Projected impact of blood pressure control interventions on cardiovascular disease and death in China: a modeling study

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A thesis
submitted in partial fulfillment of the
requirements for the degree of

Master of Public Health

University of Washington
2020

Committee:
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Program Authorized to Offer Degree:
Global Health

University of Washington

Abstract

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The objective of this project is to develop a new framework to estimate the country-level health impact of scaling up interventions that treat and prevent hypertension to achieve global targets for the prevention and control of noncommunicable disease. To do this, we developed a state-transition Markov model tested with data for a single country, China. Modeled outcomes include prevalence and deaths of ischemic heart disease, hypertensive heart disease, ischemic stroke, and hemorrhagic stroke. Secondary, publicly available data from the Global Burden of Disease Study (GBD), Noncommunicable Disease Risk Factor Collaboration (NCD-RisC), and other studies were used to populate and parameterize the model. For two interventions 1) increasing antihypertensive drug therapy to 50% effective coverage by 2025 and 2) implementing population-wide salt reduction policies to achieve 30% reduction in salt intake, we project approximately 260 million cumulative new cases of cardiovascular disease and 15 million

cumulative deaths could both be averted between 2020 and 2040. We project approximately 1.3 million lives could be saved per year by 2040 – making up 6.8% of all deaths that year. Using this simple but flexible model, we show the potential to prevent premature mortality and morbidity of these two relatively simple public health interventions.

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INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of mortality and morbidity globally, making up approximately 15% of all disability-adjusted life years (DALYs) and 32% of all deaths in 2017.[1,2] As many low -and middle-income countries progress through the epidemiologic transition, the burden of cardiovascular diseases is predicted to have an outsized impact on health loss in these areas.[3] Over the past several decades, many low- and middle-income countries have observed economic and health advancements that have led to a decrease in childhood mortality rates, fertility rates, and communicable diseases shifting the population distribution towards older ages.[4] This demographic shift, coupled with the rise in certain behavioral and environmental risk factors (diet, high blood pressure, pollution, etc.) has resulted in a higher proportion of the health burden attributable to CVDs and other noncommunicable diseases.[5,6]

In light of these trends, the United Nations Sustainable Development Goals target 3.4 calls a one-third reduction in premature mortality from noncommunicable diseases (NCDs) between 2015 and 2030, building off of the World Health Assembly global voluntary targets for 2025[7], which include:

- A 25% relative reduction in the prevalence of raised blood pressure;
- At least 50% of eligible people receiving drug therapy and counselling to prevent heart attacks and strokes;
- A 30% relative reduction in mean population intake of salt.

With nearly one-fifth of the world's population, China's progression through this epidemiologic transition has been of great interest to the public health community. There is potential to prevent an enormous number of new CVD cases and deaths in China, and some see it as an opportunity to help identify effective strategies that may be applied to other low- and middle-income countries that progress through the later phases of the epidemiologic transition.[8]

Two modifiable risk factors, raised systolic blood pressure and salt consumption, rank number one and three respectively in percentage of attributable deaths in China according to a Global Burden of Disease Study (GBD) 2017 Risk Factor Analysis.[9] Strong evidence exists for low-cost interventions targeting hypertension that shows significant impact on cardiovascular disease mortality and morbidity.[10] Studies show that population-based interventions that reduce dietary sodium intake by 15% have been estimated to cost less than $0.40 per person per year and scaling up anti-hypertensive drug treatment regimens could cost on average $1.10 per person per year in low-income countries.[11] However, in many countries including China, hypertension control remains low.[12] The gap in treatment coverage, increasing exposure to diet-related risk factors, and the aforementioned demographic shifts pose significant challenges to health systems.[13] This presents a unique opportunity to better understand the projected benefit of increased investment in cardiovascular health.

In this analysis, we employ a cohort state-transition Markov model to estimate the projected effect of increasing the coverage of antihypertensive drug therapy and implementing population-wide salt-intake reduction policies on cardiovascular disease. We estimated the projected effect these two interventions have on cardiovascular disease attributable to hypertension. Two intervention scale-up scenarios are modeled, one default scenario structured around the World Health Assembly global voluntary targets for 2025,[7] and another alternate scenario modeling a more ambitious intervention scale-up function. Using publicly available data for China, we examined the ability of this new model to make reasonable estimates of the projected number of cases that could be averted and lives that could be saved in China between 2020 and 2040.

METHODS

Markov Model

To predict the estimated future cardiovascular health burden in China, we developed a cohort state-transition Markov model to analyze the impact of blood pressure reduction interventions on cardiovascular disease prevalence and death. Four independent cause models were used to estimate morbidity and mortality from ischemic heart disease (IHD), hypertensive heart disease (HHD), ischemic stroke, and hemorrhagic stroke. “All cardiovascular diseases” is defined for this analysis as combined IHD, HHD, and ischemic stroke, and hemorrhagic stroke. Estimates were made for adults in China, age 20 and above between the year 2020 and 2040.

State-transition probabilities were calculated using age- and sex-specific rates of incidence, case fatality, and mortality from the Global Burden of Disease (GBD) Study 2019 and were assumed constant over time. Population projections for each cohort were generated assuming constant background mortality rates from GBD 2019, constant fertility rates and no net migration.

