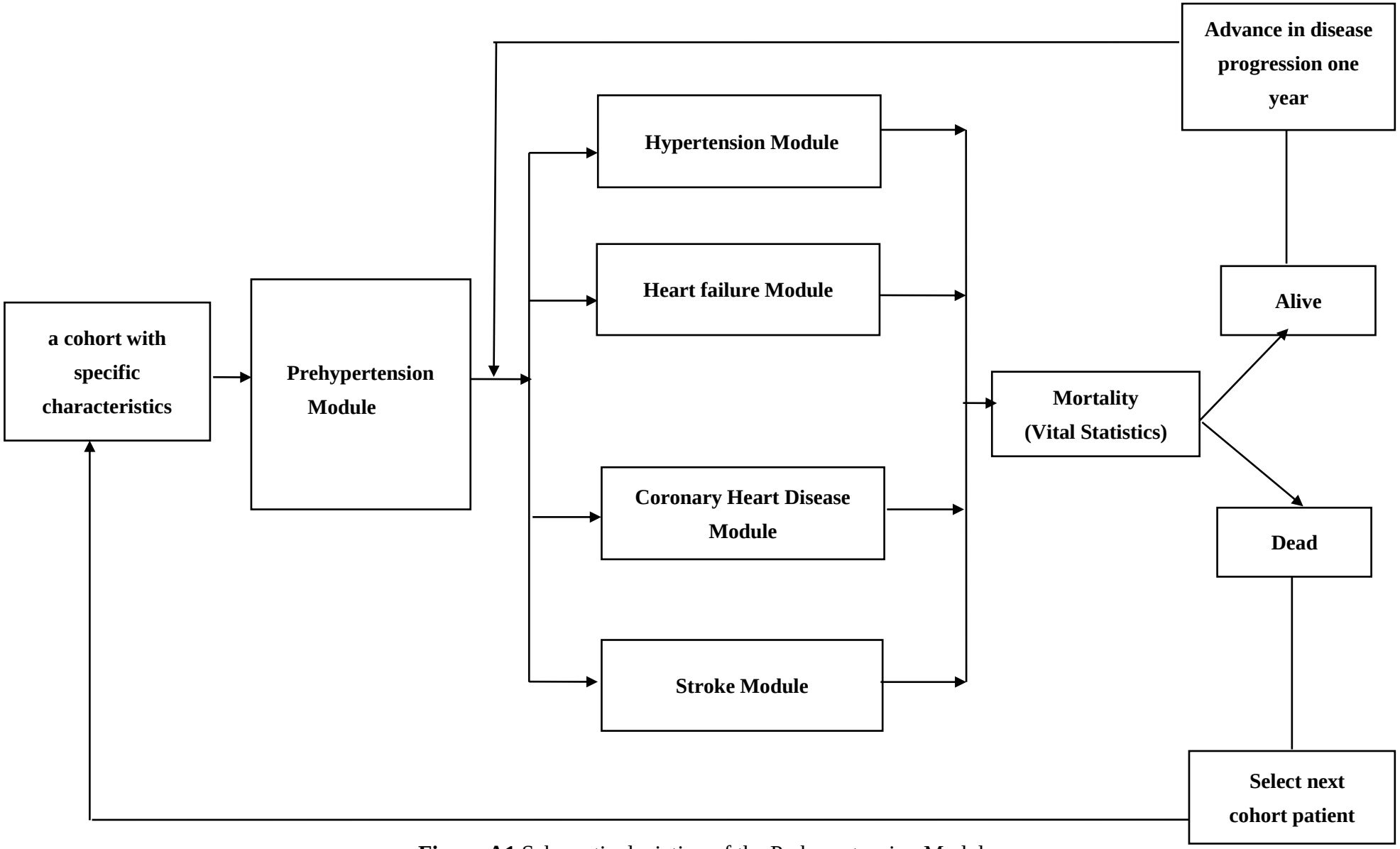

Figure A1 Schematic depiction of the Prehypertension Module

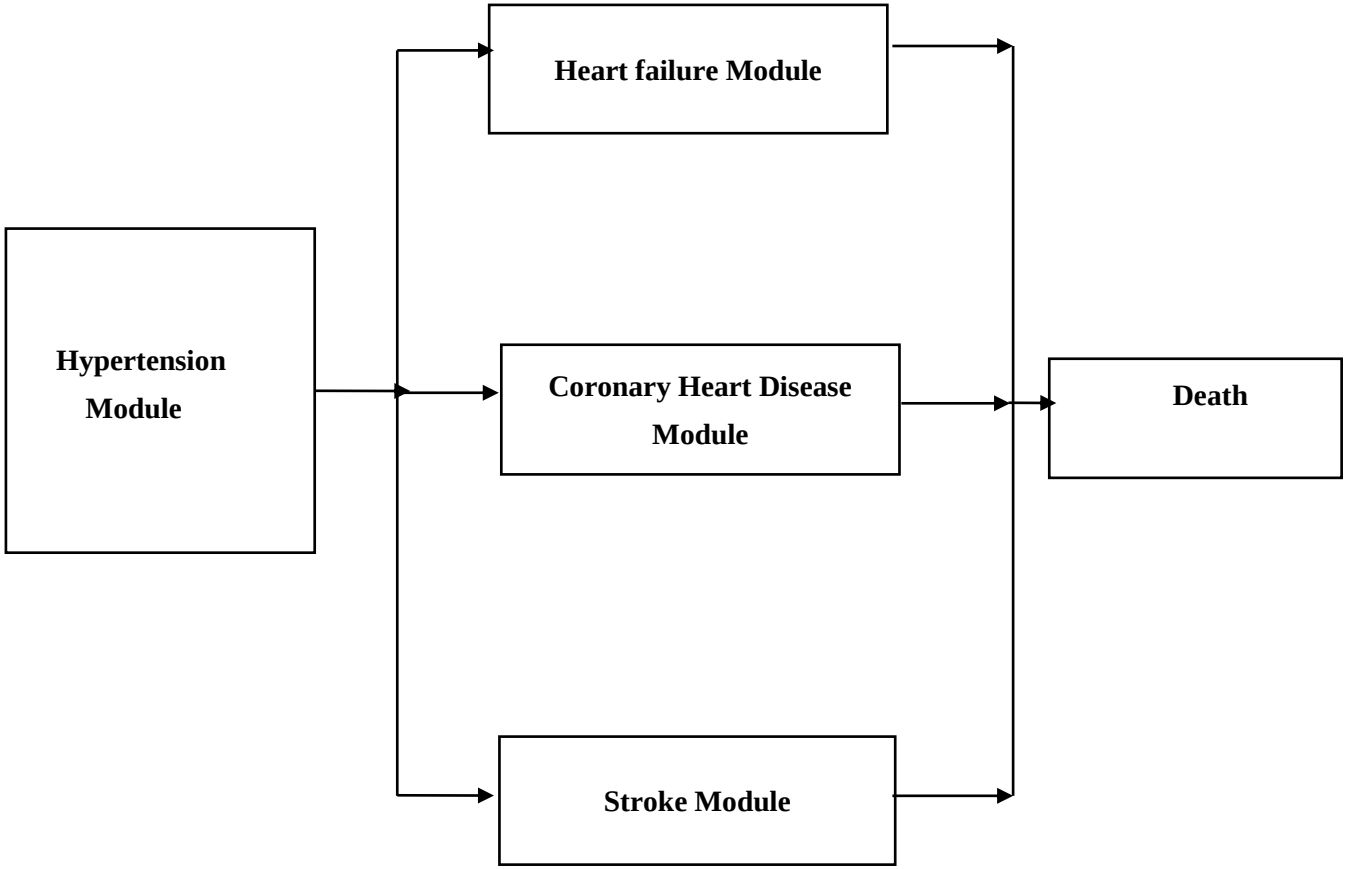

Figure A2 Schematic depiction of the Hypertension Module

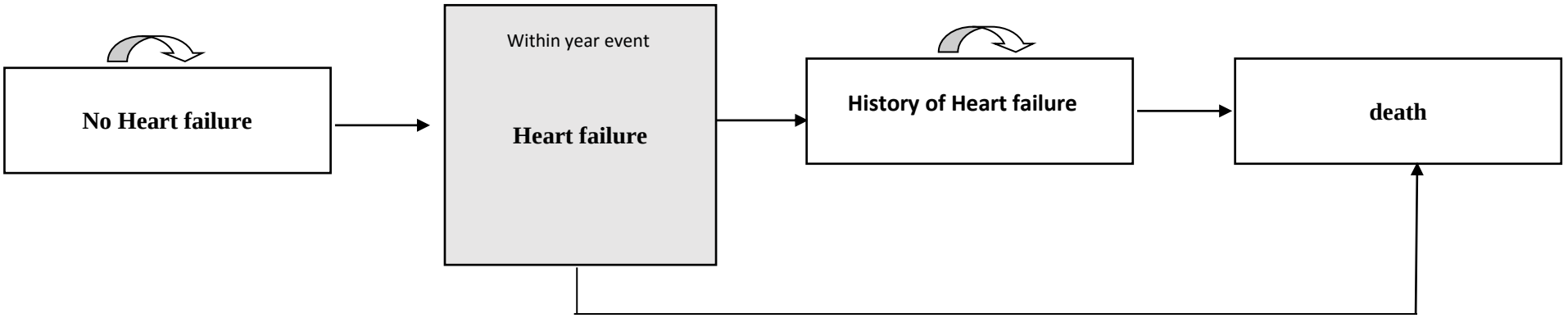

Figure A3 Schematic depiction of the Heart Failure Module

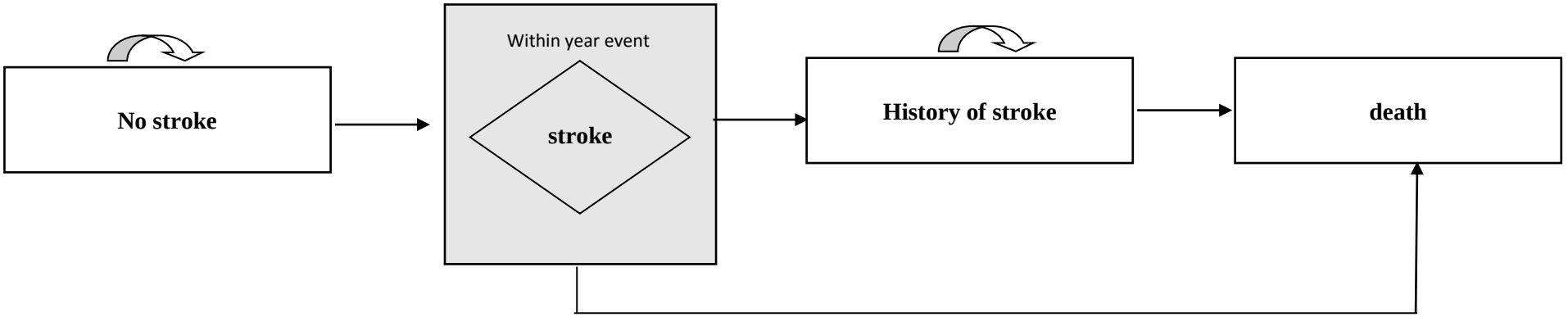

Figure A4 Schematic depiction of the stroke Module

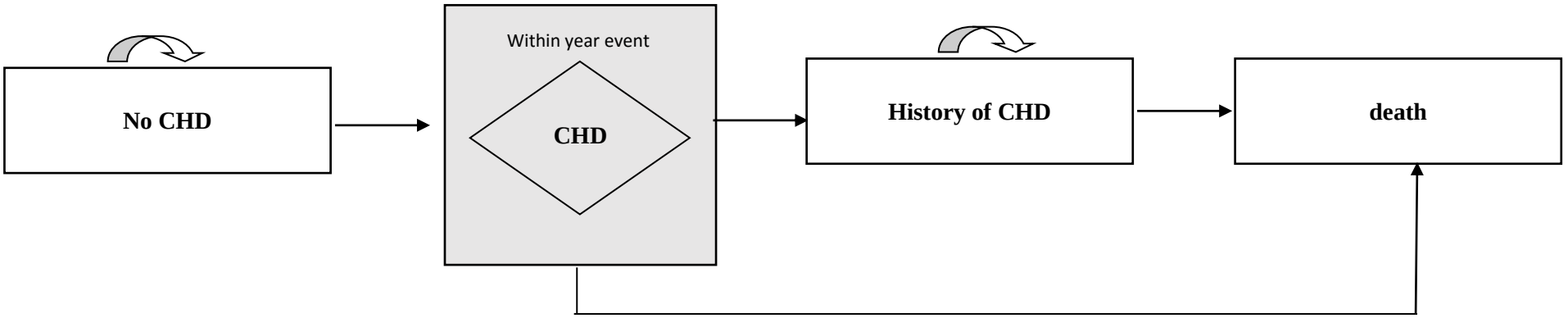

Figure A5 Schematic depiction of the stroke Module

