

# Effectiveness and cost-effectiveness of non-pharmaceutical interventions in Chinese prehypertensive patients: A network meta-analysis and Markov model analysis



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## BACKGROUND

- The 2017 guidelines of the American College of Cardiology (ACC) diagnose blood pressure (BP) >130/80 mmHg as grade 1 hypertension.<sup>1</sup> A systolic blood pressure (SBP) of 120–139 mmHg and diastolic blood pressure (DBP) of 80–89 mmHg is diagnosed as prehypertension in China.<sup>2</sup> Application of the 2017 ACC guidelines in China would result in approximately 21-44% of Chinese adults being newly diagnosed with hypertension.<sup>3</sup>
- Although patients with prehypertension may benefit from early interventions, there is still a lack of relevant empirical research on the inputs and outputs of such interventions. Application of the diagnostic criterion of 130/80 mmHg in China would need corresponding changes in chronic disease management.
- In current anti-hypertensive treatments, non-pharmacological interventions may be equally effective and potentially more cost-effective than drug interventions.<sup>4-7</sup> However, implementing non-pharmacological interventions require more human resources and thus additional professional training for management staff. Therefore, it is necessary to explore the most cost-effective type of service and possible changes in the chronic disease-management strategy.
- In this study, a meta-analysis and cost-effectiveness analysis were conducted to explore the effectiveness, cost-effectiveness, and feasibility of non-pharmacological interventions for prehypertension in China.

## METHODS

### Network meta-analysis

- PICOS  
This network meta-analysis included studies of adults aged >18 years globally who were diagnosed with prehypertension or with a BP of 120–139/80–89 mmHg. No subjects received antihypertensive agents and none had cardiovascular diseases (e.g. stroke, myocardial infarction). All the interventions included in this study were 13 specific non-pharmacological interventions. Given that the promotion of interventions at the specific practical level were not necessarily directly related to their effectiveness, we merged these 13 interventions into five groups. The standardized descriptions of the interventions are shown in **Table 1**. The main outcome indicators were changes in SBP and DBP.

**Table1 Interventions Descriptions**

Name	Content	Intensity	Name	Content	Intensity
acupuncture	Including acupuncture and moxibustion. Acupuncture refers to acupuncture of certain acupoints by professionals, leaving the needle for 30 minutes after getting it. Moxibustion refers to the use of prefabricated moxibustion grass on certain acupoints on the body's surface, burning and ironing, using heat to stimulate the acupuncture points.	Average 3 times/week, 30 minutes each time, lasting 6 weeks	Traditional Chinese Medicine Physiotherapy	Regularly receive traditional Chinese medicine interventions for lowering blood pressure, including acupuncture and massage	Average 3 times/week, lasting 4-6 weeks
Massage	Professionals will provide the guidance or education. And the professionals will use Swedish massage or patient do the self-massage.	1h/day; 3 days/week; 4 weeks in total			
Taichi	Tai Chi exercises are carried out under professional guidance, and the movements are designed by professionals	4-6 days a week, 45-60 minutes a day	Relax Exercise	Receive training by professionals, learn relaxing exercises, combine learning materials for independent exercises, including yoga, Tai Chi, and receive regular supervision	Average 4 times/week, 45Min each time, lasting 12 weeks
Yoga	Guide by a professional yoga instructor to perform yoga exercises, including asanas, breathing and meditation.	6-7 days a week, 45-60 minutes a day			
aerobic exercise	Use oxygen for energy, moderate to intensity exercise that lasts for a long time and has a rhythm, and the exercise intensity is 50-70% of the maximum heart rate. Including fast walking, jogging, cycling, mountain climbing and so on.	3-4 times/week, 30-60 minutes/time, lasting 12 weeks			
resistance exercise	Complete the specified actions according to the requirements and the purpose of the action design is to exercise the main muscle groups of the body. Totally seven actions, each action is repeated 10-15 times as a group, do 2-3 groups. Elastic ropes and other props are used under the supervision of the professionals.	1 group of 12 reps; total 2 groups lasting 45 minutes; 3 times/week; lasting 6 months		Under the guidance of professionals, perform aerobic exercise (such as jogging, brisk walking, cycling, etc.), resistance exercise, isometric exercise or a combination of multiple forms of exercise at different target intensities	Average 4 times/week, 45 minutes each time, lasting 8 weeks
normal exercise	Stretching or walking briskly for 30-60min under the supervision of professionals, the exercise intensity is about 5km/h.	45minutes/time; 3 times/week; lasting 8 weeks	Strengthen Exercise		
isometric exercise	Use isometric handle equipment to exercise at the intensity of 20-30% MVC.	10minutes/day; every day; lasting 6 weeks			
combination exercise	A comprehensive exercise program that combines endurance exercise, isometric exercise and aerobic exercise.	3 times/week, an average of 50 minutes each time, lasting 7 weeks			
Salt reduction	Provide a measuring spoon, limit salt intake (maximum 3 g/day), or use alternative salt.	≤3g/d	Diet therapy	Reasonable diet, reduce sodium intake, reduce fat intake, or adopt DASH diet	Adhere to salt control or standard diet every day
DASH	Emphasize a comprehensive diet, increase the intake of fruits, vegetables, whole grains and low-fat dairy products, and limit the intake of sodium, saturated fat and total fat	Eat according to DASH every day			
usual care	No intervention, keep the original lifestyle habits unchanged	Everyday			
Lifestyle	Give lifestyle suggestions, such as reasonable diet, reducing fat intake, proper exercise, weight control, reducing sodium intake, quitting smoking and alcohol, reducing mental stress.	Everyday	Lifestyle	Provide regular community-based chronic disease management without specific intervention. Regular blood pressure monitoring and health education is also conducted.	Follow up once a month and conduct health education once every six months