Figure 1: Markov model schematic example for ischemic heart disease

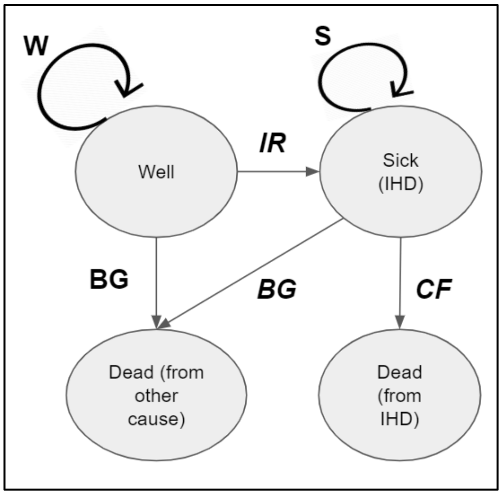


Table 1: Transition probabilities

Variable	Description	Calculation
W	Probability of remaining in the well state	W = 1 – (IR + BG)
S	Probability of remaining in the sick state	S = IR – CF – BG
BG	Probability of dying from another cause (background mortality rate)	All-cause mortality rate minus cause specific mortality rates
IR	Probability of becoming sick (incidence rate)	GBD 2019 estimates
CF	Probability of dying from the model-specific cause (case fatality rate)	Number of deaths from a specific cause divided by the prevalent cases

Data sources

Model inputs and parameters were sourced from publicly available, secondary data. Data from the Global Burden of Disease 2019 study was used to estimate disease incidence, prevalence, and death rate for each age-sex-country-specific cohort as well as for demographic projections. Mean systolic blood pressure (SBP) estimates from the NCD Risk Factor Collaboration and estimates of variance from NHANES 2015-2016 Blood Pressure Data were used to construct distributions of blood pressures by age, sex and country.

Intervention scenarios

Three intervention combinations were designed for the ‘default’ intervention scenario. First, the implementation of antihypertensive treatment intervention – a clinical intervention defined as the effective blood pressure control for those with hypertension to a target of under 140 mmHg (or 130 mmHg for those with diabetes according to AHA/ACC guidelines).[14] The coverage of this intervention is scaled up from baseline linearly over time to achieve a target effective coverage of 50% by 2025 – where effective coverage is defined as the percentage of those with hypertension who have controlled systolic blood pressure below 140 mmHg. Second, a population-wide policy intervention to reduce the consumption of salt to achieve the global recommendation for a 30% relative reduction in salt intake (from approximately 10 grams to 7 grams/per day in China).[15] This intervention may include such policy implements as market caps, excise taxes, nutrition labelling, or other population-wide policy measures to reduce salt intake.[16] The salt policy intervention is assumed to be instantaneously implemented in 2020 - a simplifying assumption based on the logistics of implementing policy-based interventions compared to clinical interventions (which require longer scale-up time for supply chain, screening, and other healthcare-access related expansion). Third, the implementation of both these interventions in a given population – wherein the salt intervention is assumed to be followed by the rollout of the antihypertensive therapy intervention.

Intervention targets for this ‘default’ scenario were chosen to align with the World Health Assembly global voluntary targets for 2025.[7] In view of blood pressure control and salt reduction rates among some of the most high preforming countries seen in Tables 2 and 3 below, these targets represent an ambitious but precedented goal.

Table 2: Hypertension Prevalence awareness, treatment, and control by country/region

Country/Region	Aware (% of hypertensives)	Treated (% of hypertensives)	Controlled (% of hypertensives)	Data source
HIC	49.0%	46.7%	19.0%	Chow et al., 2013[12]
UMIC	52.5%	48.3%	15.6%	Chow et al., 2013[12]
LMIC	43.6%	36.9%	9.9%	Chow et al., 2013[12]
LIC	40.8%	31.7%	12.7%	Chow et al., 2013[12]
Canada	84%	81%	69%	Zhou et al., 2019[17]
USA	79%	70%	49%	Zhou et al., 2019[17]
Germany	82%	70%	48%	Zhou et al., 2019[17]

Table 3: Salt reduction via multi-component strategies by country

Country	Reduction in salt consumption (g/day)	Data source
Finland	4 g/day	Hyseni et al., 2017[16]
Japan	4 g/day	Hyseni et al., 2017[16]
Turkey	3 g/day	Hyseni et al., 2017[16]
The UK	1.3 g/day	Hyseni et al., 2017[16]

We also designed an alternate, more ambitious intervention scale-up scenario based on high preforming country coverage rates for blood pressure control and reduction in salt consumption rates. In this alternate scenario, antihypertensive therapy effective coverage is scaled up to 80% by the year 2030 and a relative reduction in average salt intake target is set to

50% (which coincides with WHO guidelines of 5 grams/per day optimal salt intake).[18] This alternate scenario models a more accelerated antihypertension therapy coverage scale-up and a larger absolute reduction in sodium intake than some of the highest preforming countries and therefore represents a substantially ambitious target. Due to the ambitious nature of this antihypertensive therapy coverage target, a longer time-horizon (2020-2030) was chosen compared to the default scenario (2020-2025).

