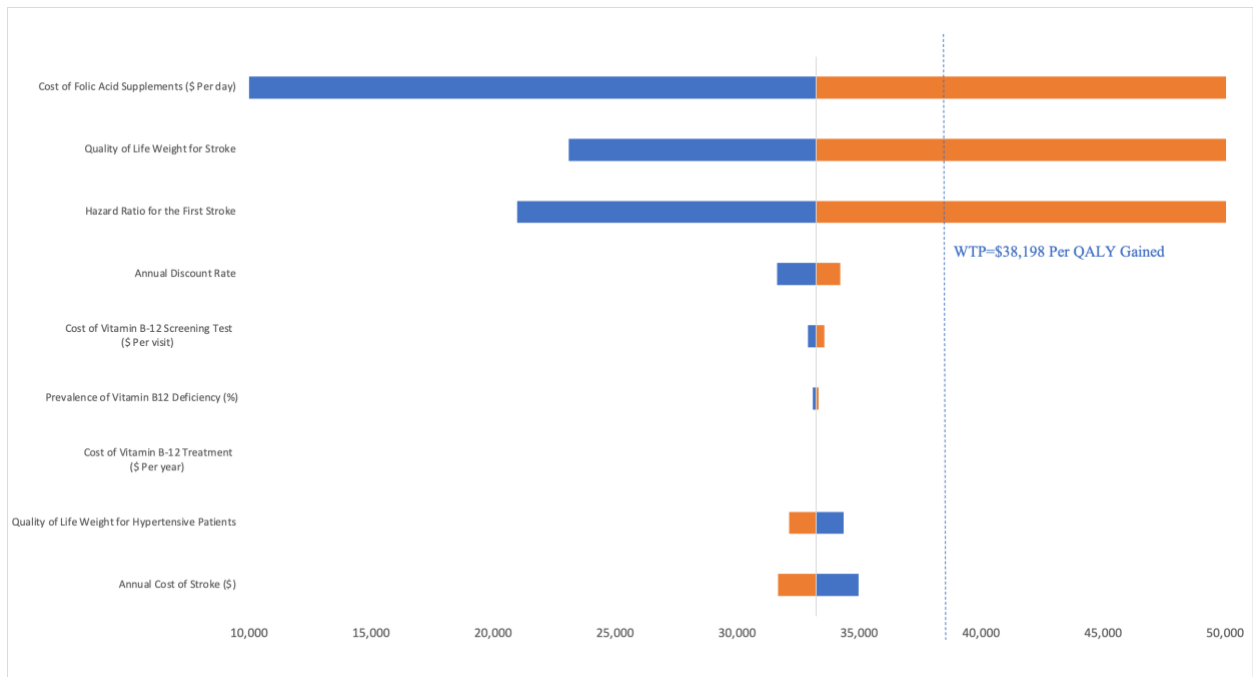
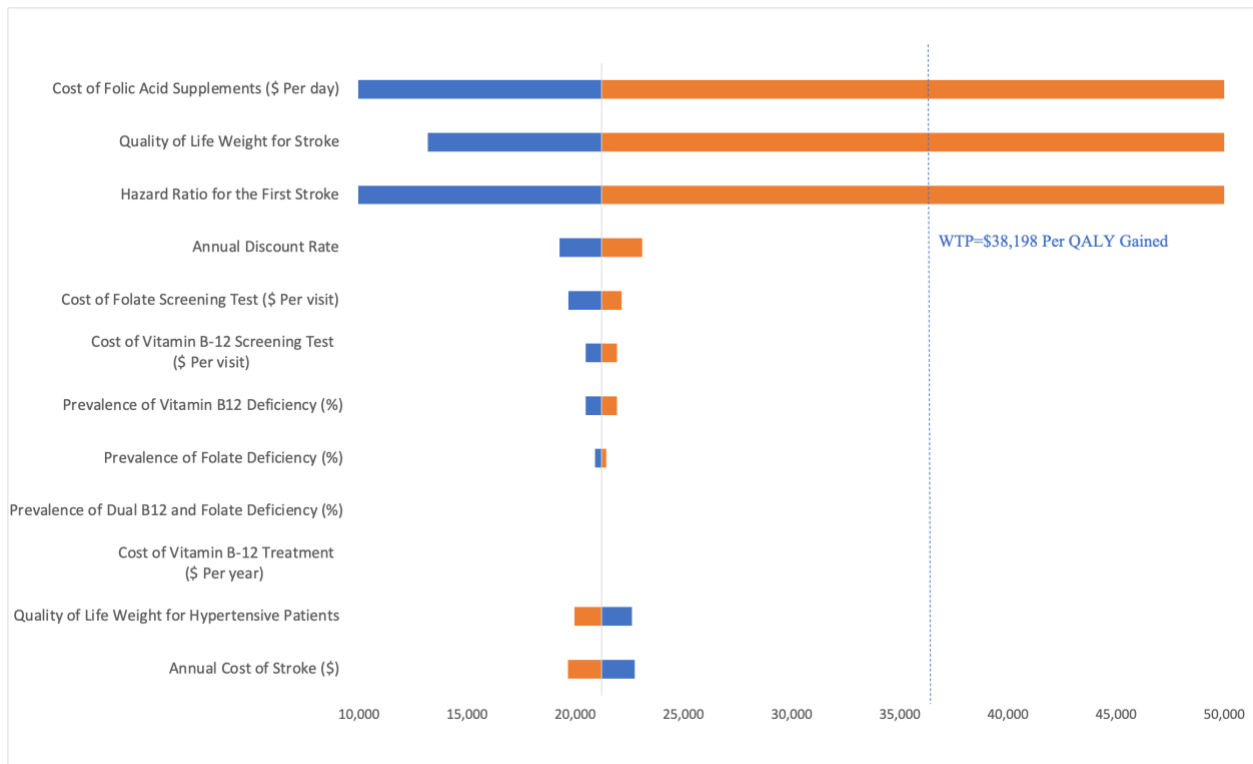


