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Revisiting Cost-effectiveness of Folic Acid Supplementation in Primary Stroke Prevention: Considering the Unmaking Issue of Vitamin B-12 Deficiency Masking

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Introduction

- China faces a significant burden of stroke.[1,2,3]
- The beneficial effects of folic acid therapy in the primary stroke prevention depend on the pre-existence of a low folate status of the underlying population, which is effective in hypertensive patients in China according to the CSPPT. [4,5]
- Patients whose vitamin B-12 deficiency (B-12 deficiency) is masked by the use of folate can develop nerve degeneration that would have been prevented had their signs of anemia triggered testing for B-12 deficiency, which creates a barrier to policies of routine folate supplementation or folate fortification of the food supply.[6]
- The risks of folate supplementation, and hence the ratio of benefit to risk, will depend heavily on the prevalence of underlying vitamin B-12 deficiency and folate deficiency. (Figure 1)
- None of the previous literature discusses the unmaking issue of B-12 deficiency masking in China when it comes to folic acid supplementation in primary stroke.

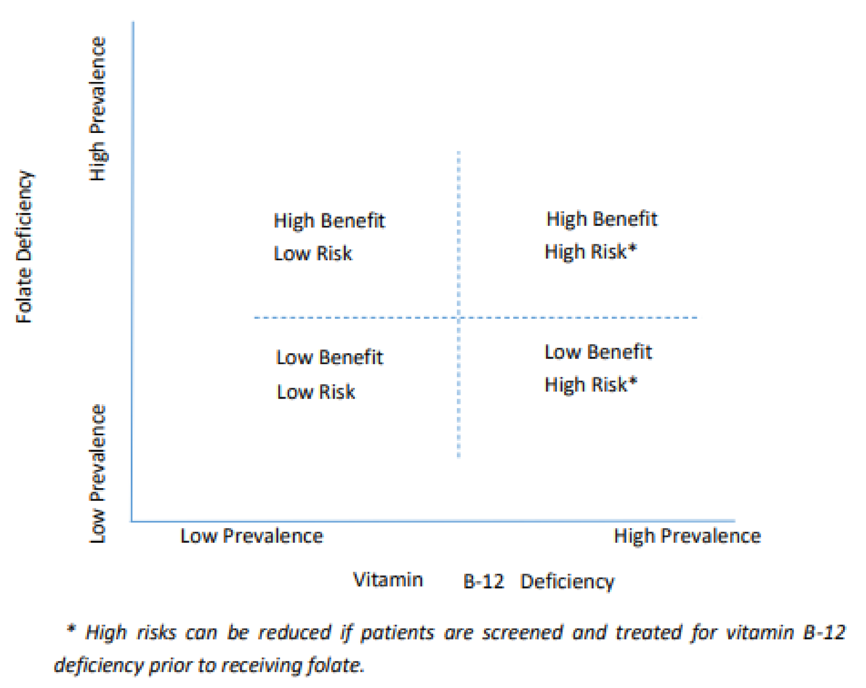

Figure 1. Benefits and risks of folate supplementation as a function of prevalence of folate and vitamin B12 deficiency

Objective

To identify the cost-effectiveness of three policy options related to folic acid supplements in primary stroke prevention for hypertensive patients in China.

A. Do nothing to address folate status in patients at risk for stroke. (Do Nothing Policy)
B. Supplement with folate but no pre-screening for B-12 deficiency. (Supp Only Policy)
C. Supplement with folate, pre-screen all patients for B-12 deficiency, and add B-12 supplements if B-12 is deficient. (Screen & Supp Policy)