Table 4: Model parameters and data sources

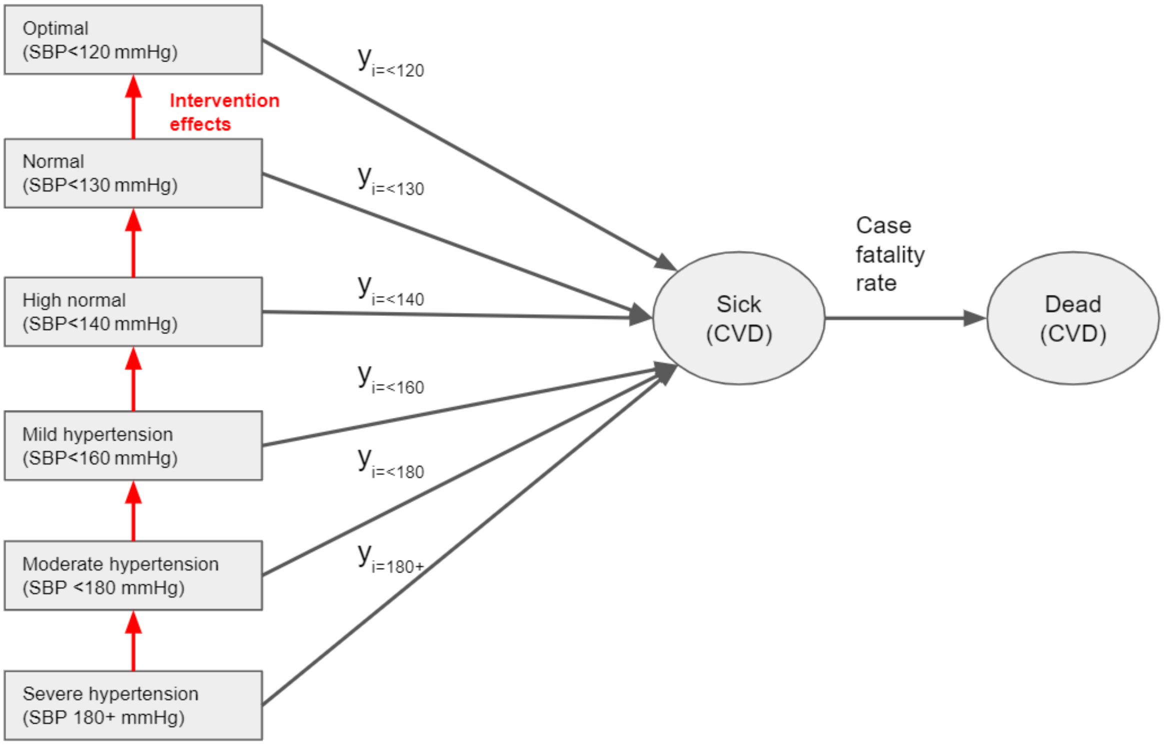
Parameter	**Value**	**Data Source**
Baseline hypertension effective coverage	19%	Feng et al., 2014[13]
Target hypertension effective coverage (default)	50%	WHO[7]
Target hypertension effective coverage (alternate)	80%	NA
Baseline salt consumption	10 g	Xian et al., 2020[15]
Target salt consumption (default)	7 g	WHO[7]
Target salt consumption (alternate)	5g	WHO[18]
Salt reduction efficacy:		
Hypertensives	-1.23 mmHg/g	He & Macgregor, 2013[19]
Normotensives	-0.55 mmHg/g	
Relative risk reduction for every 10 mmHg reduction in SBP:		Ettehad et al., 2016[20]
IHD	17%	
HHD*	18%	
Stroke	17%	

*Assuming heart failure as a proxy endpoint for hypertensive heart disease

Blood pressure-specific intervention effects

Intervention benefits in the model are conferred via their impact on blood pressure. Baseline blood pressure distributions were constructed assuming a gamma distribution; using age-, sex-, and country-specific mean SBP estimates from the NCDrisC group and NHANES blood pressure survey estimates of age- and sex-specific SBP variance.[21] For this model, variance calculated form NHANES data was assumed to be generalizable to the population of China. Each age- and sex-specific distribution is shifted according to the intervention scenario and the resultant incidence rates are calculated as described below.

Figure 2: Intervention effect schematic



For each blood pressure category (i), incidence of CVD (y_i), can be estimated using a “standardized” CVD risk (α), which is calculated the taking the sum of blood pressure-specific relative risk of CVD (RR_i) times baseline (i.e. no intervention) proportion of the population in each SBP category (p_i). The average incidence irrespective of blood pressure (y) is then multiplied by the SBP-specific relative risk (RR_i) divided by the "standardized" CVD risk (α) to give us the blood-pressure specific incidence rate of disease (y_i).

$$(1)\ \alpha = \sum_{i=1}^{n} p_i \times RR_i$$

$$(2)\ y_i = \frac{RR_i}{\alpha} \times y$$

Then, the average incidence (y^*) for the intervention scenario can be calculated by taking the population weighted average using the intervention-adjusted proportion of population in each SBP category (p_i^*) :

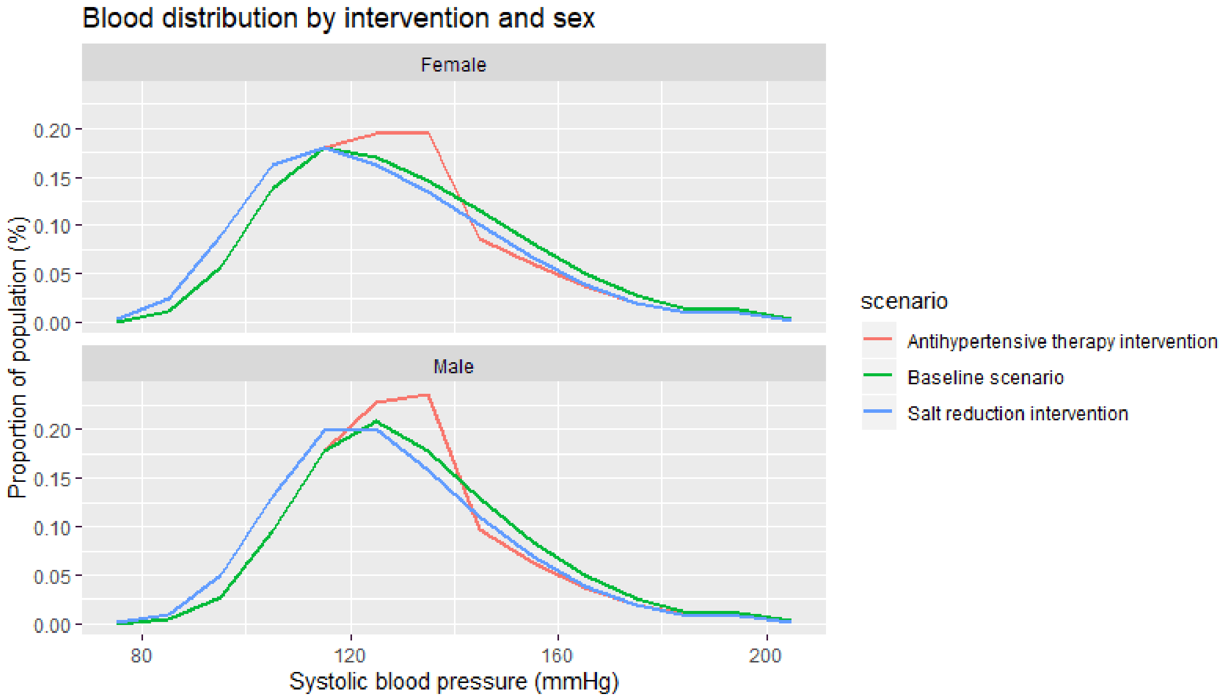
$$(3)\ y^* = \sum_{i=1}^{n} p_i^* \times y_i$$