- Search strategies and data extraction  
We conducted a systematic search of Chinese and English databases for randomized controlled trials and reasonably designed controlled trials. The following data was extracted from the included articles: title, first author, randomization, baseline characteristics (age, sex, country, number of participants), interventions, follow-up time, SBP, and DBP. We evaluated the quality of the literature according to the Cochrane Handbook and eliminated poor-quality articles.
- Statistical analysis  
We carried out a network meta-analysis using the Bayesian framework. Mean difference (MD) was selected as the effect size. We used a Markov chain Monte Carlo simulation with four chains with scattered initial values, a total of 50,000 iterations, and annealed after 5000 iterations. The convergence of the model was judged by the Brooks-Gelman-Rubin method.<sup>8</sup> Inconsistencies were evaluated by the node-splitting method and heterogeneity analysis was also done.

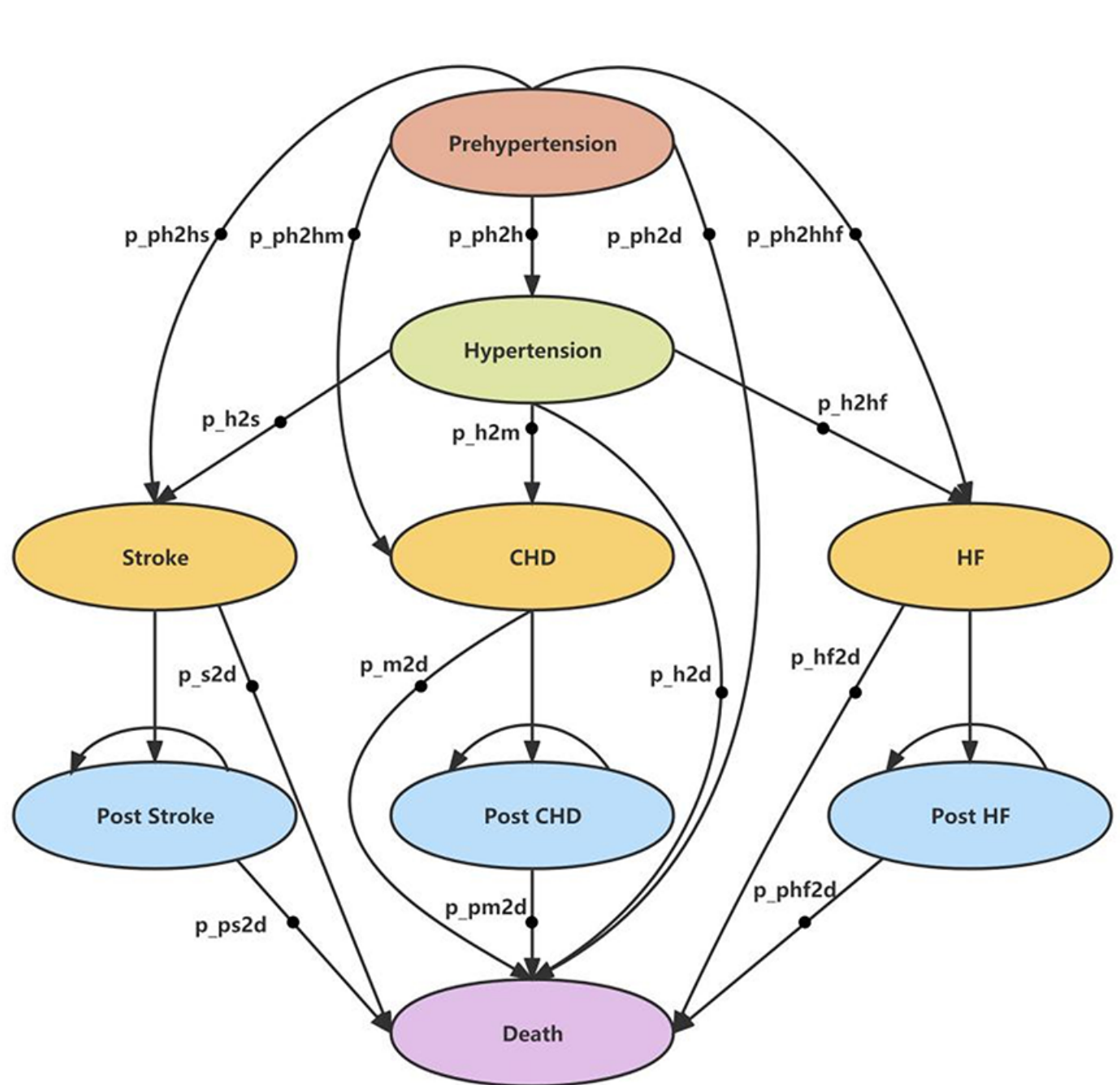
### Economic evaluation

- Overview of the model  
We used the perspective of the Chinese healthcare system and therefore only considered the direct medical costs. A nine-state Markov model was constructed (**Figure 1**). The initial input age was 45 years, the simulation time was limited to 55 years, and the simulation period of one cycle was 1 year. The discount rate was set as 5%. Transition probabilities were extracted from published articles or calculated from prediction models.
- Cost and utility  
The cost of interventions was calculated by decomposing the intervention into detailed items. Utilities were extracted from other studies.
- Decision-making process  
We used ICER (Incremental Cost-effectiveness Ratio) as the decision indicator and the 2020 GDP per capita in China (\$11,300) as the willingness to pay (WTP) threshold.<sup>9</sup> A simple budget impact analysis model to estimate when the investment in managing prehypertensive patients by each potentially advantageous intervention would be reclaimed.<sup>3</sup>
- Sensitivity analysis  
We performed single-factor sensitivity analysis (DSA) and probability sensitivity analysis (PSA). DSA used the 95% confidence intervals (CI) of a single effect size as the fluctuation interval. The DSA results were displayed in a tornado chart. PSA was carried out using a Monte Carlo simulation (expected 10,000 iterations). The PSA results were represented on a scatter plot.