Tables A3 Characteristic for individuals with prehypertension(130-139mmHg/85-89 mmHg)

Age(year)	SBP(mmHg)	DBP(mmHg)	TC(mmol/L)	HDL-C(mmol/L)	BMI(Kg/m^2)	Female(%)	Smoking(%)	DM(%)
30-	129.8(5.4)	83.0(6.2)	3.99(0.69)	1.21(0.23)	24.94(3.71)	52.63	15.79	1.20
35-	130.6(5.9)	82.9(5.7)	4.29(0.84)	1.25(0.32)	24.42(3.77)	51.62	27.20	2.50
40-	130.61(6.1)	83.4(5.4)	4.47(0.96)	1.30(0.31)	24.75(3.52)	51.94	30.28	3.89
45-	131.5(5.7)	83.5(4.9)	4.55(0.95)	1.32(0.33)	24.82(3.80)	55.86	31.23	5.12
50-	131.8(5.5)	82.9(5.3)	4.71(0.94)	1.37(0.31)	24.53(3.26)	58.38	29.36	7.78
55-	132.5(5.2)	82.5(5.4)	4.79(0.93)	1.36(0.30)	24.81(4.52)	56.24	27.98	8.70
60-	133.3(4.5)	80.4(5.9)	4.79(0.95)	1.37(0.30)	24.06(3.40)	54.25	29.06	8.96
65-	134.3(4.1)	79.1(6.3)	4.89(0.92)	1.40(0.30)	23.87(3.72)	51.05	31.17	12.34
70-	134.5(4.6)	76.5(6.7)	4.74(0.86)	1.38(0.27)	24.66(3.67)	45.78	25.30	13.25
Overall	131.86(5.56)	82.40(5.73)	4.61(0.95)	1.33(0.32)	24.54(3.79)	54.41	29.23	6.57
CNHS	131.9(5.6)	80.2(7.2)	na	na	23.1(3.7)	47.7	39.9	2.3
InterASIA*	127.76(7.65)	83.75(3.86)	4.74(1.19)	1.33(0.43)	23.72(3.95)	43.23	na	5.27