These calculated average incidence rates are used in the intervention scenario Markov models to predict the CVD morbidity and mortality prevented by each intervention. In this model, we assume no impact on case fatality.

RESULTS

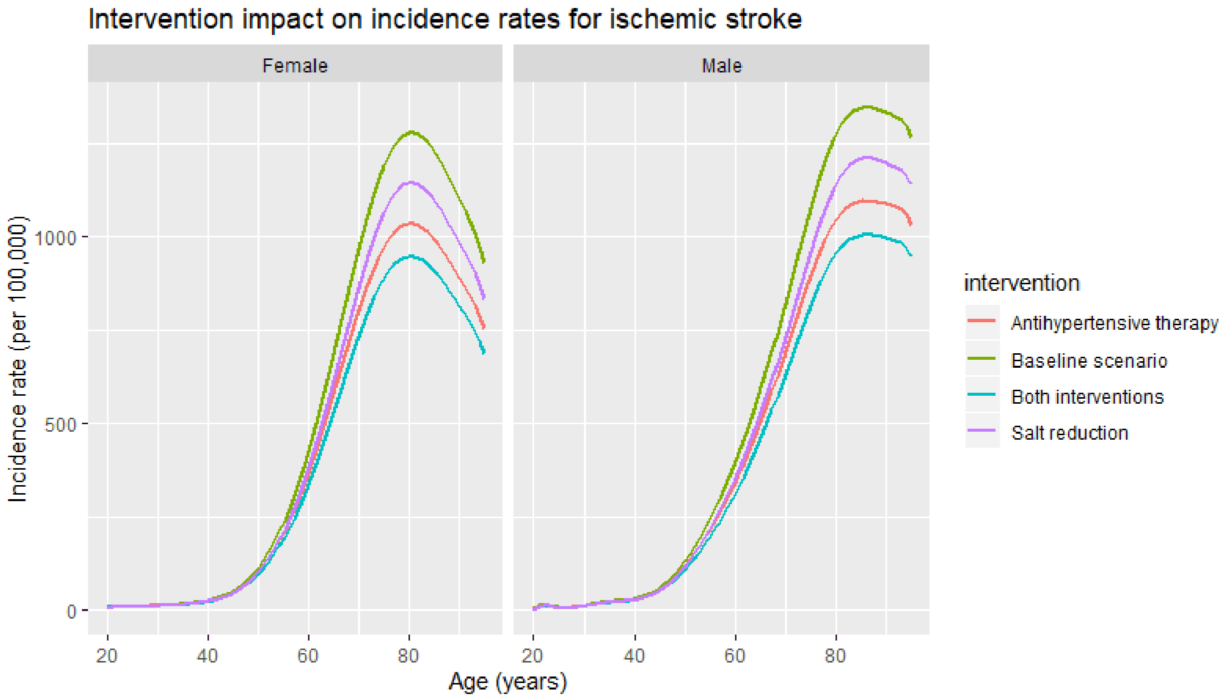
By its definition, the antihypertensive therapy intervention largely acts on the shape of blood pressure distribution in a given population, only targeting those in the right tail of the distribution with raised blood pressure. The salt reduction intervention acts on the mean of the distribution, therefore shifting the entire distribution to the left.

Figure 3: Blood pressure intervention impacts on blood pressure distributions



These blood pressure distribution shifts result in the reduced average incidence rates in cardiovascular disease, with increasing benefit conferred to older populations, as seen in the example of ischemic stroke below in Figure 4. Results for all cardiovascular diseases are presented in Figures A2-A5 in the Appendix.

Figure 4: Blood pressure specific incidence rates



Baseline projections

For all cardiovascular diseases (ischemic heart disease, hypertensive heart disease, ischemic stroke, and hemorrhagic stroke) our model predicts deaths to rise from 4.5 million in 2020 to 9.1 million in 2040 in the baseline (no interventions) scenario for all ages and both sexes. Per year, this results in a 2-3% relative increase in number of deaths. For all cardiovascular diseases, our model predicts the number of prevalent cases to increase from 86 million in 2020 to 148 million in 2040 for all ages and both sexes, similarly showing 1-3% relative increase in number of cases per year. These increases can be seen in the "Projection" data in Figure 5 below, in context of historic trends in CVD deaths and prevalence per GBD 2019 results.