## RESULTS

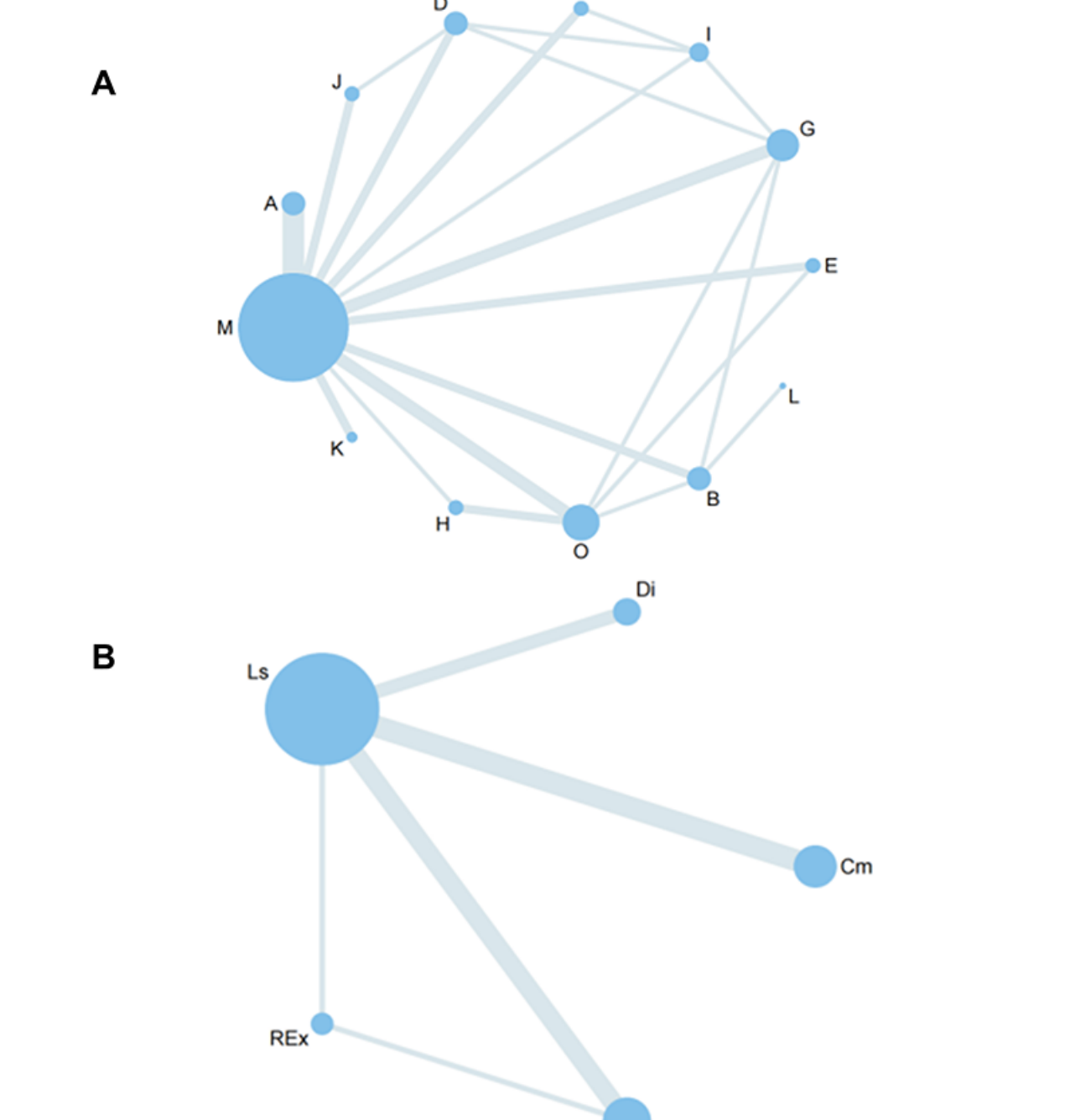
- Our search identified a total of 7389 references. After deduplication, 4023 studies underwent further analysis, of which 3376 were excluded after reading the title or abstract and a further 617 were excluded after reading the full text. The remaining 30 studies involved 13 interventions in 4846 patients, including 2074 males, with an average age of 47.79 years. The qualities of the included studies evaluated according to the Cochrane Handbook were moderate.
- We conducted a network meta-analysis of 13 intervention items including 30 studies (**Figure2A**) and a network meta-analysis for all five intervention groups including 24 studies (**Figure2B**). Traditional Chinese Medicine (TCM) physiotherapy was the most advantageous intervention compared with lifestyle changes in SBP (MD =-6.27 mmHg, 95% CI -9.65 to -2.95), strengthening exercise (-0.76 mmHg, -5.51 to 3.95), relaxation (-0.56 mmHg, -6.31 to 5.22), and diet therapy (-2.84 mmHg, -8.12 to 2.40). Tai chi, combined exercise, and massage were the three most effective specific interventions. Through detecting statistics indicators like I<sup>2</sup>, DIC and p value, all models had no inconsistency but with slight local heterogeneity.
- Strengthening exercise was more cost-effective than lifestyle changes, with an ICER of \$7107.87, which was less than the threshold (**Table 2**). The cost-effectiveness acceptability curve (CEAC) is shown in **Figure 3**. When the WTP was <\$7107.87, lifestyle change was the most cost-effective intervention, but when the WTP was >\$7107.87, strengthening exercise was the most cost-effective. However, when the WTP reached \$18,298.38, relaxing exercise had the highest probability of being the most cost-effective.
- Strengthening exercise and relaxation reclaimed the costs in the third year, when the intervention costs were about \$110 billion and \$150 billion, respectively, while TCM physiotherapy reclaimed costs in the fourth year, when the intervention cost was approximately \$230 billion (**Figure 4**).

