

MTHFR: folic acid

7204/7205

677CC = homozygous for MTHFR gene variant with normal activity, 677CT = heterozygous for MTHFR gene variant with reduced activity, 677TT = homozygous for MTHFR gene variant with reduced activity, 1298AA = homozygous for MTHFR gene variant with normal activity, 1298AC = heterozygous for MTHFR gene variant with slightly reduced activity, 1298CC = homozygous for MTHFR gene variant with slightly reduced activity, BMI = body-mass index, CI = confidence interval, HR = hazard ratio, M = molar (mol/L), MTHFR = methylenetetrahydrofolate reductase, NS = non-significant, OR = odds ratio, OR_{adj} = adjusted odds ratio, S = significant

Brief summary and justification of choices:

Folic acid is converted to tetrahydrofolate by the enzyme dihydrofolate reductase (DHFR). Tetrahydrofolate is required for the synthesis of purine nucleotides and following conversion to 5,10-methylenetetrahydrofolate, it is also required for the synthesis of thymidine nucleotides by thymidylate synthase.

The enzyme MTHFR converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. 5-methyltetrahydrofolate is required for the methylation of homocysteine to methionine and is converted to tetrahydrofolate in this process. Methionine is required for protein synthesis and DNA methylation. Reduced activity of the enzyme MTHFR results in decreased intracellular tetrahydrofolate concentrations.

Because MTHFR is involved in folate metabolism, gene variants that result in reduced MTHFR enzyme activity might influence the effect of folates like folic acid.

Gene variant 677C>T:

Studies showed that the effect of therapy with folic acid either was not changed (Jin 2018 and Huo 2015) or was increased (Huang 2018 and Colson 2017) in patients with the 677T variant that results in reduced MTHFR activity. Patients with this variant had lower baseline folate concentrations and higher baseline homocysteine concentrations than patients without this variant (Jin 2018, Huang 2018, Colson 2017, and Crider 2011). Folic acid therapy partially corrected for this (Huang 2018, Colson 2017, and Crider 2011). Although this correction is only partial, there are no indications for adverse clinical effects for patients with the 677T variant after folic acid treatment. Despite indications for inadequate folic acid supplementation in the majority of pregnant women, Kondo 2014 found no increased risk for offspring with neural tube defects in women with the 677T variant. In addition, Crider 2011 reported periconceptional supplementation with folic acid 0.4 mg/day to decrease the incidence of neural tube defects with up to 85% in a population in which 35% had the 677TT genotype and 48% the 677CT genotype. Huo 2015 showed no difference between 677C>T genotypes in the decrease in stroke risk in hypertensive patients by treatment with folic acid 0.8 mg/day for 4.5 years. The meta-analysis of Shao 2017 showed the risk for methotrexate toxicity in studies with folic acid co-medication to be increased for patients with the 677T variant. In addition, this risk was numerically more increased in studies with 100% folic acid co-medication than in all studies together (so with full, with partial or without folic acid co-medication). However, Shao 2017 did not show whether this risk was significantly more increased in studies with folic acid co-medication than in studies without folic acid co-medication, and even if they would have, it would not have been clear whether this increase would have been due to a diminished effectiveness of folic acid in reducing methotrexate toxicity or to an increased effect on the toxicity of the folate antagonist methotrexate in studies with folic acid co-medication. Folic acid is added to methotrexate to suppress methotrexate toxicity, so used especially in regimens expected to give high methotrexate toxicity. In addition, none of the studies reported an increase in adverse events of folic acid treatment in subjects with the 677T variant. Den Dekker 2018 found some differences in respiratory parameters of children aged 10 years of mothers with or without the 677T variant using folic acid supplementation during pregnancy, but no difference in current asthma. For this reason, the KNMP Pharmacogenetics Working Group concludes that there is a MTHFR-folic acid interaction, but that there is insufficient evidence for a clinical effect that makes therapy adjustment useful (yes/no-interactions).

You can find an overview of the clinical and kinetic effects per genotype in the background information text of the gene-drug interactions in the KNMP Kennisbank. You may also have access to this background information text via your pharmacy of physician electronic decision support system.

Other gene variants:

For gene variant 1298A>C, Du 2018 showed a decreased risk of failure of treatment with folic acid 5 mg/day for 90 days for hyperhomocysteinaemia (fasting total plasma homocysteine concentration \geq 15 µM) for carriers of a 1298C variant. The direction of this effect was opposite to the increased risk Du 2018 found for carriers of a 677T variant, while the effect of both variants on MTHFR is reported to be a reduction of activity. The authors indicated that there was a strong linkage disequilibrium between 677C>T and 1298A>C with 99.5% of alleles with a 677T-variant having a 1298A-variant. In addition, the reduction in the risk for treatment failure was similar for alleles with a 677C-variant

having either a 1298A-variant or a 1298C-variant. So, the observed effect is most likely due to the linkage disequilibrium with 677C>T and not to 1298A>C itself. Therefore, it was decided that there was not enough evidence for an clinically significant effect of 1298A>C on MTHFR activity and thus, no cause for inclusion of this gene variant in the MTHFR pharmacogenetic interactions.

For <u>gene variant 1781G>A</u>, Du 2018 did not show an effect on the risk of failure of treatment with folic acid 5 mg/day for 90 days for hyperhomocysteinaemia (fasting total plasma homocysteine concentration \ge 15 µM). Therefore, it was decided that there was not enough evidence for an effect of this gene variant on MTHFR activity and thus, no cause for inclusion of this gene variant in the MTHFR pharmacogenetic interactions.