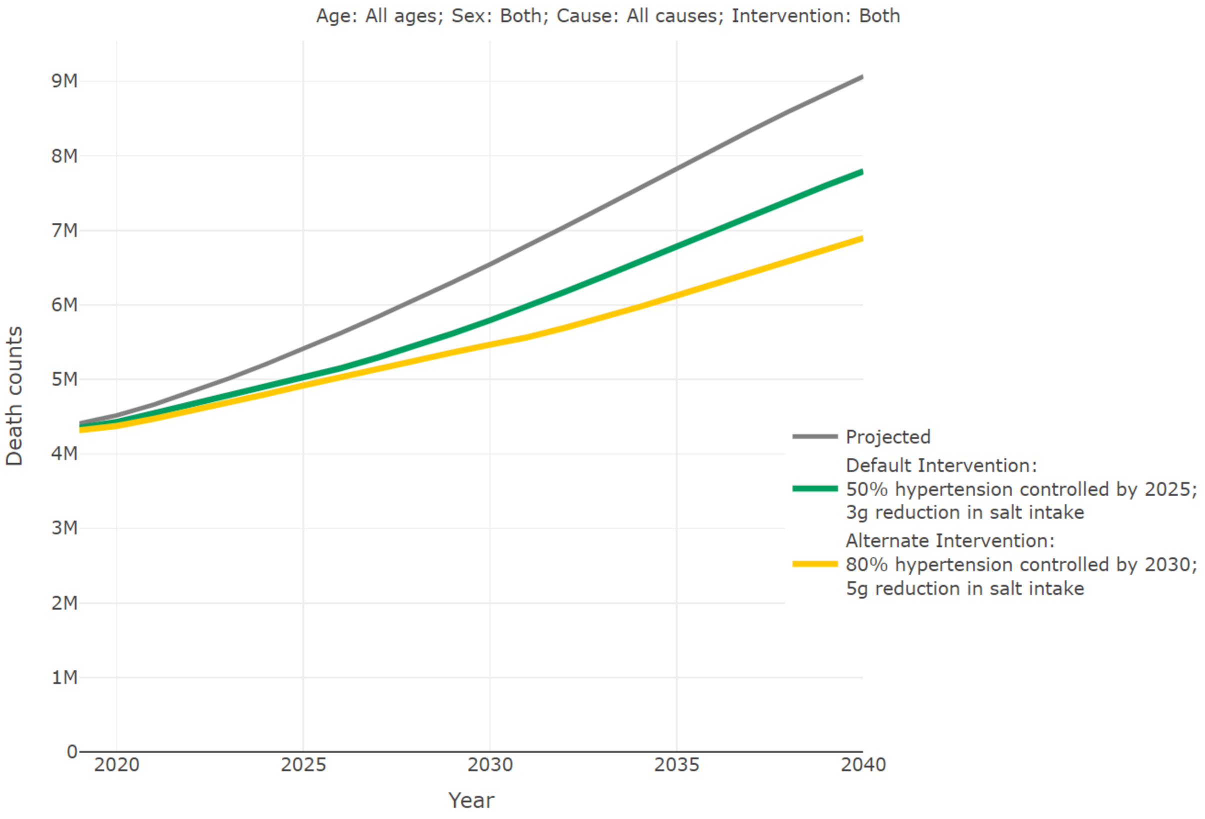
Figure 5: Projected baseline deaths and prevalence of all CVDs compared to GBD 2019 results

Intervention impact projections

When employing both the antihypertensive therapy and salt reduction interventions in the default intervention scenario (50% effect coverage of antihypertensive drug therapy by 2025, 3g reduction in population mean salt intake to 7g from 10g) the projected number of deaths from all cardiovascular disease rose from 4.4 million in 2020 to 7.8 million in 2040. The projected number of cumulative lives saved between 2020 and 2040 in this scenario is estimated to be 15 million. The projected number prevalent cases of cardiovascular disease in this intervention scenario rose from 84 million in 2020 to 128 million in 2040, resulting in 260 million cumulative cases averted between 2020 and 2040.

In the alternate intervention scenario where we increase antihypertensive therapy coverage to 80% by 2030 and reduce mean daily salt intake by 5 grams, we see larger benefits in projected deaths and prevalent cases of cardiovascular disease. In this alternate scenario, the number deaths from all cardiovascular diseases is 6.9 million in 2040, resulting in 23 million cumulative lives saved between 2020 and 2040. We project approximately 115 million prevalent cases of cardiovascular disease in 2040 in the alternate intervention scenario for a total number of 390 million cumulative cases averted between 2020 and 2040.

Figure 6: Projected deaths for all ages, both sexes, all CVDs by intervention scenario



Notably in the two intervention scenarios, default and alternate, the number of deaths averted in 2040 makes up a significant proportion of all deaths. In 2040, the number of deaths averted by the default intervention scenario is estimated to be 2.2 million, approximately 11% of all projected deaths that year. In the alternate scenario, we estimate 1.3 million deaths are averted, approximately 6.8% of all projected deaths in 2040. These estimates result in the relative reduction in deaths of 14.3% and 24.1% in the default and alternate intervention scenarios respectively.