**Figure1 Markov model**



Abbreviations: HF: heart failure; CHD: coronary heart disease

**Figure2 Network plot**

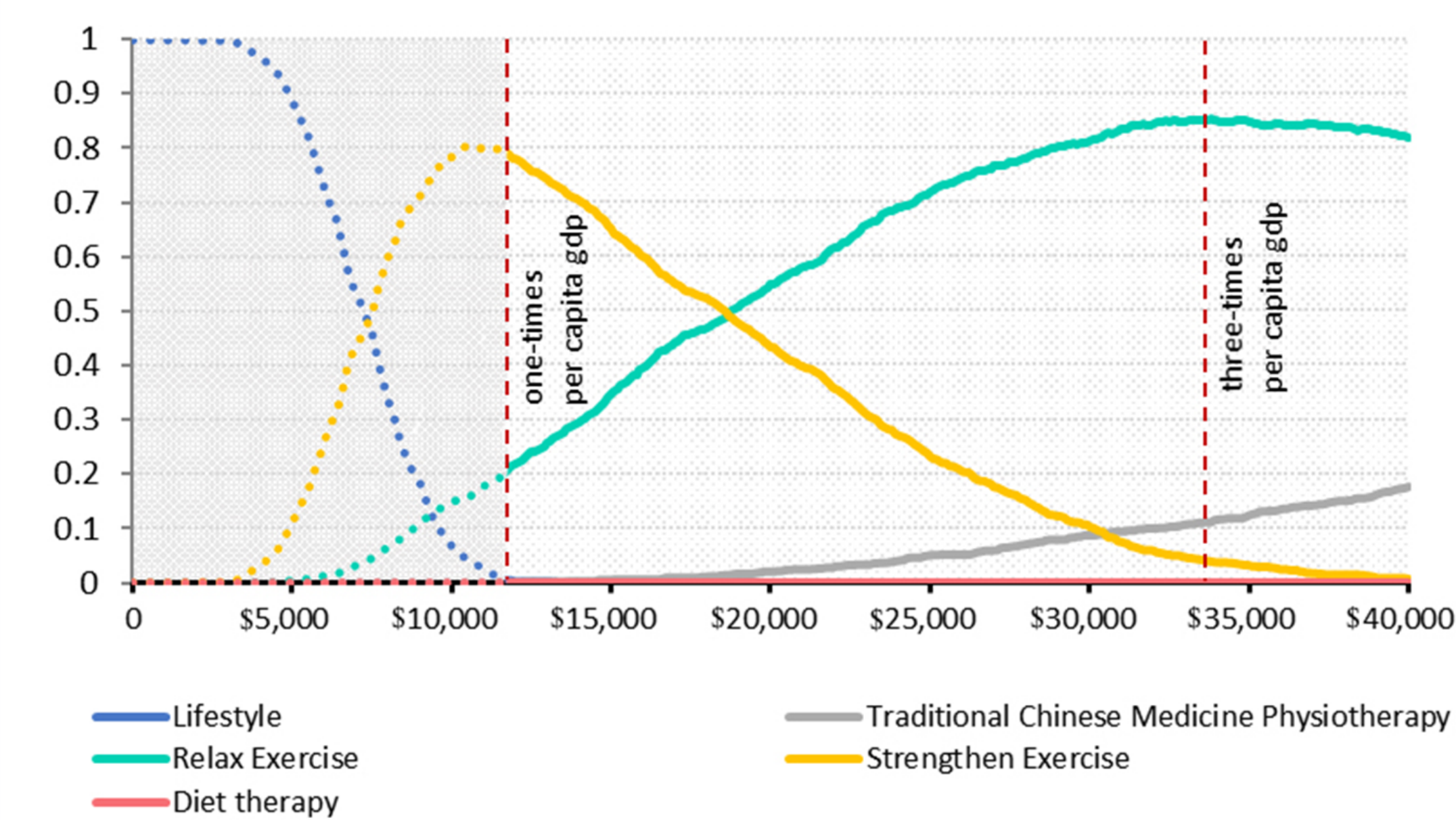


Abbreviations: A: acupuncture; B: aerobic exercise; D: combination exercise; E: DASH; G: isometric exercise; H: massage; I: normal exercise; J: resistance exercise; K: salt restriction; L: Tai chi; M: usual care; N: yoga; O: Lifestyle; Cm: Traditional Chinese Medicine Physiotherapy; SE: Strengthen Exercise; REX: Relax Exercise; Di: Diet therapy; La: Lifestyle