The table below follows the KNMP nomenclature for MTHFR gene variants. The nomenclature used in the table below may therefore differ from the nomenclature used by the authors in the article.

Source	Code	Effect					Comments
ref. 1	4	941 women without					Authors' conclu-
Chen MY et al.		acid (0.1 mg/day (in		sion:			
Defining the		once daily, or 4 mg					"The relation be-
plasma folate		same study as Cride	er 2011. 6 ma	onth data we	re available f	or 909	tween red blood
concentration		women.					cell and plasma
associated with		To promote optimal					folate concentra-
the red blood		level, WHO recently					tions was modi-
cell folate		folate concentration					fied by BMI and
concentration		ng/mL) in women of		•			genotype and
threshold for		preventing megalob					substantially by
optimal neural		The correlation coef					low plasma vita-
tube defects		between natural log				ation and	min B-12. This
prevention: a		natural logarithm of					suggests that the
population-		677CC and 677CT					threshold of 25.5
based, rando- mized trial of		without anaemia an group with anaemia					nmol/L for opti- mal neural tube
folic acid		included women we					defect prevention
supplementa-		excluded women.		y 10 be < 25	lears or age		may be appropri-
tion.		The median plasma	folate conce	ntrations cor	responding t	o the red	ate in popula-
Am J Clin Nutr		blood cell folate con					tions with similar
2019;109:1452-		multivariate Bayesia				a with a	characteristics,
61.							but it should not
PubMed PMID:		Genotyping:					be used in vita-
31005964.		- 163x 677CC					min B-12 insuffi-
		- 448x 677CT					cient popula-
		- 330x 677TT					tions."
		Results:					
		Results compared	to 677CC:	1	•		
				677TT	677CT	value for	
		a a malation as affi		NO	NO	677CC	
		correlation coeffi-	pretreat-	NS	NS	0.45	
		cient between	ment 6 months	NS	NS	0.60	
		plasma and red blood cell folate	6 months	s indicate that			
		concentrations		ic acid treatm			
		Concentrations		ases when th			
				6 months of			
				er concentrati			
				fference is a			
			tage chang				
		estimated median		+ 3.1	NS	23.2 nM	
		folate concentratio		(95% CI:			
		ponding to the red		0.2 - 5.9)			
		folate concentratio		(S)			
		based on both pre					
		and month 6 data					
					concentration		
	1	11					
				nmol/L thre	shold.		
	677TT:	estimated median folate concentratio		nmol/L thre	shold. NS	24.9 nM	

ref. 1, continu-		ponding to the red blood cell			
ation	677CT:	folate concentration of 906 nM	1		
	AA	at month 6			
ref. 2 Jin H et al. An evidence- based approach to globally assess the covariate- dependent effect of the MTHFR single nucleotide polymorphism rs1801133 on blood homocys- teine: a syste- matic review and meta-ana- lysis. Am J Clin Nutr 2018;107:817- 25. PubMed PMID: 29722849.	4 677TT: AA 677CT: AA	at month 6 Meta-analysis of the effect of 6 cysteine and meta-regression a intake. Of the approximately 19 intake data, approximately 70 h to approximately 25000 subject intake in mandatory food fortifie intake or high folic acid intake a intake was defined as no supple Meta-analyses were performed pective registration of the proto selection strategy was transparsed. Risk-of-bias of the included obs Item Bank on Risk of Bias and Selection bias resulting from the ral population (e.g. sampling from worker's bias), detection bias reselective outcome reporting we Heterogeneity between the studt there were indications for a slig homocysteine-elevating effect f Genotyping (based on subjects - 44% 677CC - 43% 677CT - 13% 677TT Results: Results: Results: Results: Results: Results: The authors indicate that desp total homocysteine concentrat 677CT, the majority of the sub did not have hype	analysis of the effective analysis of the effective analysis of the effective analysis of the folic acid in the section of the stude o	to f high folic acid bups with folic acid ntake, corresponding ntake was defined as acid supplement udy. Low folic acid d fortification. ects model, but pros- oned. The search and tion was standardi- alysed by using the vational Studies. fation from the gene- s and the healthy y techniques, and the halyses was high and toward a total for 677CT. olic acid intake):	Authors' conclu- sion: "The effect of rs1801133 (677 C>T) on total homocysteine exhibits signifi- cant variability that can be attri- buted to effect modification as well as confoun- ding by these covariates (sex, age, race, folic acid intake, smo- king, and alcohol consumption)."
ref. 3	4	638 patients with hyperhomocy		eated with folic acid	Authors' conclu-
Du B et al. Genetic poly- morphisms of key enzymes in folate metabo- lism affect the efficacy of fola- te therapy in patients with hyperhomocys- teinaemia. Br J Nutr 2018;119:887- 95.		5 mg/day for 90 days. Hyperhomocysteinaemia was d cysteine concentration ≥ 15 µM hyperhomocysteinaemia still pr Co-medication and supplement excluded. ORs were adjusted for age, sey parameters. Genotyping: 677C>T: 1298A - 106x 677CC - 487x - 274x 677CT - 136x	sion: "The MTHFR rs1801133 CT genotype, TT ge- notype and T al- lele; the MTHFR rs1801131 AC genotype, CC genotype and C allele; the MTRR rs1801394 GA genotype, GG genotype and G allele; and the		