*** prehypertension was defined as 120-139mmHg/80-89 mmHg**

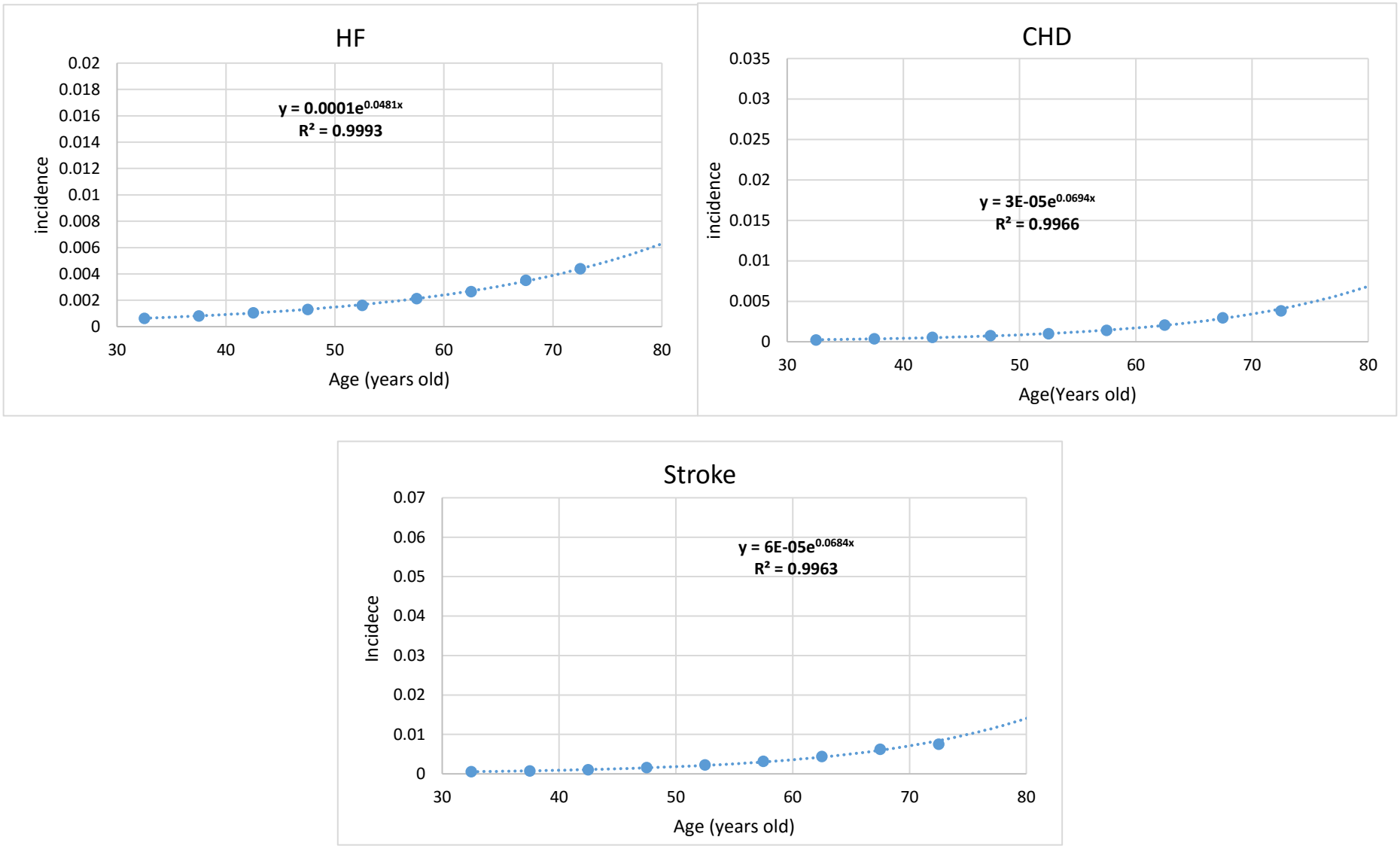

Figure A6 Exponential projection of incidence of HF, CHD and Stroke for individuals with prehypertension(130-139mmHg/85-89 mmHg)

Tables A4 Characteristic for individuals with hypertension (>140mmHg/90 mmHg or on antihypertensive treatment)