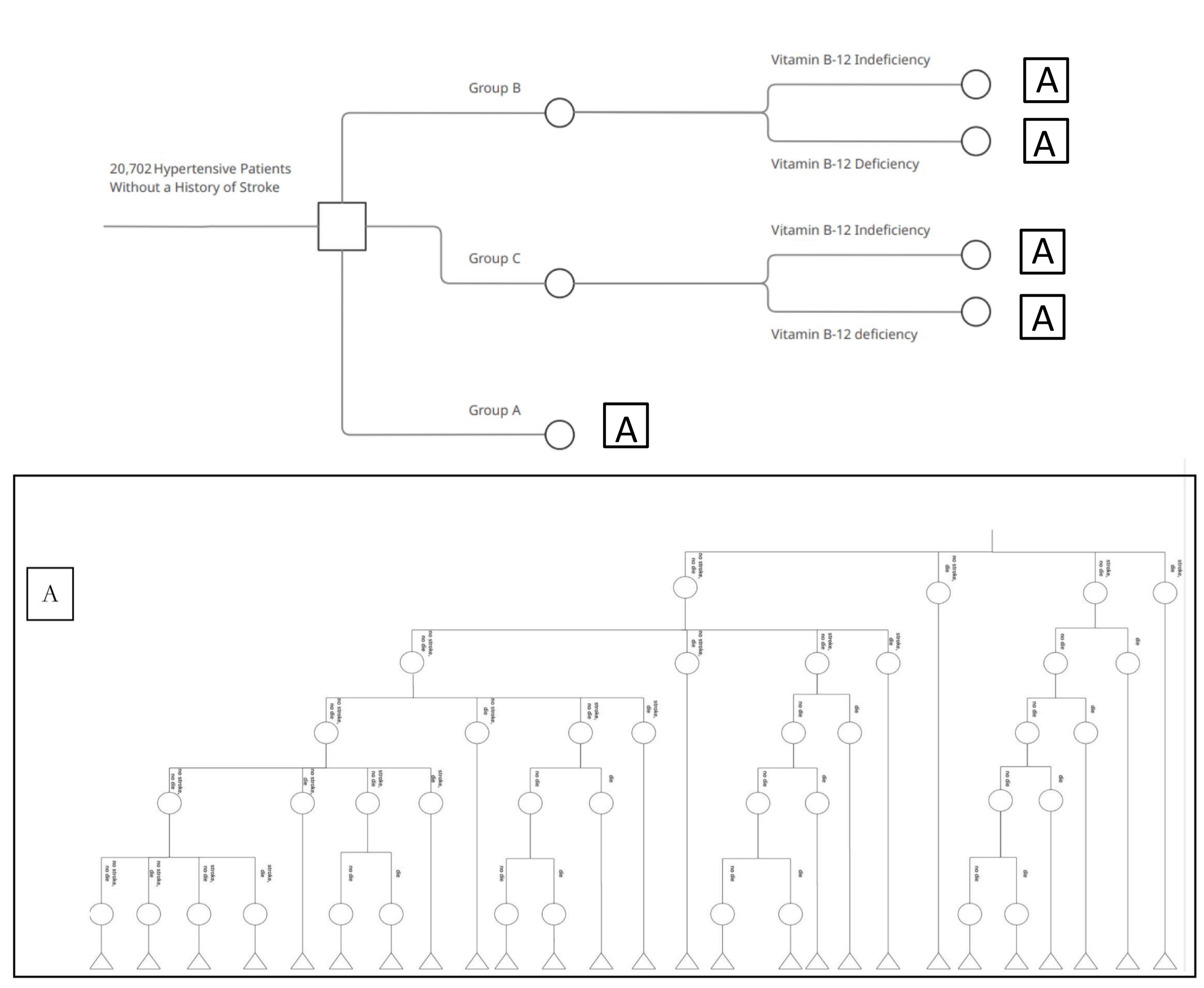

Figure 2. Decision Tree depicting three policy pathways in primary stroke prevention

Methods

Model Input A total of 20,702 hypertensive patients without a history of stroke from 32 communities in Jiangsu and Anhui provinces in China were randomized to enalapril-folic acid (n=10,348) or enalapril alone (n=10,354).[5] The study participants had an average age of 60.0 years (SD, 7.5 years), and approximately 59% were female. Based on CSPPT data, Each group's stroke and stroke-free probabilities, and the death and survival probabilities were calculated, then converted from a five-year probability *P* into an annual probability using *Formula 1*. Prevalence of B-12 deficiency, costs of annual stroke, B-12 screening test, and utility weights for pre-stroke, stroke, and neurological abnormalities states and etc. were collected from published literature. Costs of enalapril, folate acid and B-12 supplements were obtained from the 2022 median bidding price of local official documents.