PubMed PMID:		- 258x 6	677TT	- 15x 1298CC	,		MTRR rs162036
29644956.		Results:					AG genotype and AG + GG geno-
ref. 3, continu-		r	compa	red to homozygous wi	ld type:		types were asso-
ation				homozygous variant	heterozygous	value for ho- mozy- gous wild	ciated with the efficacy of folic acid therapy for hyperhomocys- teinaemia."
	677TT: B 677CT: B 1298 CC: AA [#] 1298 AC: AA [#] 1781 GA: AA	betwee variant failure v either a <u>1298C-</u> For the for histo and his ficant e showed ry of hy	n 677C> having a vas simi 1298A- variant (MTHFR ory of ca tory of c ffect on l 677C> pertensi	$OR_{adj} = 2.68 (95\%)$ CI: 1.59-4.54) (S) $OR_{adj} = 0.26 (95\%)$ CI: 0.07-0.91) (S) - dicate that there is a stand T and 1298A>C with a 1298A-variant. In ad larly reduced for alleled variant (OR = 0.69 (95%) OR = 0.60 (95%) CI: OCC CR gene variants, the audition rdiovascular heart distinguished indetes, despite these treatment failure. How T, history of cardiovast on to be independent (95% CI: 3.98-16.70)	99.5% of alleles with dition, the risk for trea es with a 677C-varian 5% CI: 0.53-0.89) (S) 0.43-0.84) (S)). athors did not adjust th ease, history of hyper e parameters showing vever, multivariate and scular heart disease a predictors of treatme	type 32% 52% 49% brium a 677T- atment t having) or a ne ORs rtension, a signi- alysis nd histo- nt failure	
ref. 4 Huang X et al. MTHFR gene and serum folate interac- tion on serum homocysteine lowering: pros- pect for preci- sion folic acid treatment. Arterioscler Thromb Vasc Biol 2018;38:679- 85. PubMed PMID: 29371246.	4	combin 8218 hyp cardiova enalapril received Huo 2019 Target to Supplem but other tensive of did not d treatmen Difference patients sex, smo vitamin E pressure during th Genotyp - 2238x 6 - 4029x 6 - 1951x 6	ed. pertensive scular e 10 mg/o enalapro- tal serue ents affor relevare lrugs, lipe iffer signet. es in fol- with anco- king stal 312, esti a systoli e treatmon ing of the 577CT 577TT for folice e in oncen-	ve patients without prevents were treated with day for 4.5 years. The il 10 mg/day only. Thi m homocysteine conce- ecting folate metabolis at co-medication was r bid- or glucose-lowering hificantly between grou late and total homocys without folic acid treat tus, alcohol drinking, mated glomerular filtra c blood pressure, aver hent period and body-r e folic acid group: <u>acid treatment compa</u> <u>677TT 6</u> <u>11.2 (95% CI: 1</u> <u>10.4-12.1) (S) 1</u> Both before and af the folate concentr increasing number 8.6 versus 9.5 ng/r versus 24.8 versus	e-existing stroke and r th folic acid 0.8 mg/da control group of 8195 s concerns the same entration was < 10 µM sm (B vitamins) were not. However, other an og drugs, and antiplate ups stratified by genot steine concentrations atment were adjusted total homocysteine, for ation rate, systolic blo rage systolic blood pro- mass index.	major by and 5 patients study as M. excluded, ntihyper- elet drugs type and between for age, blic acid, od essure eatment: <u>C</u> (95% CI: 12.6) (S) c acid, er for versus nd 23.3 tment for	Authors' conclu- sion: "Compared with CC or CT, total homocysteine in the TT group manifested a heightened L- shaped curve from low to high folate levels, but this difference in total homocys- teine by geno- type was elimina- ted when plasma folate levels reach ≈15 ng/mL or higher. Our data raised the prospect to tailor folic acid therapy according to indi- vidual MTHFR C677T genotype and folate sta- tus."