Age(year)	SBP(mmHg)	DBP(mmHg)	TC(mmol/L)	HDL-C(mmol/L)	BMI(Kg/m^2)	Female(%)	Smoking(%)	DM(%)
30-	142.41(12.49)	93.16(10.07)	4.67(0.93)	1.38(0.30)	24.81(4.46)	50.00	18.18	4.55
35-	145.44(14.24)	93.22(9.07)	4.47(0.98)	1.27(0.34)	25.63(4.02)	45.01	31.49	3.65
40-	147.00(14.78)	94.45(9.29)	4.54(0.89)	1.30(0.31)	25.62(4.02)	52.25	26.83	6.55
45-	149.37(15.23)	94.18(9.29)	4.65(0.88)	1.33(0.32)	25.54(3.93)	56.31	27.36	5.95
50-	151.18(14.93)	93.07(9.05)	4.79(0.96)	1.37(0.33)	25.21(3.62)	57.72	27.67	8.42
55-	154.05(15.76)	92.41(9.66)	4.84(0.94)	1.38(0.32)	25.14(3.87)	55.37	28.24	10.05
60-	154.76(16.35)	90.82(10.15)	4.92(0.94)	1.39(0.32)	24.75(4.13)	53.27	29.63	11.54
65-	158.13(16.52)	88.76(10.56)	4.97(0.97)	1.42(0.32)	24.43(3.83)	53.8	28.67	11.92
70-	160.31(17.76)	87.39(10.62)	4.81(0.93)	1.40(0.35)	24.43(5.10)	44.17	30.42	11.67
overall	151.80(16.00)	92.39(9.80)	4.75(0.95)	1.36(0.32)	24.91(3.97)	53.74	28.39	8.54
CNHS	154.67(11.12)	89.87(10.08)	na	na	23.74(3.97)	51.29	36.36	3.28

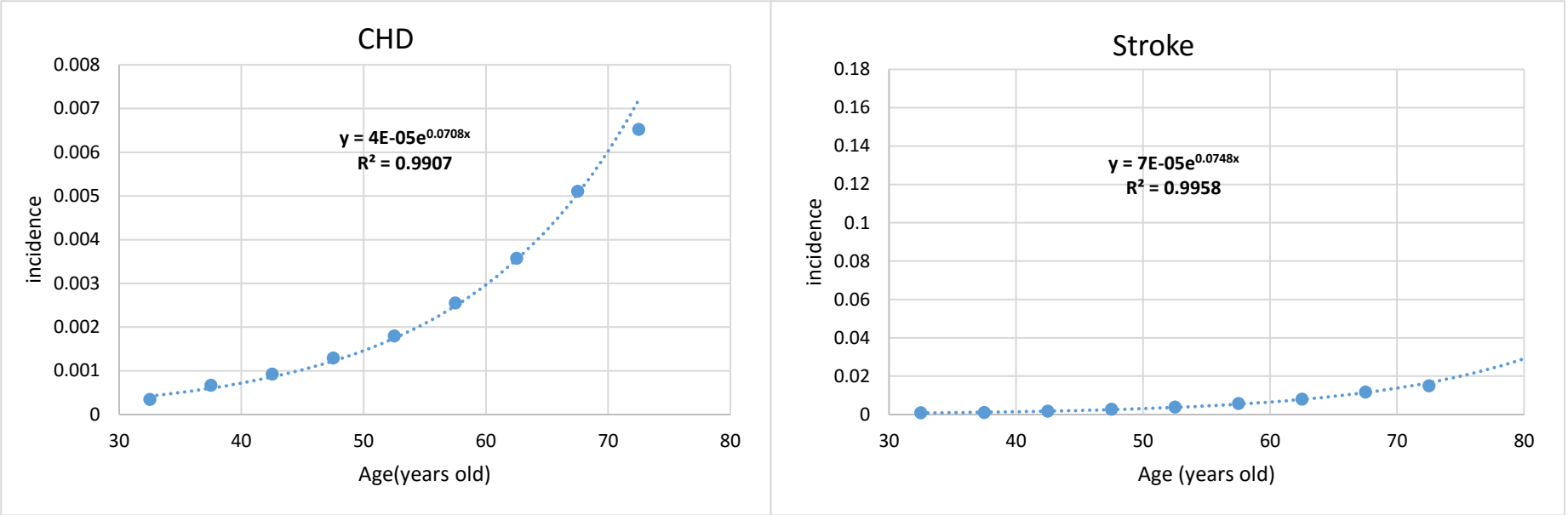

Figure A7 Exponential projection of incidence of HF, CHD and Stroke for individuals with hypertension

Table A5 Probability of new events after disease

Description	Value	Distributions*	Reference
Heart failure during the first year after MI	0.121	Beta	[14]
Stroke during the first year after MI	0.012	Beta	[14]
Reinfarction during the first year after MI	0.067	Beta	[14]
Stroke after reinfarction	Assumed to be the same with the first MI	Beta	[14]
HF after reinfarction	Assumed to be the same with the first MI	Beta	[14]
Death after reinfarction	Assumed to be the same with the first MI	Beta	[14]
Long-term heart failure after MI	0.03822	Beta	[14]
Long-term stroke after MI	0.01403	Beta	[14]
Long-term reinfarction after MI	0.018868	Beta	[14]
MI first year after Stroke	0.065	Beta	[15]
Recurrent during the first year after Stroke for men	0.164	Beta	[16]
Recurrent during the first year after Stroke for women	0.1988	Beta	[16]
Probability of Death after recurrent Stroke	0.183	Beta	[15]
Long-term recurrent Stroke after Stroke	0.0998	Beta	[15]
Stroke during the first year after HF	0.0184	Beta	[12]
Long-term stroke during the first year after HF	0.012	Beta	[12]

* uncertainty in event rates was presented through Beta distributions based on the number of events that occurred and the number of patient at risk.

