

平成 21 年度厚生労働科学研究費補助金（循環器疾患等生活習慣病対策総合研究事業）

日本人の食事摂取基準を改定するためのエビデンスの構築に関する研究

－微量栄養素と多量栄養素摂取量のバランスの解明－

平成 19 年度～21 年度 総合研究報告書

主任研究者 柴田克己

I. 総合研究報告

8. 日本人の食事摂取基準の理解を手助けするための資料

－葉酸－

主任研究者 柴田 克己 滋賀県立大学 教授

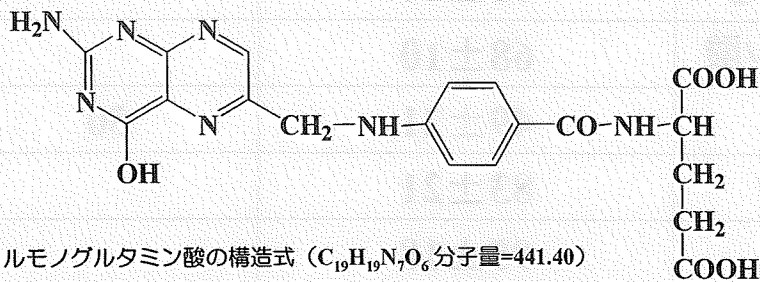
研究要旨

「日本人の食事摂取基準 2010 年版」の水溶性ビタミンの食事摂取基準作成のワーキンググループ長を勤めた。ここでは、葉酸の食事摂取基準に使用した資料の概説を図としてまとめた。

葉酸の食事摂取基準策定に用いた根拠

プテロイルモノグルタミン酸相当量として数値を策定

葉酸とは、狭義にはプテロイルモノグルタミン酸を指すが、広義には補酵素型、すなわち、還元型、一炭素単位置換型およびこれらのポリグルタミン酸型も含む総称名である。五訂増補日本食品標準成分表¹⁾に記載された値は広義の意味の葉酸の値を、図1に示したプテロイルモノグルタミン酸相当量として示したものである。そこで、食事摂取基準もプテロイルモノグルタミン酸相当量として策定した。



プテロイルモノグルタミン酸の構造式 (C₁₉H₁₉N₇O₆ 分子量=441.40)

相対生体利用率の検討結果 1

ビタミン	平均値±SD (%)	
	めしを主食(1日の食事)	2005年版採用値
B ₁	67±20	
B ₂	64±16	
B ₆	73±5	75
ナイアシン	67±19	
パントテン酸	69±11	
葉酸	—	50
ビオチン	—	
C	—	

福渡努, 柴田克己. 遊離型ビタミンに対する食事の中のB群ビタミンの相対利用率, 日本家政学会誌, 59, 403-410 (2008).

相対利用率の検討結果 2

ビタミン	平均値±SD (%)	
	食パンを主食(1日の食事)	2005年版採用値
B ₁	51±17	
B ₂	47±14	
B ₆	90±12	75
ナイアシン	61±14	
パントテン酸	68±10	
葉酸	49±21	50
ビオチン	83±21	
C	95±18	

福渡努, 柴田克己. パンを主食とした食事に含まれる水溶性ビタミンの遊離型ビタミンに対する相対利用率.
日本家政学会誌, 印刷中

葉酸必要量の算定方法

数字は引用番号	DFE μg/d	Duration	RBC change 括弧内は実験終了時の値 (カットオフ値は300 nmol/L以下)	tHcy change 14μmol/L未満が正常	
5 Saubertlich 1987	Food 20+PGA80 (N=4)	180	92d	↓ (380 nmol/L) 低下したがカットオフ値以上	-
	Food 200(N=3)			↓ (330 nmol/L) 低下したがカットオフ値以上	-
	Food 300(N=3)			200	→ (470 nmol/L)
Jacob 1994	Food 25+PGA74 (N=10)	173	108d	→	→
7 Milne 1983	Food 200 (N=40)	200	6m	↓ (520±100nmol/L) 低下したがカットオフ値以上	-
8 O'Keefe 1995	Food 30+PGA170 (N=5)	370	70d	↓ (380 nmol/L) 低下したがカットオフ値以上	
	Food 30+PGA270 (N=6)			↑	
	Food 30+PGA370 (N=6)			↑	
11 Venn 2003	Food 241 (N=50)	241	24w	→	→
	Food 241+5MTHF100 (N=53)			↑	↓
	Food 241+PGA100 (N=52)			↑	↓
10 Brouwer 1999	Food 210 (N=22)	210	4w	→	→
	Food 560 (N=23)			↑	↓
	Food 210+PGA250 (N=22)			↑	↓
9 Cuskelly 1996	Food 200 (N=9)	200	3m	→	-
	Food 268 (advice, N=7)			→	-
	Food 400 (N=10)			→	-
	Food 186+PGA269 (N=6)			↑	-
	Food 200+PGA400 (N=9)			↑	-