ref. 4, continu- ationFolate concentration also increased in the pa- tients receiving enalapril treatment only (increase with 4.4-4.8 ng/ml).677TT: AA#decrease in total homocys- teine concen- tration (in μM)3.3 (95% CI: 2.7-3.8) (S)1.3 (95% CI: 1.3 (95% CI: 1.3 (95% CI: 1.1-1.5) (S)1.0 (95% CI: 0.8-1.2) (S)677CT: AA677CT: AADecrease in total homocysteine concentra- tion compared to 677CC was higher for 677TT (S), but not for 677CT (NS).Despite the stronger decrease in total homocysteine concentra- teine for 677TT, the	
677TT: AA#decrease in total homocys- tration (in μM)3.3 (95% CI: 1.3 (95% CI: 1.1-1.5) (S)1.0 (95% CI: 1.0 (95% CI: 0.8-1.2) (S)677CT: AA	
677TT: AA#decrease in total homocys- teine concen- tration (in μM)3.3 (95% CI: 1.3 (95% CI: 1.1-1.5) (S)1.0 (95% CI: 0.8-1.2) (S)677CT: AAThe decrease in total homocysteine concentra- tration (in μM)The decrease in total homocysteine concentra- tion compared to 677CC was higher for 677TT (S), but not for 677CT (NS).677CT: AADespite the stronger decrease in total homocys-	
 AA[#] teine concentration (in μM) 677CT: AA The decrease in total homocysteine concentration compared to 677CC was higher for 677TT (S), but not for 677CT (NS). Despite the stronger decrease in total homocysteine 	
677CT:tration (in μM)tion compared to 677CC was higher for 677TT (S), but not for 677CT (NS).AADespite the stronger decrease in total homocys-	
677CT:(S), but not for 677CT (NS).AADespite the stronger decrease in total homocys-	
AA Despite the stronger decrease in total homocys-	
tration after folic acid treatment was still numeri-	
cally higher for this genotype (14.1 versus 12.4 versus 12.1 µM after treatment and 19.3 versus	
13.1 versus 12.5 µM before treatment for 677TT	
versus 677CT versus 677CC) (NS).	
The difference in total homocysteine concentra-	
tion between 677TT and 677CC was significant	
when stratified by folate concentration, but ap- proached zero at folate concentrations between	
15 and 25 ng/ml (between 34 and 57 nM) (mean	
$< 1.2 \ \mu$ M, upper limit 95% CI $< 1.8 \ \mu$ M). The	
difference seemed to increase slightly at folate	
concentrations ≥ 25 ng/ml (mean 1.35 μM, upper limit 95% Cl 2.32 μM).	
Total homocysteine was similar after treatment	
with enalapril only (decrease with 2.2 versus -0.6	
versus -0.7 µM for 677TT versus 677CT versus	
677CC) (NS).	
Percentage of patients achieving the indicated targets after treat-	
ment with folic acid (FA) and without folic acid (-) (significance of	
differences in percentages not determined):	
677TT 677CT 677CC	
folate concentration ≥ - 24.2% 32.7% 41.3% 15 ng/ml FA 70.1% 74.0% 76.5%	
total homocysteine - 12.2% 18.4% 21.4%	
concentration < 10 μ M FA 20.5% 27.0% 29.2%	
total homocysteine - 54.6% 74.3% 76.9%	
concentration < 15 μM FA 73.5% 82.9% 84.8%	
ref. 53Children of 2815 mothers using folic acid supplements during preg- nancy (50% start preconceptional, 34% start < 10 weeks of pregnancy sionAuth	uthors' conclu-
	Preconceptional
	art of maternal
	lic acid supple-
	ent use and gher vitamin
	12 concentra-
	ons at birth
	ight adversely
6	fect childhood
	pending on
	THFR-C677T
	rriership. The
	nical implica-
	ons need to be aluated."
Genotyping of the folic acid group:	
mothers: children: - 1391x 677CC - 1101x 677CC	
- 1424x 677CT+TT - 1256x 677CT+TT	
Results:	

ref. 5, continu-		Results for f	olic acid supplem	entation (FA) compa	ared to no	folic	
ation			mentation (↓ indica					
				genotyp	e mother	genoty	pe child	
1				CT+TT	CC	CT+TT	CC	
		current	any FA	NS	NS	NS	NS	
		asthma	start FA pre-	NS	NS	NS	NS	
			conceptionally start FA ≤ 10	NS	NS	NS	NS	
			weeks			NO		
			start FA > 10	NS	NS	NS	NS	
			weeks			NO	N 0	
		forced expiratory	any FA	NS	↑ (S)	NS NS	NS NS	
		volume in	start FA pre- conceptionally	NS	↑ (S)	113	NO	
		1 second	start FA ≤ 10 weeks	NS	↑ (S)	NS	↑ (S)	
			start FA > 10 weeks	NS	↑ (S)	NS	NS	
		forced vital	any FA	NS	↑ (S)	↑ (S)	↑ (S)	
		capacity	start FA pre-	NS	↑ (S)	↑ (S)	↑ (S)	
			conceptionally		(2)	(=)	(2)	
			start FA ≤ 10 weeks	NS	↑ (S)	↑ (S)	↑ (S)	
			start FA > 10 weeks	NS	↑ (S)	↑ (S)	NS	
	677CT	ratio (for-	any FA	↓ (S)	NS	NS	↓ (S)	
	+TT: A	ced expira- tory volu-	start FA pre-	↓ (S)	NS	↓ (S)	↓ (S)	
		me in 1 se-	conceptionally start FA ≤ 10	NS	NS	NS	NS	
		cond)/(for- ced vital capacity)	weeks start FA > 10	NS	NS	NS	NS	
		forced expiratory flow be- tween 25% and 75% of forced vital capa- city	weeks any FA	NS	↑ (S)	NS	NS	
			start FA pre-	↓ (S)	<u>↑ (S)</u> ↑ (S)	NS	NS	
			conceptionally					
			start FA ≤ 10 weeks	NS	NS	NS	NS	
			start FA > 10 weeks	NS	NS	NS	NS	
		forced	any FA	NS	NS	NS	NS	
		expiratory flow at	start FA pre- conceptionally	NS	NS	NS	NS	
		75% of forced vital	start FA ≤ 10 weeks	NS	↑ (S)	NS	NS	
		capacity	start FA > 10 weeks	NS	NS	NS	NS	
		For both ma	iternal and child 6	I 77CT+TT	the effect	on forced	expira-	
		tory flow bet with increas	ween 25% and 75 ing duration of foli nificant effects of	5% of forc	ed vital ca	pacity inc tion (S).	reased	
		observed.						
ref. 6 Shao W et al. Association	3	Meta-analyse methotrexate of 1100 patie	es of the effect of 6 combined with fo nts (569x 677T ca	lic acid. 7 arriers and	included s I 531x 677	studies wit CC) inves	th a total stigated	Authors' conclu- sion: "In addition,
between MTHFR C677T		677T carriers	, of which 5 studie and 352x 677CC) reported	l data for 6	77CT and	677TT	rheumatoid arthritis patients
polymorphism and methotre-		677T carriers	0 included studies and 851x 677CC) investiga	ated toxicit	y, of whic	h 8	with the MTHFR C677T polymor-
xate treatment outcome in		677CC) report	a total of 1657 pati rted data for 677C	T and 67	7TT separa	ately.		phism who were supplemented
rheumatoid		Meta-analyse	es were performed	l with a ra	ndom-effe	cts model	in case of	with folic acid