$$\textit{Annual Probability} = 1-\exp((\ln(1-P))/5) \qquad \textit{Formula 1}$$

Model Structure Figure 2 shows the decision tree model representing a five-year period of intervention in the three groups from the Chinese healthcare system perspective. The model components contained are shown in Table 1. The incremental effect and costs were summarized using an incremental cost-effectiveness ratio (ICER) with reference to Policy A using *Formula 2*. Additionally, one-way and probabilistic sensitivity analyses of Policy C versus Policy A was conducted.

$$ICER = \frac{(C_1 - C_0)}{(E_1 - E_0)} \qquad \textit{Formula 2}$$

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Table 1. The components contained in each group in the decision tree

Group	Year 1 to 5 Model Includes	Cumulative
A. Do Nothing	Intervention cost (Zero) Stroke costs QALYs lost from stroke	Costs QALYs
B. Supp Only	Intervention cost Stroke costs QALYs lost from stroke QALYs lost from Neuropathy	Costs QALYs
C. Screen & Supp	Intervention cost Stroke costs QALYs lost from stroke	Costs QALYs

Note: QALYs, quality-adjusted life years.

Results

- Over the five-year period, the incremental cost and quality-adjusted life years (QALYs) of Group B vs. Group A are estimated to be $99.88 and negative (-0.11), respectively. The ICER of Policy B versus Policy A is negative, which indicates that Policy B is unacceptable because it raises costs and lowers health.
- In Policy C, the incremental costs and QALYs of Group C vs. Group A are estimated to be $125.20 and 0.0066, respectively, and finally the ICER of Policy C vs. Policy A is $19,046.03 per QALY, indicating that Policy C would be cost-effective, assuming a WTP threshold of three times national GDP per capita ($38,160 per QALY). The results tend to be entirely sensitive to the cost of enalapril-folic acid drug combinations, which implies that it would not be cost effective anymore if the cost of enalapril-folic acid pill is greater than $0.25 per day adjusting for other variables.
- The probabilistic sensitivity analysis indicates that there would be a 62.8% chance that the additional cost of Policy C, compared with Policy A, is at or below 3 times the GDP per capita threshold as shown in Figure 3. The cost effectiveness probabilistic acceptance curves are depicted in Figure 4. Additionally, the probability of enalapril-folic acid being cost-effective based on a threshold of 3 times the GDP per capita fall to 25.3% under the Policy B (Supp only) and rapidly fall to 1% under the assumption that we treat hypertensive patients with daily enalapril-folic acid combo pill.

Table 2. Results of the base case cost-effectiveness analysis

Components	Group A Do Nothing	Group B Supp only	Group C Screen & Supp
Expected medical costs of intervention	US$140.59	US$283.63	US$295.06
Expected medical costs of stroke	US$137.34	US$94.20	US$108.08
Total medical costs	US$277.94	US$377.82	US$403.14
Total expected QALYS*	3.87	3.76	3.88
Incremental cost vs. A		99.88	125.20
Incremental QALYs vs. A		Negative	0.0066
ICER with respect to Group A		NA	19,046.03