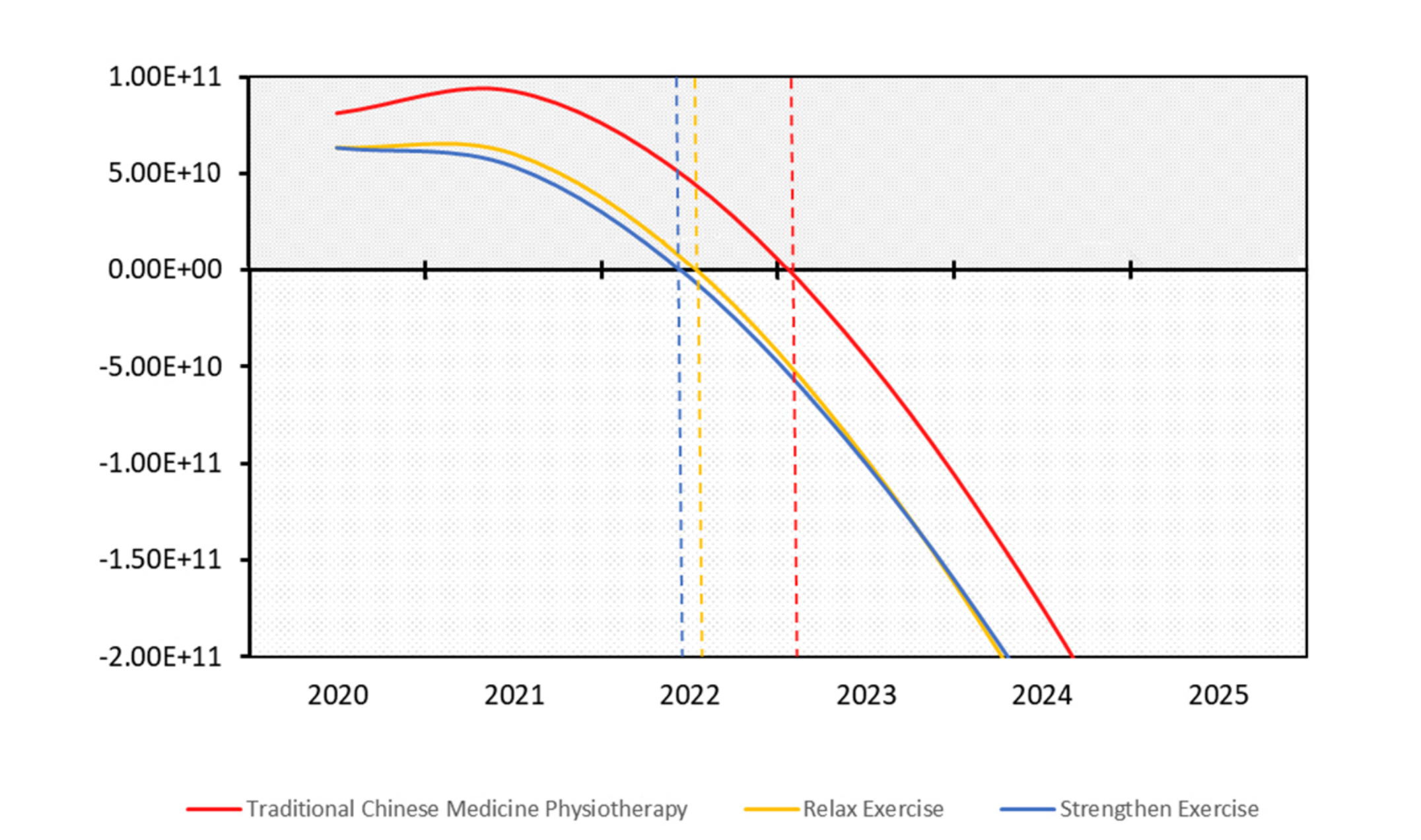
**Table2 Base-case analysis results**

Intervention	Average time to be diagnosed as hypertension (Years)	Cost	QALY	Comparison	Acost	Aqaly	ICER
Lifestyle	7.99	5226.23	28.50	/	/	/	/
Strengthen Exercise	10.18	7214.96	28.78	ICER1: Strengthen Exercise vs Lifestyle	1988.73	0.28	7107.87
Relax Exercise	10.05	8443.13	28.85	ICER2: Relax Exercise vs Strengthen Exercise	1228.17	0.07	18298.38
Traditional Chinese Medicine Physiotherapy	9.67	10055.63	28.87	ICER3: Traditional Chinese Medicine Physiotherapy vs Strengthen Exercise	2840.67	0.09	31271.66
Diet therapy	9.19	16172.63	28.70	Dominate			

**Figure3**



**Figure4**



## CONCLUSIONS

- This was the first study to evaluate the effectiveness and cost-effectiveness of non-pharmacological interventions in prehypertensive patients. The results thus not only supplement existing evidence in this area, but also have important implications for the management of chronic diseases in China and provide a transformation or task-sharing plan for chronic disease-management staff in China.
- The results of the current study suggest that the professional training of community-based chronic disease-management staff to provide strengthening exercise, relaxing exercise, and TCM physiotherapy would be more effective and cost-effective than just providing follow-up and health education to prehypertensive patients. In addition, the intervention-related expenditure could be reclaimed within 3–4 years after investing in management of patients with prehypertension.
- Our findings also suggested that different management models should be promoted in communities with different economic conditions, considering the uneven development in different regions. In poor communities, health education and regular follow-up may be adopted. However, communities with moderate economic conditions should consider training management staff to provide aerobic and resistance exercise training, and providing suitable places and equipment, while more-developed communities could consider training management staff to provide relaxation, such as yoga and Tai Chi training, as well as related sports guidance and design.

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## DECLARATION OF INTERESTS

The authors have no conflicts of interest to declare. Scan the QR code to get the abstract in text.



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