arthritis patients: a systematic review and meta-analysis. Genet Test Mol Biomarkers 2017;21:275- 85. PubMed PMID: 28277784.		model in case of low tes that the statistical selection strategy w not mentioned. Quality of the includ Publication bias and ly for the studies wit	v heterogeneity between al method was chosen at as transparent, but the c led studies was not judge d sensitivity analysis wer h folic acid supplementa acid supplementation) t	e not performed separate- ation, only for all studies	displayed signi- ficantly elevated risk for metho- trexate toxicity."
ref. 6, continu- ation			677TT	677CT	
ation		effectiveness	NS	NS NS	
		toxicity	OR = 2.54 (95% CI: 1.36-4.75) (S)	OR = 1.66 (95% CI: 1.01-2.71) (S) 6 CI: 1.05-2.36) (S)	
		Heterogeneity betw	ween studies was high fo		
		677TC compared to compared to 677C	ween studies was absen	veness and 677TT+TC	
			ere numerically somewhat		
				cid supplementation, 8 or d 7 or 5 without folic acid	
	677TT: AA	supplementation) of	compared to only the stu	idies with 100% folic acid	
				strongly overlapped. So, T-allele on methotrexate	
	677CT: AA	toxicity is higher in not receiving folic a	patients receiving folic a acid.	acid compared to patients	
ref. 7 Colson NJ et al. The impact of MTHFR 677 C/T genotypes on folate status markers: a meta-analysis of folic acid intervention studies. Eur J Nutr 2017;56:247- 60. PubMed PMID: 26497154.	3	with a minimum of C 4 to 24 weeks. To a synthetic folates, 1 r either 1 mg food fola potential interaction status, with supplem dietary folic acid equ folate source, with s status, or with pregr sis. Of the 9 include 4 were quasi-experi the 9 included studie (Rosendal score ≥ 6 Rosendal scores (54 mentation and post- teine, included 9 stu 391x 677TT) and 6 and 171x 677TT), re mentation and post- ded 9 studies with a 677TT) and 8 studie 288x 677TT), respe One of the studies to also included in our Meta-analyses were effects model, which tional to the within-s tion of the protocol v strategy was transpa Quality of the include	0.4 mg dietary folic acid e djust for bioequivalence mg dietary folic acid equi ate or 0.6 mg folic acid w of other medications/sup nentation greater than 1 uvalents) per day, with r subjects with chronic illne nant women were exclud d studies, 5 were randor mental trials. Based on t es were of excellent met 5% and 57%). The meta supplementation fasting dies with a total of 841 s studies with a total of 32 espectively. The meta-ar supplementation serum total of 686 subjects (37 es with a total of 589 sub ctively. hat was (partially) includ risk analysis separately e performed with the Der n assigns a weight to eac study sampling variance, was not mentioned. The arent and data exaction led studies was assessed	ivalents was defined as with food. Studies with pplements with folate mg folic acid (1.67 mg natural food folate as only ess that would affect folate led from the meta-analy- mised controlled trials and the Rosendal score, 7 of thodological quality s had slightly lower -analyses for pre-supple- plasma total homocys- subjects (450x 677CC and 26 subjects (155x 677CC nalyses for pre-supple- folate concentration, inclu- 71x 677CC and 315x jects (301x 677CC and ed in the meta-analyses is (Crider 2011). Simonian-Laird random- ch study, inversely propor- but prospective registra- search and selection was standardised.	Authors' conclu- sion: "This meta-ana- lysis confirms observations from observatio- nal and interven- tion studies that MTHFR TT genotype is associated with increased plas- ma homocys- teine and lowered serum folate and less response to short-term sup- plementation."