Tables A6: Comparison of the 5-year incidences or life years with published data

	Model predict	**Published data**
Hypertension(%)	31.37	22.4-63[17-19]
CHD(%)	0.8	0.19-1.50[2, 20-24]
Stroke(%)	1.46	0.33-2.61[2, 20-24]
HF(%)	0.95	No data
CVD mortality(%)	0.59	0.29-1.96[2, 24]
All-cause mortality (%)	3.08	2.61-6.90 [2, 25]
Expected life	30.20(Female) 26.69(Male)	31.31(Female);27.21 (Male) *

***** Calculated based the China life tables in 2013

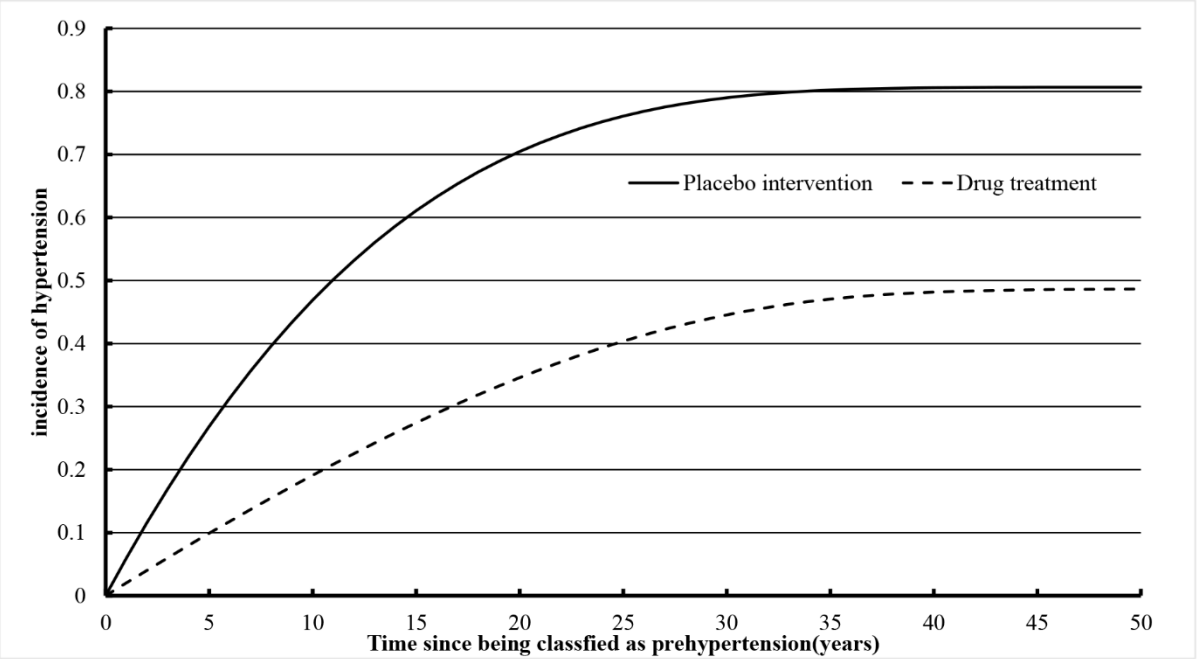

Figure A8: Simulated cumulative incidence of hypertension among adults with prehypertension