食事性葉酸として200μg/日この値をEARとする

葉酸のEAR算定の根拠

EARとは、当該集団の50%のヒトが必要量を満たすと推定される摂取量

Folate requirement and metabolism in nonpregnant women¹⁻³

Howerde E Sauberlich, PhD; Mary J Kretsch, PhD; James H Skala, PhD; Herman L Johnson, PhD; and Peter C Taylor, BS

ABSTRACT Folate metabolism and requirements were studied in 10 adult nonpregnant women maintained for 92 d in a metabolic unit. After a folate depletion period of 28 d, the subjects received increasing supplements of folate from food items or as pteroylmonoglutamic acid (PGA). Plasma folate levels fell 60% during the depletion period and continued to fall until 200 µg/d of naturally occurring food folates were provided. Supplements of 300 µg/d of naturally occurring folates produced a small rise in plasma folate levels although erythrocyte folate levels continued to fall. Lymphocyte deoxyuridine suppression, neutrophil hypersegmentation, and other measurements related to folate metabolism were performed. When compared with PGA, dietary folates appeared to be no more than 50% available. A daily intake of 200-250 µg of dietary folates appears to meet the folate requirements of nonpregnant adult women whereas an intake of 300 µg/d provides an allowance for storage. *Am J Clin Nutr* 1987;46:1016-28.

TABLE 1
Subject information

Subject #	Age y	Height cm	Weight kg	Race
Group A				
1	22	178.0	82.5	Caucasian
2	33	170.0	60.35	Caucasian
3	33	151.5	60.9	Caucasian
4	23	168.0	60.7	Caucasian
Group B				
5	40	157.0	45.0	Caucasian
7	25	163.0	61.4	Hispanic*
8	21	169.0	85.2	Polynesian
Group C				
9	33	155.0	50.4	Caucasian
10	23	166.5	54.1	Caucasian
11	28	168.0	67.1	Caucasian

* Subject # 7 chose to leave the study on day 84 for personal reasons.

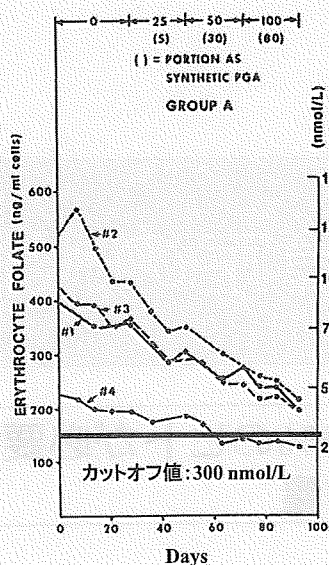


TABLE 2
Summary of the experimental design of the study

Period	Duration	Groups	Diets	Folate content	
				Natural µg/d	PGA* µg/d
Orientation	3 d	A	Ad libitum	400†	0
		B	Ad libitum	400†	0
		C	Ad libitum	400†	0
I: Depletion (days 0-28)	4 wk	A	Formula	0	0
		B	Formula	0	0
		C	Formula	0	0
II: Low repletion (days 29-49)	3 wk	A	Menus A-1	20	5
		B	Menus B-1	50	0
		C	Menus C-1	100	0
III: Marginal repletion (days 50-70)	3 wk	A	Menus A-2	20	30
		B	Menus B-2	100	0
		C	Menus C-2	150	0
IV: Adequate repletion (days 71-92)	3 wk	A	Menus A-3	20	80
		B	Menus B-3	200	0
		C	Menus C-3	300	0
Post-control	2 d	A	Ad libitum	400†	0
		B	Ad libitum	400†	0
		C	Ad libitum	400†	0

* PGA = synthetic folic acid (pteroylglutamic acid).
† Calculated value. All other values were obtained by microbiological assay of the actual menu.