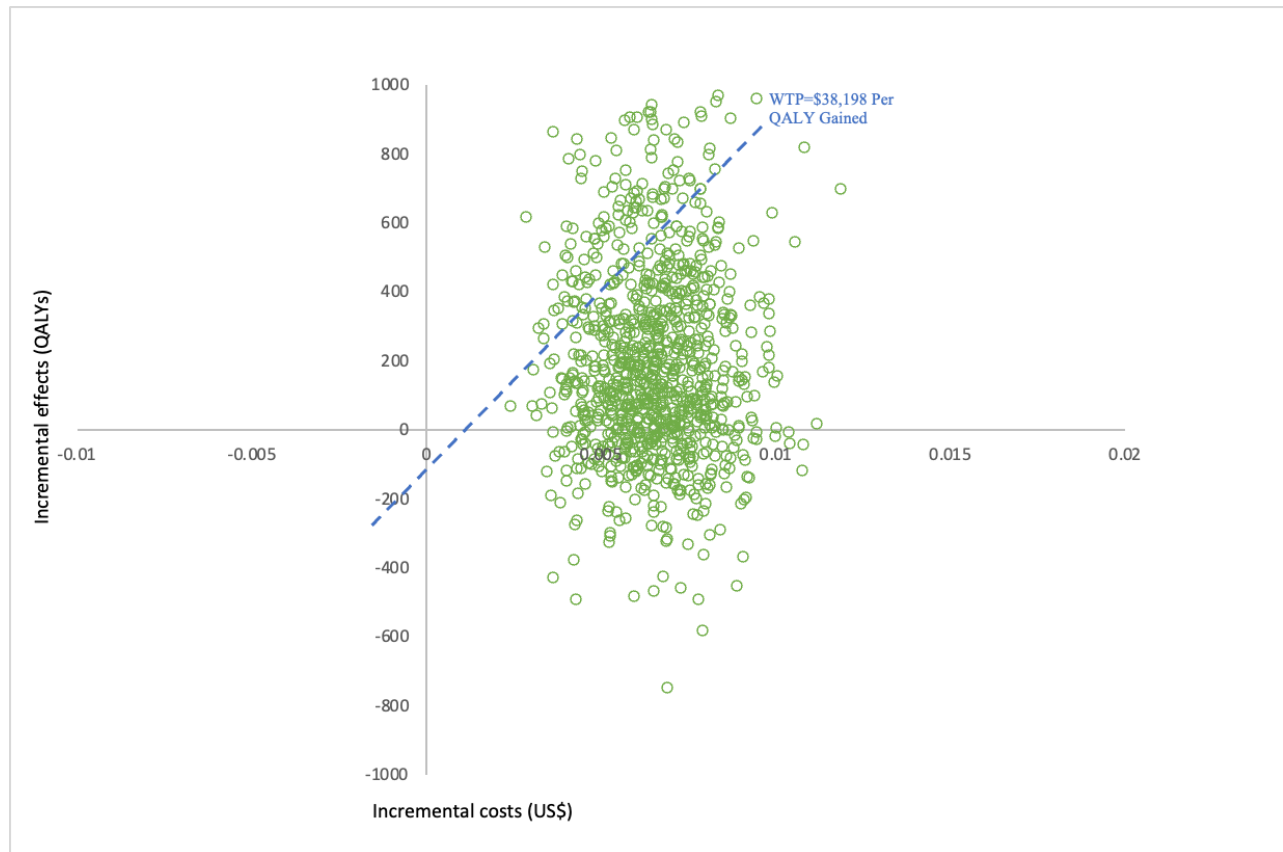
SFigure 1. Tornado diagram of Policy C (Screen for B12 & Supply) vs. Policy A (Do Nothing)