ref. 7, continu- ation		total homocyst	eine conc	assessed, but for the pre-supplementation entration, the effect was similar after exclu- a largest difference between 677TT and
		Results:		
			nce for 67	7TT compared to 677CC:
		total homo-	pre-	2.8 µM (95% CI: 1.5-4.2) (S)
		cysteine	sup-	The 677TT genotype group in one of the
		concentra-	ple-	studies had mean homocysteine levels
		tion	men- tation	corresponding to hyperhomocysteinaemia (>15 μ M), compared to none of the 677CC
			lation	genotype groups.
				The difference was also significant:
				- for random controlled trials only $(n = 308)$
				- for females only $(n = 482)$
				 after removal of the study with the largest folic acid dose (1 mg/day) (n = 789)
				- after removal of the study with the largest
				difference (n = 618)
	677TT:			- for Chinese populations only (n = 192)
	AA [#]		post-	NS
			sup- ple-	No studies in either genotype group had mean homocysteine levels >15 μM, but the
			men-	study included in the pre-supplementation
			tation	meta-analysis with mean homocysteine
				levels >15 μ M in the 677TT group was not
				included in the post-supplementation
				meta-analysis. A significant difference was also lacking:
				- for random controlled trials only $(n = 247)$
				- for females only (n = 274)
				- after removal of the study with the largest
		serum folate	pro	folic acid dose (1 mg/day) (n = 274) -3.6 nM (95% CI: -2.1 – -5.0) (S)
		concentra-	pre- sup-	The mean serum folate concentration for
		tion	ple-	all groups was above the threshold for
			men-	folate deficiency (7 nM). The lowest mean
			tation	concentrations were 7.3 nM and 9.1 nM in
				the 667TT group of two studies. The difference was also significant:
				- for random controlled trials only $(n = 458)$
				- for females only (n = 456)
				- after removal of the study with the largest
				folic acid dose (1 mg/day) (n = 634) - after removal of studies with depletion
				diets for a minimum of 6 weeks because
				of folic acid fortification of food in the
				countries (n = 633)
	677TT: A		naat	- for Chinese populations only $(n = 237)$
			post- sup-	- 8.7 nM (95% CI: -6.3 – -11.0) (S) All groups in all studies showed an increa-
			ple-	se in mean serum folate concentration with
			men-	the lowest mean concentrations being 14
			tation	nM and 19 nM for the 677TT and 677CC
				groups for the same study. The difference was also significant:
				- for random controlled trials only (n = 357)
				- for females only $(n = 397)$
				- for studies with supplementation for ≥ 8
				weeks $(n = 319)$
				 after removal of the study with the largest folic acid dose (1 mg/day) (n = 537)
				1000 acid dose i mayaayi $m = 530$

ref. 7, continu-				diata fa	a minimum of 6	wooke before	
ation					nentation because		
					ion of food in the		
				536)		\ -	
				- for Ćhin	ese populations c		
					s high for all 4 co		
ref. 8	4				t pre-existing stro		Authors' conclu-
Huo Y et al.					with folic acid 0.8		sion:
Efficacy of folic acid therapy in					he control group (ntention to treat a		"The results from
primary preven-					study protocol inc		the joint analyses of MTHFR geno-
tion of stroke					re also included in		type and base-
among adults				ere every 3 month		5	line folate level
with hyperten-					olism (B vitamins)		showed that
sion in China:					s not. However, o		among partici-
the CSPPT					ering drugs, and a		pants with the
randomized clinical trial.		treatment.	rsignii	icantiy between g	roups stratified by	y genotype and	CC or CT geno- types, the
JAMA			Rs wer	e adjusted for age	e, sex, systolic an	d diastolic blood	highest risk of
2015;313:1325-					and diastolic bloc		stroke and the
35.		during treat	ment, k	body-mass index,	study centres, ba	seline homocys-	greatest benefit
PubMed PMID:					cholesterol, triglyc		of folic acid
25771069.		cholesterol,	fasting	g glucose levels, s	moking, and alco	hol consumption.	therapy were in
		Genotyping	of the	folic acid group:			those with the lowest baseline
		- 2821x 677		Tolic acid group.			folate levels. In
		- 5095x 677					addition, our data
		- 2432x 677	TT				suggest that
		_					individuals with
		Results:	(. l'				the TT genotype
		Results for	TOILC 9	677TT	npared to no folic 677CT	677CC	may require a higher dosage
		systolic blo	bod	NS	NS	NS	of folic acid sup-
		pressure d			lood pressure dur	-	plementation to
		treatment	_	was 139.8 mm l	0	-	overcome biolo-
		diastolic bl		NS	NS	NS	gically insufficient
		pressure d	uring		olood pressure du	ring treatment	levels (as reflec- ted in the rela-
		treatment risk of first		was 83.1 mm H HR = 0.72	g. NS	HR = 0.65	tively greater
		stroke		(95% CI: 0.53-	110	(95% CI: 0.48-	folate require-
	677TT:			0.97) (S)		0.89) (S)	ment with the TT
	AA				id not influence th	e treatment	genotype)."
	677CT:			effect (NS).	f first stroke was	2.70/ in the folio	
	AA				3.4% in the group		
				acid.			
		risk of	Q1	NS	trend for a de-	$HR_{adj} = 0.37$	
		first			creased risk (p	(95% CI: 0.19-	
		stroke			= 0.10) (NS)	0.73) (S);	
		accor-				absolute re-	
		ding to baseline	Q2	NS	NS	duction 2.4% trend for a de-	
		folate	32			creased risk (p	
		concen-				= 0.06) (NS)	
		tration	Q3	NS	NS	NS	
		quartiles	Q4	$HR_{adj} = 0.24$	NS	NS	
				(95% CI: 0.10-			
				0.58) (S); absolute re-			
				duction 2.8%			
				The effect of	Trend for a	The effect of	
				folic acid was	stronger effect	folic acid was	
	1	11	1	lower for Q1	of folic acid for	stronger for	
				compared to	Q1 compared	Q1+Q2 com-	