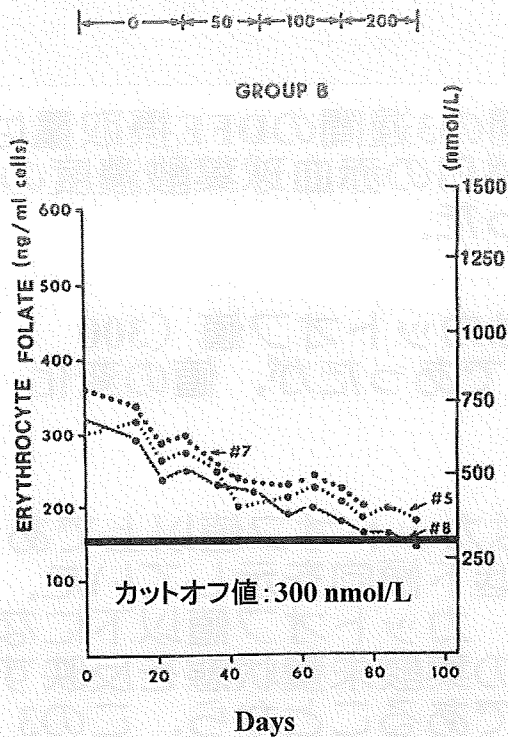


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Period	Duration	Groups	Diets	Folate content	
				Natural μg/d	PGA* μg/d
Orientation	3 d	A	Ad libitum	400†	0
		B	Ad libitum	400†	0
		C	Ad libitum	400†	0
I: Depletion (days 0-28)	4 wk	A	Formula	0	0
		B	Formula	0	0
		C	Formula	0	0
II: Low repletion (days 29-49)	3 wk	A	Menus A-1	20	5
		B	Menus B-1	50	0
		C	Menus C-1	100	0
III: Marginal repletion (days 50-70)	3 wk	A	Menus A-2	20	30
		B	Menus B-2	100	0
		C	Menus C-2	150	0
IV: Adequate repletion (days 71-92)	3 wk	A	Menus A-3	20	80
		B	Menus B-3	200	0
		C	Menus C-3	300	0
Post-control	2 d	A	Ad libitum	400†	0
		B	Ad libitum	400†	0
		C	Ad libitum	400†	0

* PGA = synthetic folic acid (pteroylglutamic acid).

† Calculated value. All other values were obtained by microbiological assay of the actual menu.