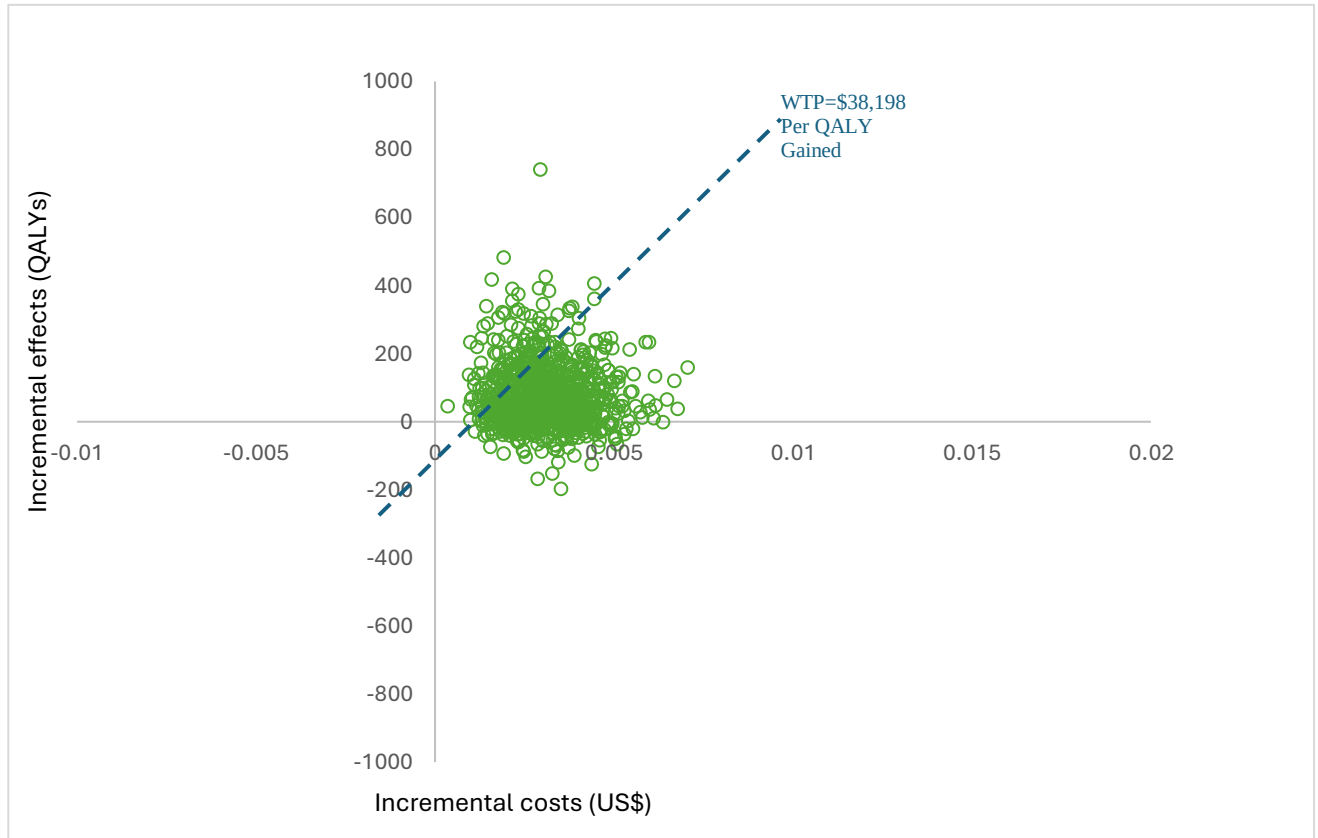
SFigure 2. Tornado diagram of Policy D (Screen for B12 and folate & Supply for only folate deficient) vs. Policy A (Do Nothing)