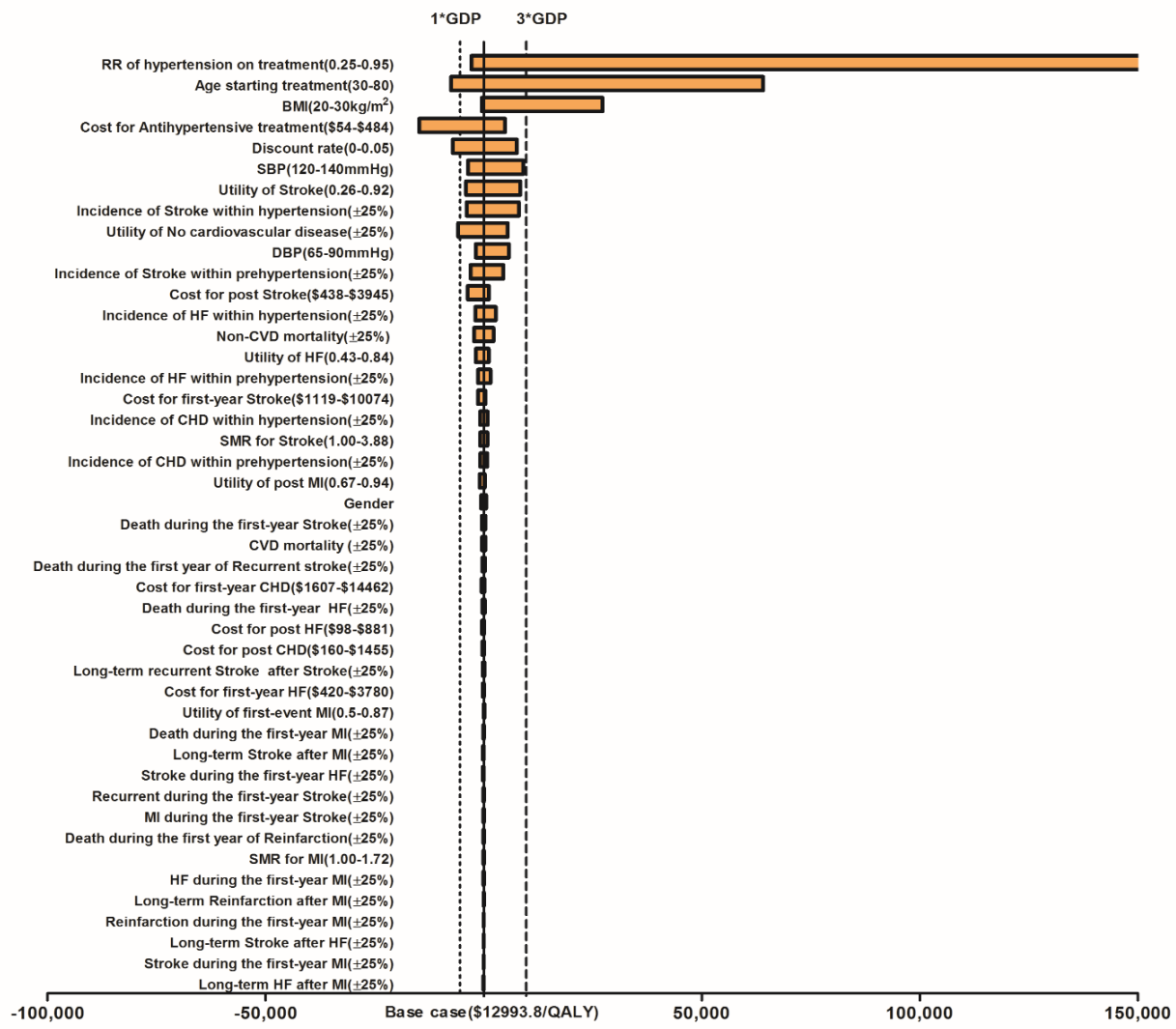

Figure A9 Sensitivity analysis of model variables

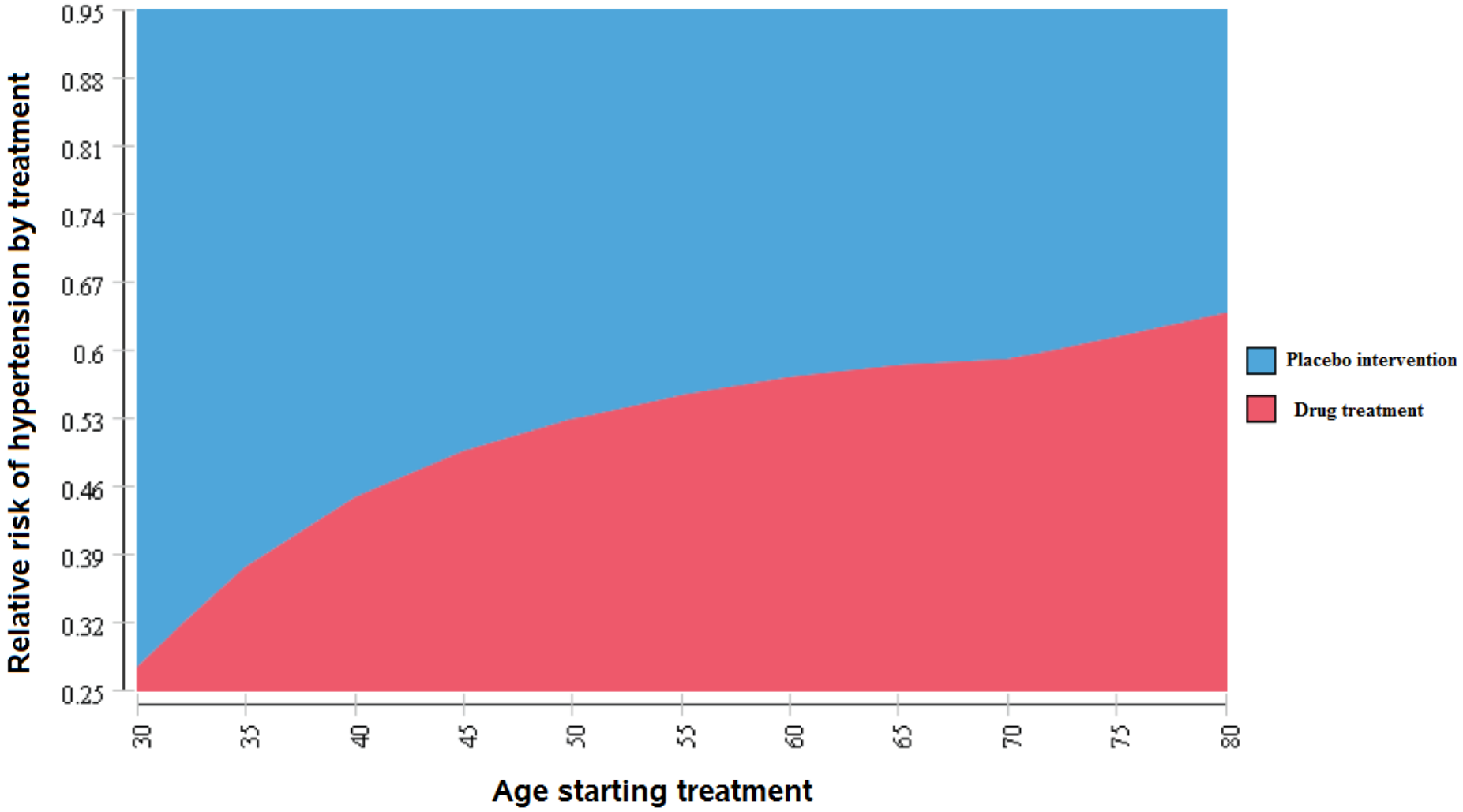

Figure A10 Sensitivity Analysis of Potentially Important Model Variables