		Г	
ref. 8, continu-			Q4 (S) and for to Q2+Q3+Q4 pared to Q4
ation			Q2+Q3 com- $(p = 0.083)$ (S).
			pared to Q4 (NS).
			(S).
			Baseline folate quartiles within each of the geno-
			types were 677CC: <6.6, 6.6-<9.0, 9.0-<11.5,
			≥11.5 ng/ml; 677CT: <5.7, 5.7-<8.2, 8.2-<10.5,
			≥10.5 ng/ml; 677TT: <4.8, 4.8-<6.5,6.5-<9.1,
			≥9.1.
			In the group without folic acid, among subjects
			with the 677CC genotype, there was an inverse
			relationship between baseline folate level and
			risk of stroke (S for linear trend). A similar pat-
			tern, to a lesser degree, was observed among
			subjects with the 677CT genotype (S for linear
			trend). In contrast, subjects with the 677TT geno-
			type had a persistently high risk of stroke across
			all folate quartiles (NS for linear trend).
		any adverse	NS
		event other	
		than the study	
		outcomes	NC
		any drug-rela-	NS
		ted adverse	
		event	NC
		other safety	NS
		outcomes,	
		including any	
		serious adverse	
		events, adverse	
		events leading	
		to drug withdra-	
		wal, and abnor-	
		mal laboratory	
		test results with	
		clinical signifi-	
not 0	0		
ref. 9 Kondo A et al.	3		cies in 115 mothers who had given birth to a spina Authors' conclu-
			ompared to genotype frequencies in 4517 popula-
C677T muta-			s. For the prevention of affected pregnancy every "In conclusion, it
tion in methy-			o conceive has to take folic acid supplements 0.4 is not necessary
lenetetrahydro-			r, a previous study showed that the majority of for Japanese
folate reduc-			e women in the 1 st trimester neither consumed women to under-
tase gene and			44 mg/day equivalent to the recommended dietary go genetic scree-
neural tube			k folic acid supplements daily (Kondo et al. 2011). ning C677T
defects: should			cation was not excluded and frequency and duration mutation of the
Japanese		of folic acid intake	•
women under-		Constuning of the	a predictive mar-
go gene scree-		- 47x 677CC	spina bifida mothers: ker for spina bifi-
ning before		- 47x 677CC - 56x 677CT	da prior to preg-
pregnancy? Congenit Anom		- 12x 677TT	nancy, because the TT genotype
(Kyoto)			is not a risk fac-
2014;54:30-4.		Results:	tor for having an
PubMed PMID:			iving birth to a spina bifida child compared to affected infant."
24588777.	677CT:	677CC:	
	AA	677CT	NS
		677TT	NS
	677TT:		o NS for the 677T-allele compared to the 677C-
	AA	allele.	
		Note: The outborn	mention that similar results were published for 13
			nly a Dutch study found a significantly increased risk
			er Put 1995). However, since mothers were recruited
			shortly after folic acid was proven to diminish neural
	L		10

ref. 9, continu- ation		mentation Indeed, Va overcome a mechani bifida in 67	in this s an der P the effe ism for t 77TT inc	tudy was eve ut et al. indic cts of reduce he protective lividuals.	role of folate	han in Kondo folate admir ivity, their fin in the etiolog	o 2014. histration may dings provide by of spina	
ref. 10 Crider KS et al. MTHFR 677C- >T genotype is associated with folate and homocysteine concentrations in a large, population- based, double- blind trial of folic acid sup- plementation. Am J Clin Nutr	4	acid (0.1 n doses) (n 135)) for 6 nuation of Use of sup Bonferroni Genotypin - 162x 677 - 443x 677 - 327x 677 <u>Results:</u>	ng/day (= 317), 4 5 months folic aci oplemen i correcti g: 7CC 7CT 7TT	in 1 or 4 dose 4 mg once da and were fo d treatment. ts and presci	nd vitamin B1: es) (n = 313), aily (n = 167), llowed up for iption drugs v ed to adjust fo	0.4 mg/day (or 4 mg once 3 months after vas excluded	in 1 or 4 e weekly (n = er disconti-	Authors' conclu- sion: "MTHFR geno- type was an independent predictor of plas- ma and red blood cell folate and plasma homo- cysteine concen- trations and did not have a signi- ficant interaction with folic acid dose during sup-
2011;93:1365-			•		677TT	677CT	value for	plementation."
72. PubMed PMID: 21508090.		plasma folate con- centra-		atment (0 s, all pa-	x 0.88 (S)	NS	677CC 10.3 nM	
			folic	0 months	NS	NS	9.5 nM	
		tion	acid	1 month	x 0.79 (S)	NS	20.0 nM	
			0.1 mg/	3 months	x 0.73 (S)	NS	22.5 nM	
			folic acid 0.4 mg/ day	6 months 3 months	x 0.70 (S) x 0.81 (S)	NS NS	24.4 nM 15.9 nM	
				post- treatment	x 0.01 (0)	NO	13.3 110	
				0 months	x 0.80 (S)	NS	11.1 nM	
				1 month	NS	NS	32.1 nM	
				3 months 6 months	NS x 0.71 (S)	NS NS	41.6 nM 40.8 nM	
				3 months post-	x 0.76 (S)	NS	18.5 nM	
			folic	treatment 0 months	x 0.71 (S)	NS	11.7 nM	
			acid	1 month	x 0.63 (S)	NS	70.9 nM	
			4	3 months	NS	NS	84.3 nM	
			mg/	6 months	NS	NS	57.6 nM	
			day	3 months post- treatment	NS	NS	20.3 nM	
			folic	0 months	NS	NS	10.6 nM	
			acid	1 month	NS	NS	25.5 nM	
			4 mg/	3 months	NS NS	NS NS	32.8 nM	
			week	6 months 3 months post-	x 0.70 (S)	NS	29.1 nM 18.4 nM	
	677TT:		od, the	e plasma fola	nd during the te concentration	on increased	for all	
	A 677CT:		the inc	rease and th	es (S). For all e resulting pla the number o	asma folate c	oncentra-	
	A		Betwee the pla (NS).					
			Àt a do	ose of 4 mg/c ed a plateau a				