SFigure 3. Scatterplot of 1000 Iterations of Monte Carlo Simulations for Cost-effectiveness plane for Policy C (Screen for B12 & Supply) vs. Policy A (Do Nothing)



SFigure 4. Scatterplot of 1000 Iterations of Monte Carlo Simulations for Cost-effectiveness plane for Policy D (Screen for B12 and folate & Supply for only folate deficient) vs. Policy A (Do Nothing)



SFigure 5. Cost-effectiveness Probabilistic Acceptance Curve

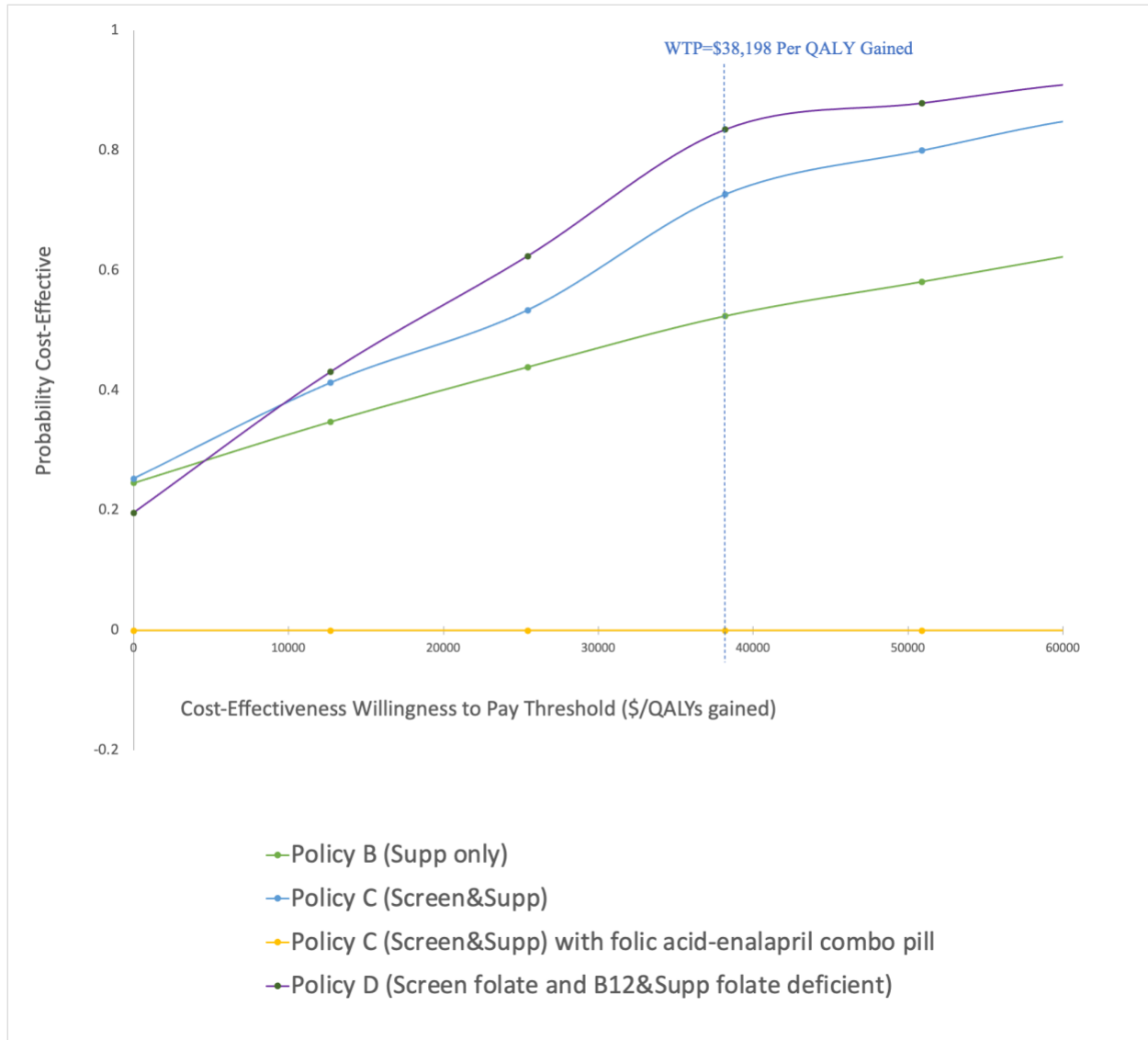


Table S1. Cost-effectiveness for Policy C (Screen for B12 & Supply) vs. Policy A (Do Nothing) results for subgroups

Subgroup	Cost (\$)			QALYs			ICER	%<1 time of GDP/capita	%<2 times of GDP/capital	%<3 times of GDP/capita
	Policy C	Policy A	Δ	Policy C	Policy A	Δ	(\$/QALY)	per QALY	per QALY	per QALY
Sex										
Male	\$503.26	\$311.49	\$191.77	3.8757	3.8661	0.0097	\$19,854.15	40.10%	52.10%	69.30%
Female	\$491.63	\$256.46	\$235.17	3.8772	3.8725	0.0046	\$50,621.61	32.20%	43.00%	59.00%
Age, yrs										
<55	\$460.16	\$223.91	\$236.25	3.8811	3.8763	0.0047	\$50,199.00	37.60%	46.30%	60.80%
≥55 - <65	\$488.65	\$285.43	\$203.22	3.8775	3.8691	0.0084	\$24,179.03	43.10%	58.10%	77.90%