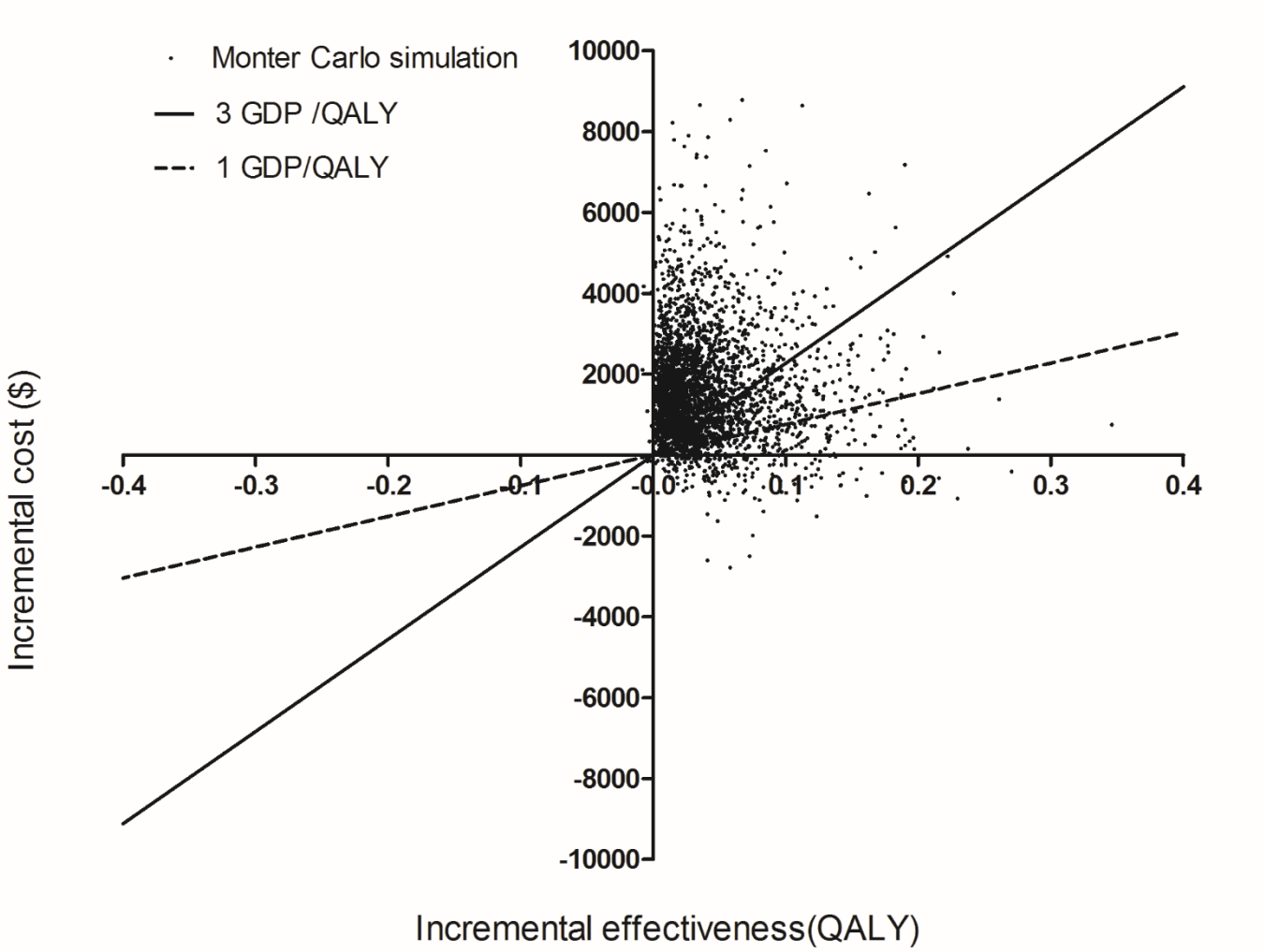

Figure A11: Incremental cost-effectiveness scatter plots

Reference:

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