Table 5: Projected prevalence and deaths for all ages, both sexes, all CVDs by intervention; 2040

Scenario	**Prevalence (millions)**	**Cases averted (millions)**	**Relative reduction in prevalence**	**Deaths (millions)**	**Deaths averted (millions)**	**Relative reduction in deaths**
Baseline	148	NA	NA	9.1	NA	NA
Antihypertensive therapy (default)	134	14	9.5%	8.2	0.9	9.9%
Salt reduction (default)	140	8	5.4%	8.6	0.5	5.5%
Both (default)	128	20	13.5%	7.8	1.3	14.3%
Antihypertensive therapy (alternate)	122	26	17	7.3	1.8	19.8%
Salt reduction (alternate)	135	13	8.8%	8.3	0.8	8.8%
Both (alternate)	115	33	22.3%	6.9	2.2	24.1%

Looking at the interventions individually, we see that on prevalence and deaths, antihypertensive therapy has a larger impact for all ages and both sexes. Note that the effect of the two interventions are not additive, which follows with how they are layered in the model where we assume the salt reduction intervention to be instantaneously implemented and followed by the antihypertensive therapy. This means that for some individuals, the salt reduction intervention may lower their blood pressure, but not sufficiently below 130/140 mmHg.

Subsequently, the antihypertensive therapy intervention is introduced, achieving the desired target SBP of <130/140 mmHg. In a scenario where the salt reduction intervention is not employed, that same individual, should they receive the antihypertensive therapy intervention would still achieve a target SBP of <130/140 mmHg by the "treat-to-target" definition of the intervention. Therefore, as we see in Table 5, we would expected the impact of both interventions together to be less than the sum of their parts. However, we see in Figure A6 in the appendix that the different interventions have varying impacts depending on age. For those under 40 years old, the salt reduction intervention has a larger impact on prevalence compared to those who are age 70 and above; for whom the antihypertensive therapy has a larger impact. For adults age 30-69, there is a fairly even impact on CVD prevalence between the two interventions.

DISCUSSION

This study demonstrates the potential to save lives and prevent cardiovascular disease in China by increasing coverage of antihypertensive drug therapy and implementing population-wide salt reduction policies in line with World Health Assembly global voluntary targets. For the default intervention scenario, we project approximately 260 million new CVD cases could be averted between 2020 and 2040. In this scenario, we also predict that 1.3 million lives could be saved per year by the year 2040 or 6.8% of all deaths in 2040. If a more accelerated alternate intervention scenario is employed, approximately 2.2 million deaths could be averted per year by the year 2040. Our results are consistent with the number of deaths attributable to systolic blood pressure (SBP) as estimated by the GBD Risk Factor Analysis for China in 2017 which estimates approximately 2.5 million deaths attributable to systolic blood pressure per year.[9] However, more local data from China is necessary to validate these results and make our analysis more useful.

Though the benefits of these interventions on CVD prevalence death are substantial, achieving this will be a major challenge as only a few countries have achieved this level of hypertension control coverage. Furthermore, the estimated health gains still may not be enough to outpace demographic trends to achieved ambitious global targets (e.g. SDG3.4: reduce by one third premature mortality from non-communicable diseases). In Figure 6, we see that even in an accelerated alternate intervention scenario (80% coverage of antihypertensive therapy by 2030 and 5g reduction in mean salt intake), deaths are still on the rise. To achieve global NCD goals, policy makers and public health officials likely will need to target additional modifiable risk factors like smoking, obesity, trans fats, and others.

One limitation to this study is only examining hypertension as a risk factor for CVD in isolation. In doing so we essentially hold other risk factors as constant. This is especially important to note as other CVD risk factors are not likely to remain stagnant over time. For a more complete assessment of preventable CVD cases and deaths, the effect of modifying other risk factors could be added into the model. Secondly, we have assumed that case fatality remains constant from 2020 to 2040, when in reality it is likely that some secular trends will impact this parameter. As access to healthcare and health infrastructure are improving in many areas in China, it is foreseeable that the case fatality rate of CVDs could decrease from 2020 to 2040. This could mean a higher estimate of prevalence due to longer duration living with the disease. For policy-makers budgeting the cost of long-term disease management, this would be an extremely important factor to consider.

The intervention design in this model limits our ability to make conclusions on the effectiveness of specific implementation strategies. As we are assuming impact on hypertension control as the last step in the hypertension care cascade, we are unable to make any insights into what is specifically required by way of screening or adherence to achieve the health gains outlined in this analysis. These types of insights would be crucial in order to estimate cost-effectiveness, which would be a valuable avenue for future work. Lastly, another limitation is the use of single-study estimates for some parameters like effective coverage and current salt intake. Since we only utilized publicly available data, we are limited in the robustness of these input data. Projected impact of the interventions is reliant on the estimate of how many people are currently covered by those intervention now and therefore, more accurate baseline coverage data could help strengthen our predictions.

Our results show that these two relatively low-cost interventions could have a large impact on future CVD morbidity and mortality in China. Furthermore, our model results show promise in serving as a starting point for more robust analysis in China and other countries as well. Due to its simplicity and flexibility, this type of model may be useful for policy-makers and public health officials to adapt for further analyses of various CVD prevention and treatment interventions.

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APPENDIX

The cohort state-transition Markov was developed using R version 3.5.3. Below is a schematic of the modeling inputs, processes, and out outputs.