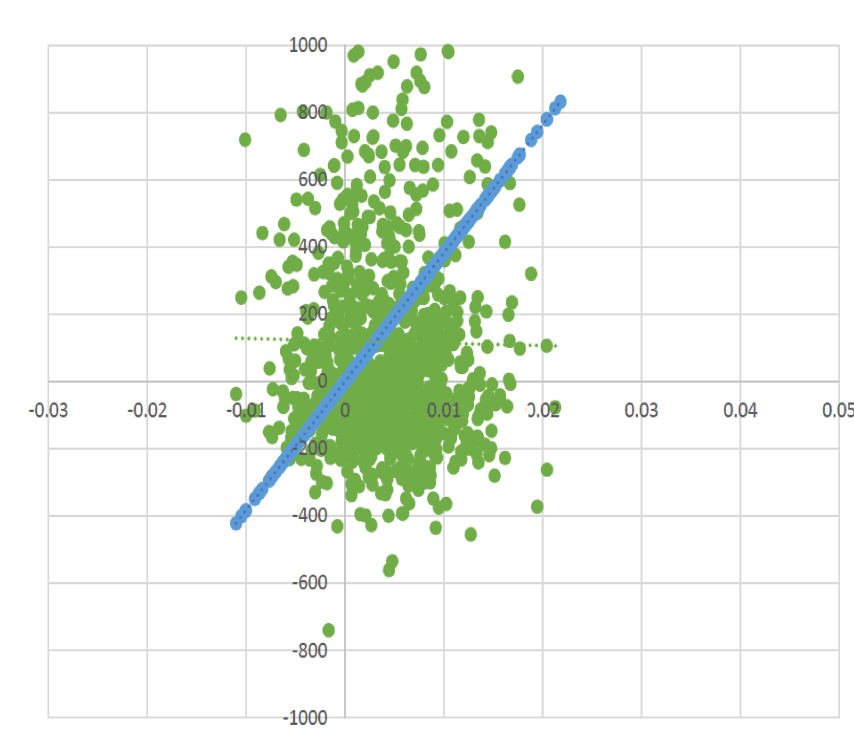

Figure 3. Scatter plot of 1,000 Iterations of Monte Carlo Simulation for Cost-Effectiveness Plane for Policy C vs. Policy A

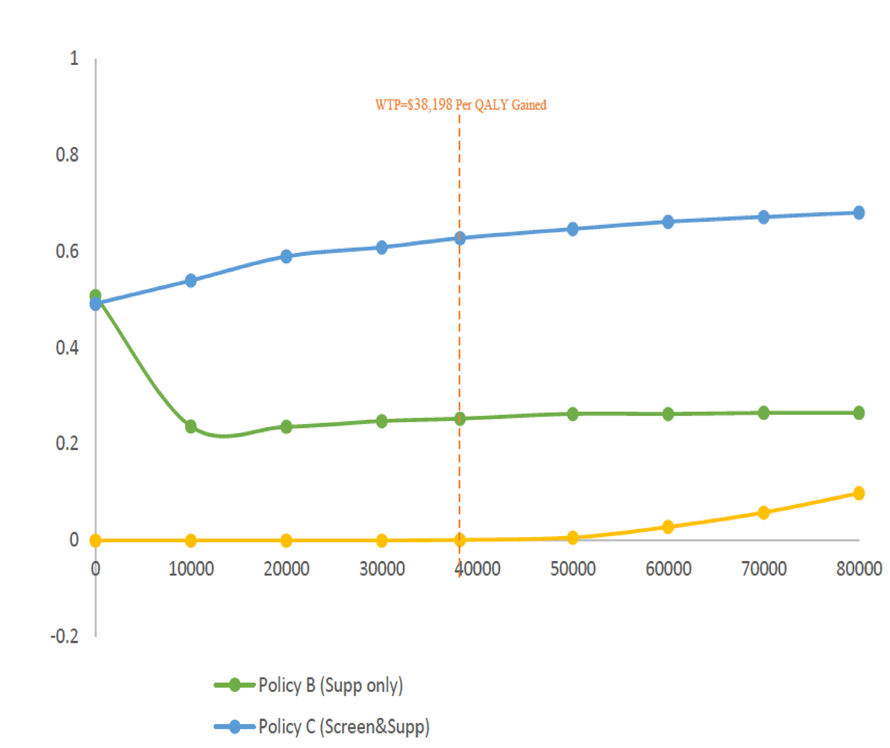

Figure 4. Cost-Effectiveness Probabilistic Acceptance Curves

Conclusions

- Folate supplementation with vitamin B-12 deficiency screening before starting folate supplements was found to be cost-effective for the hypertensive population in China. In contrast, the use of folate supplements without B-12 screening was not cost-effective since it would cost more and create more health harm than doing nothing due to delayed diagnosis of B-12 deficiency. Our model shows that screening policies can control the side effects when B-12 deficiency is prevalent and can make the folate supplementation intervention cost-effective.
- Accordingly, our conclusion would advocate scaling up the folate supplementation policy in primary stroke prevention for hypertensive patients in China if combined with pre-screening and supplementing for B-12 deficiency and if patients took folate and enalapril as separate generic pills instead of as a combo pill.

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