≥65	\$543.96	\$323.41	\$220.56	3.8707	3.8647	0.0060	\$36,475.03	30.10%	41.00%	57.80%
Smoking status										
Never	\$482.43	\$262.44	\$219.99	3.8783	3.8718	0.0065	\$33,961.53	39.60%	54.30%	71.60%
Former	\$523.94	\$320.96	\$202.99	3.8732	3.8650	0.0082	\$24,685.28	45.10%	56.20%	70.70%
Current	\$527.05	\$311.51	\$215.54	3.8728	3.8661	0.0067	\$32,003.16	39.20%	51.80%	68.60%
MTHFR C677T genotype										
MTHFR CC	\$479.66	\$282.62	\$197.04	3.8787	3.8695	0.0092	\$21,461.00	53.60%	67.40%	85.10%
MTHFR CT	\$501.21	\$263.11	\$238.10	3.8760	3.8718	0.0042	\$56,072.62	31.90%	42.20%	56.90%
MTHFR TT	\$505.77	\$305.47	\$200.30	3.8754	3.8668	0.0086	\$23,168.72	45.60%	59.40%	76.00%
Homocysteine, μmol/L										
≤10.5	\$473.07	\$237.79	\$235.28	3.8795	3.8747	0.0047	\$49,608.67	33.10%	42.20%	58.90%
10.5 - <12/5	\$483.97	\$264.43	\$219.54	3.8781	3.8716	0.0065	\$33,660.97	42.40%	53.60%	72.20%
12.5 - <15.5	\$499.90	\$299.43	\$200.47	3.8762	3.8675	0.0087	\$23,148.41	45.80%	60.40%	78.10%
≥15.5	\$520.31	\$309.41	\$210.90	3.8736	3.8663	0.0073	\$28,820.55	42.90%	53.30%	68.70%