Figure A1: Model flowchart

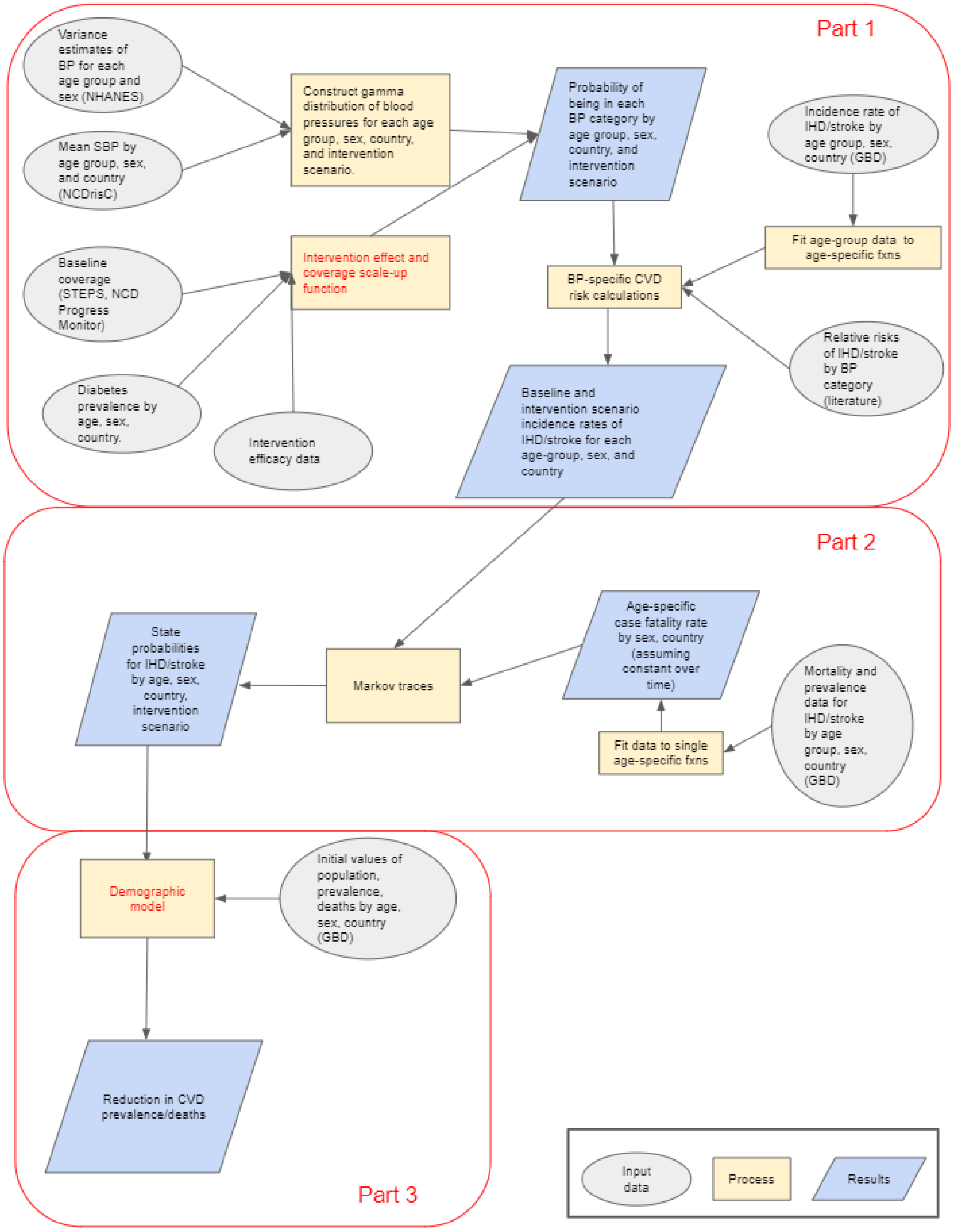

Figure A2: Incidence rate curves for hemorrhagic stroke

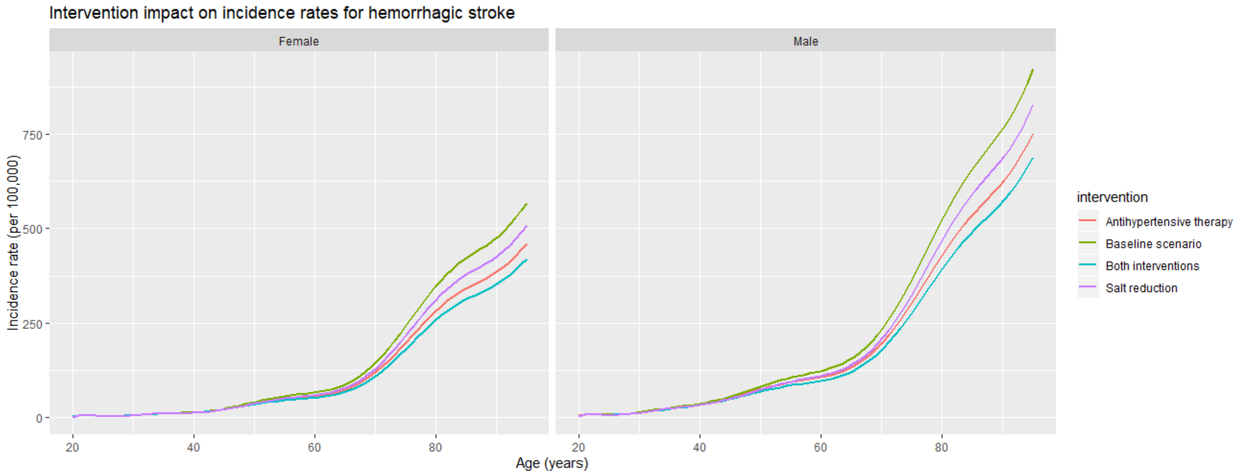

Figure A3: Incidence rate curves for ischemic heart disease

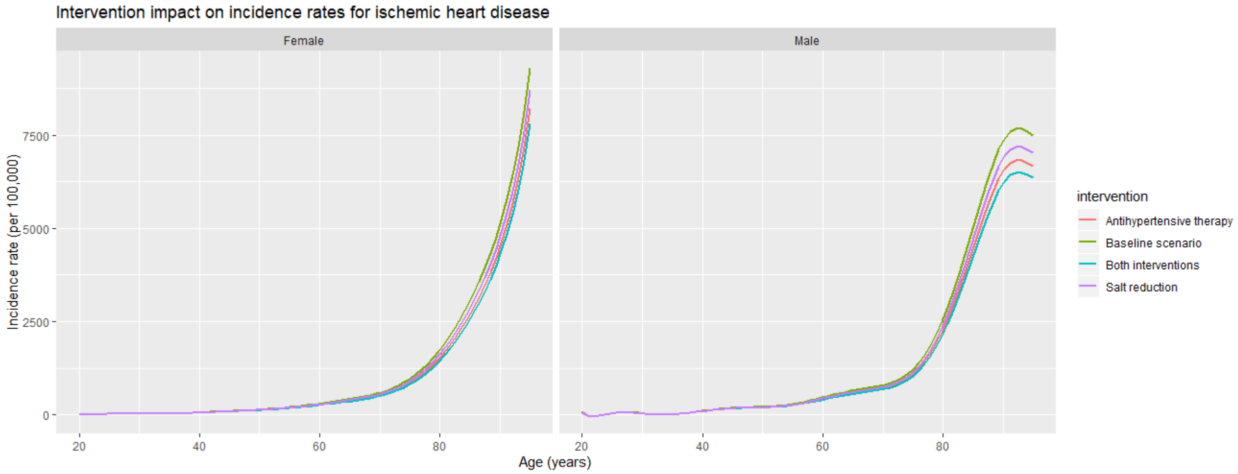