action For all doses and genotypes, the plasma folate concentration during this 3 months did not vary with the number of 6777-alleles (NS). During the treatment period, there was a significant effect of the genotype on the plasma folate concentration, which did not vary with folic acid doses (S). Genotype and folic acid dose veri independent predictors of plasma folate concentration. red pertereatment (0 x 0.83 (S) NS 669 nM folic acid dose veri independent predictors of plasma folate concentration. folic acid dose veri independent predictors of plasma folate concentration. central 0.1 3 months NS 669 nM folic 0 months. NS NS 669 nM central 1 month NS 620 nM core 3 months NS 633 nM post- 1 month NS 633 nM post- 1 months NS 633 nM post- 1 months 0.76 (S) NS 1040 nM add 1 months N.07 (S) NS 1040 nM add 1 months N.07 (S) NS 1040 nM add 3 months N.07 (S) NS 1040 nM add 3 months N.07 (S) NS		<u> </u>	-		6 A)	/·	
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ref. 10, continuation the same area, showed that periconceptional supplementation with folic acid 0.4 mg/day increased the incidience of neural tube defects by up to 85%. In this study, folic acid 0.4 mg/day increased the red blocd cell folate concentrations in 677TT women to the baseline concentration of the 677CT group after 1 month and to the baseline concentrations observed in the 0.4 mg/day group approximate those necessary to reduce neural tube defect occurrence. plasma perferatament (0 x 1.7 (S) x 1.1 (S) 6.1 µM onon- centra- ine oncent the plasma and red blocd cell folate concentrations observed in the 0.4 mg/day group approximate those necessary to reduce neural tube defect occurrence. oon- centra- tion onths x 1.6 (S) NS 6.2 µM on- centra- tion 1 month x 1.6 (S) NS 6.2 µM odd 3 months x 1.6 (S) NS 6.1 µM odd 3 months x 1.6 (S) NS 6.1 µM odd 3 months x 1.6 (S) NS 5.5 µM odd 3 months x 1.6 (S) NS 5.1 µM odd 3 months x 1.6 (S) NS 5.4 µM odd 3 months x 1.6 (S) NS 5.4 µM odd 3 months x 1.6 (S) NS 5.4 µM odd 3 months x 1.6 (S) NS 5.4 µM							, ,	
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Three months after the end of treatment, plasma homo- cysteine concentration increased with the number of 677T-alleles for all doses, except 0.1 mg/day (S). In all dose groups, the concentration for 677TT was higher than for 677CC genotype (S). The plasma homocysteine concentration did not change in the three months after the end of treatment with 0.1 mg/day for any of the geno- types. Three months after the end of treatment, plasma homo- cysteine concentration was only still reduced for 677TT								
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cysteine concentration was only still reduced for 677TT								
treated with 0.4 mg/day or 4 mg/day (S).			-		•		tor 677TT	
			treated	a with 0.4 mg	/day or 4 mg/	day (S).		

ref. 10, conti- nuation	During the treatment period, there was a significant effect of the genotype on the plasma homocysteine concentra- tion, which did not vary with folic acid dose (S). Genotype and folic acid dose were independent predictors of plas- ma homocysteine concentration.						
	% of patients with high plasma ho- mocysteine		OR = 23.0 (95% CI: 9.2-57.6) (S)	NS	3.1%		
	concentra- tion (> 10.4 µM)	posttreat- ment	OR = 17.9 (95% CI: 6.4-50.0) (S)	NS	2.5%		
			There was also an association with folic acid dose, with 0.4 mg/day and 4 mg/day resulting in a lower risk than 0.1 mg/day, whereas 4 mg/ week did not.				

Risk group

Comments:

Due to the large number of studies, studies and meta-analyses in which the dose of folic acid supplementation was not known were only included if they provided data on more than 1000 supplemented persons and studies and meta-analyses in which the dose of folic acid supplementation was known only if they provided data on more than 500 supplemented persons. In addition, studies with outcomes other than outcomes of established indications of folic acid or adverse events occurring during treatment for these indications (like cancer in adults or hypospadia) were excluded. An exception was made for Huo 2015 investigating stroke, because this was the primary outcome measure of this study and it is important to know whether differences in prophylaxis of folic acid deficiency or correction of homocysteine metabolism disorders translate into clinical effects. For the China Stroke Primary Prevention Trial, only two of the published articles were included: the first publications on the effect of MTHFR 677C>T on stroke and on homocysteine (Huo 2015 and Huang 2018).

Date of literature search: 8 January 2021.

	Genotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics	677CT	4 B	yes	no	7 June 2021
Working Group decision	677TT	4 B	yes	no	

Mechanism:

Folic acid is converted to tetrahydrofolate by the enzyme dihydrofolate reductase (DHFR). Tetrahydrofolate is required for the synthesis of purine nucleotides and following conversion to 5,10-methylenetetrahydrofolate, it is also required for the synthesis of thymidine nucleotides by thymidylate synthase.

The enzyme MTHFR converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. 5-methyltetrahydrofolate is required for the methylation of homocysteine to methionine and is converted to tetrahydrofolate in this process. Methionine is required for protein synthesis and DNA methylation. Reduced activity of the enzyme MTHFR results in decreased intracellular tetrahydrofolate concentrations.

Because MTHFR is involved in folate metabolism, gene variants that result in reduced MTHFR enzyme activity might influence the effect of folates like folic acid.