Table S2. Hazard ratios and 95% CI for the first stroke for subgroup analysis

Variable	HR	95% CI	
Sex			
Male	0.68	0.54	0.86
Female	0.90	0.73	1.12
Age, yrs			
<55	0.87	0.60	1.26
55 -65	0.70	0.55	0.89
≥65	0.86	0.67	1.10
Smoking status			
Never	0.79	0.64	0.96
Current	0.80	0.60	1.06
Former	0.76	0.60	1.26
MTHFR C677T genotype			
MTHFR CC	0.65	0.48	0.89
MTHFR CT	0.93	0.74	1.16
MTHFR TT	0.72	0.53	0.97
Homocysteine, μmol/L			
≤10.5	0.88	0.61	1.26
10.5 - <12/5	0.78	0.56	1.10
12.5 - <15.5	0.71	0.53	0.96
≥15.5	0.79	0.59	1.05

Table S3. Baseline characteristics of the study participants

Characteristics	Enalapril-folic acid group	Enalapril group (n=10354)
	(n=10348)	
Age, yrs (SD)	60.0 (7.5)	60.0 (7.6)
Male, n (%)	4245 (41.0)	4252 (41.1)
Body mass index, kg/m ² (SD)	25.0 (3.7)	24.9 (3.7)
Methylenetetrahydrofolate Reductase (MTHFR) C677T genotype, n (%)		
CC	2821 (27.3)	2831 (27.3)
CT	5095 (49.2)	5081 (49.1)
TT	2432 (23.5)	2442 (23.6)
Smoking status, n (%)		
Never	7119 (68.8)	7135 (68.9)
Former	761 (7.4)	809 (7.8)
Current	2461 (23.8)	2408 (23.3)
Baseline Systolic Blood Pressure, mm Hg (SD)	166.8 (20.4)	166.9 (20.4)
Mean Systolic Blood Pressure during treatment, mm Hg (SD)	139.7 (11.1)	139.8 (11.3)
Total cholesterol, mg/dL (SD)	213.6 (46.0)	213.2 (45.8)
High-Density Lipoprotein Cholesterol, mg/dL (SD)	52.0 (14.0)	51.8 (13.9)
Fasting glucose, mg/dL (SD)	104.5 (30.6)	104.5 (30.6)
Baseline folate, ng/mL (SD)	8.5 (4.0)	8.5 (4.0)
Homocysteine, μ mol/L (IQR)	12.5 (10.5 - 15.5)	12.5 (10.5 - 15.5)
Vitamin B12, pg/mL (IQR)	379.6 (314.3 - 475.2)	379.6 (315.7 - 478.2)