Figure A4: Incidence rate curves for ischemic stroke

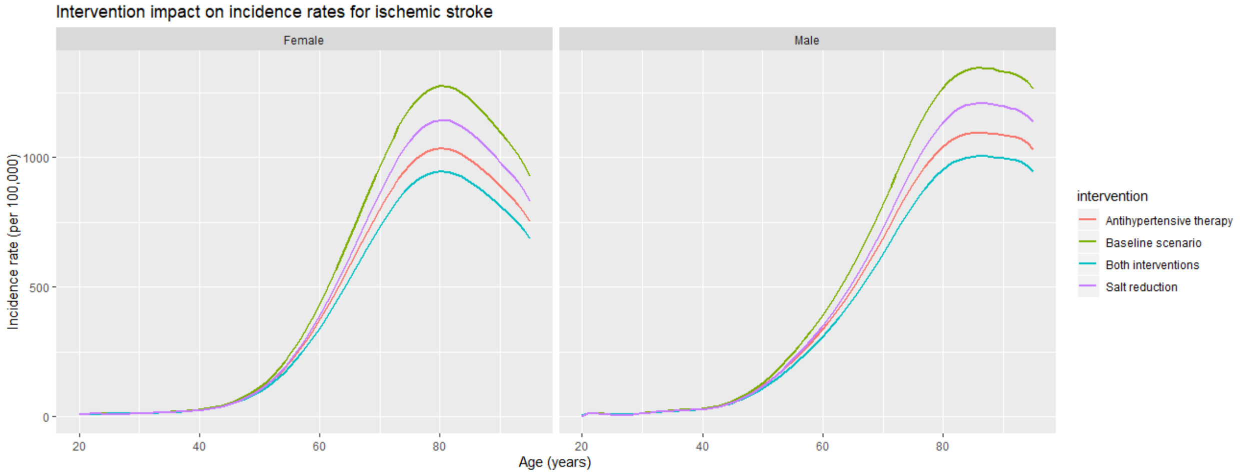

Figure A5: Incidence rate curves for hypertensive heart disease

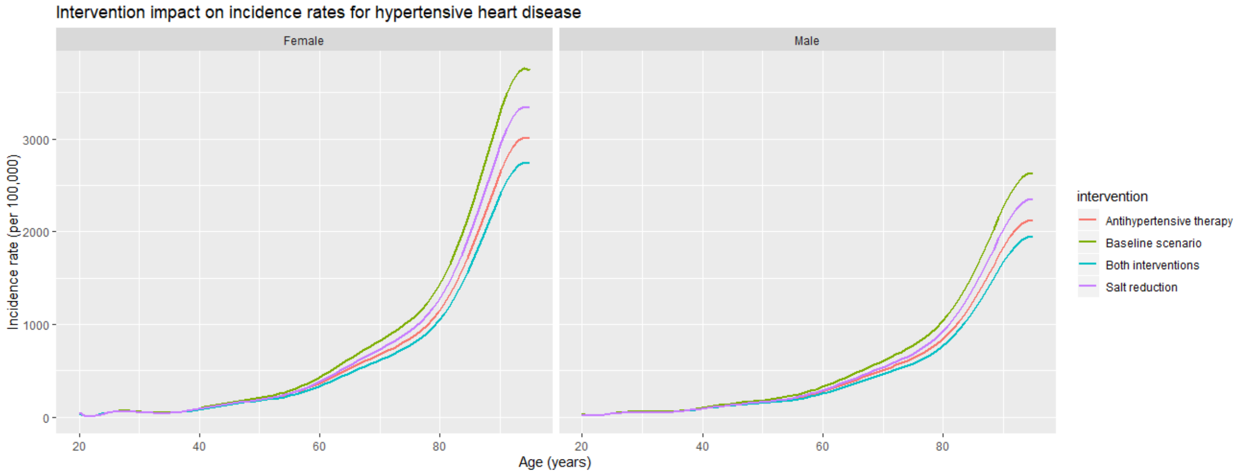

Figure A6: Intervention effect age-pattern by cause for both sexes