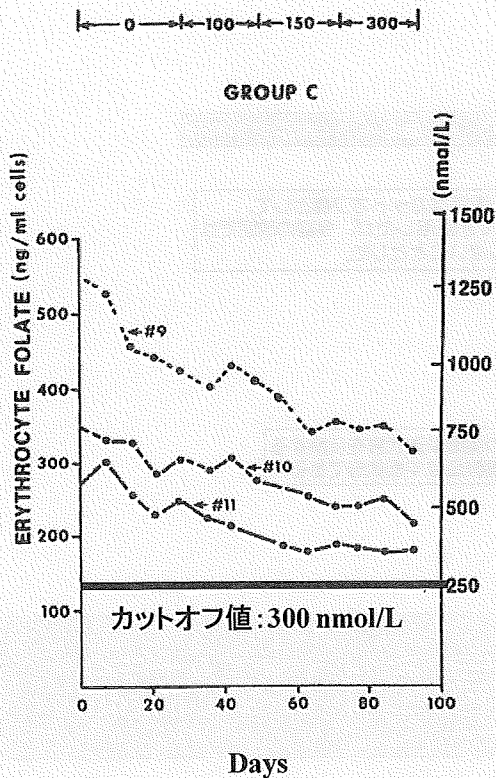


TABLE 2
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Orientation	3 d	A	Ad libitum	400†	0
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		C	Ad libitum	400†	0
I: Depletion (days 0-28)	4 wk	A	Formula	0	0
		B	Formula	0	0
		C	Formula	0	0
II: Low repletion (days 29-49)	3 wk	A	Menus A-1	20	5
		B	Menus B-1	50	0
		C	Menus C-1	100	0
III: Marginal repletion (days 50-70)	3 wk	A	Menus A-2	20	30
		B	Menus B-2	100	0
		C	Menus C-2	150	0
IV: Adequate repletion (days 71-92)	3 wk	A	Menus A-3	20	80
		B	Menus B-3	200	0
		C	Menus C-3	300	0
Post-control	2 d	A	Ad libitum	400†	0
		B	Ad libitum	400†	0
		C	Ad libitum	400†	0

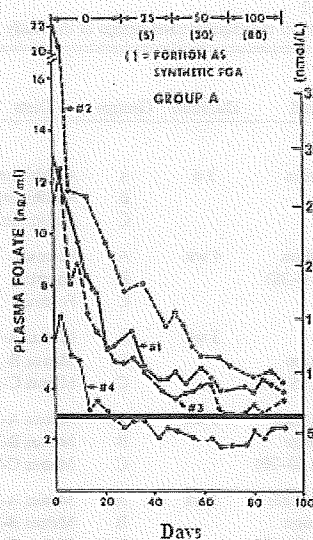
* PGA = synthetic folic acid (pteroylglutamic acid).

† Calculated value. All other values were obtained by microbiological assay of the actual menu.

赤血球中葉酸濃度の変動

引用文献5のまとめ

- グループAの最終実験期間の3週間のDFE摂取量は180 μ g/日である。実験最終日の赤血球葉酸濃度の平均値は380 nmol/Lであった。
- グループAの4名の内1名はカットオフ値 (300 nmol/L)以下の250 nmol/Lであったが、値の変化はほぼ平衡に達していた。
- グループAの4名の内3名はカットオフ値以上であったが、実験最終日でも低下傾向を示していた。さらに実験を継続すると、カットオフ値以下になる危険性もあるが、直近の葉酸栄養状態を反映する血清葉酸値は平衡状態であることから、この3名の赤血球葉酸濃度も平衡状態に近づいていると推測される。



グループAの血中葉酸濃度の推移

2005年版ではカットオフ値として、7 nmol/Lを使用したが、今回の改定では使用しないこととした。

直近の葉酸栄養状態を反映する血清葉酸値は平衡状態である

引用文献5から得られる結論

- DFEとして、180 μ g/日がEARに近い値であると判断した。

引用文献

Folate status of adult males living in a metabolic unit: possible relationships with iron nutriture^{1,2}

David B Milne, PhD, Lillian K Johnson, MS, Janet R Mahalko, MS, and Harold H Saubstead, MD

with the technical assistance of Sandra K Gallagher, CLT

ABSTRACT Folate and iron status was monitored at monthly intervals in 40 adult males who were living in a metabolic unit for 2 to 6 months and consuming diets containing 150 to 250 µg of folate per day. There were significant ($p < 0.02$) declines in hematocrit, serum folate, and serum ferritin. Men who participated in studies for 6 months or more or those with initial serum folate levels more than 10.5 ng/ml and erythrocyte folate levels more than 461 ng/ml also exhibited a highly significant ($p < 0.001$) decline in red blood cell folate. Men with erythrocyte folate below 460 ng/ml or serum folate below 10 ng/ml and who participated in the studies for less than 5 months showed little or no change in folate status. The findings may reflect adjustments in body folate to reflect dietary intakes. Also a folate intake of 200 ± 68 µg/day appeared to be adequate for maintenance of folate stores in adult males. A correlation between iron stores and folate status was also observed. However, this relationship may be coincidental. *Am J Clin Nutr* 1983;37:768-773.

DFEの摂取量：150～250µg/日。平均200±68µg/日の集団
被験者 j：男子40名、19～54歳

TABLE 2
Changes in folate status with time on unit in all volunteers consuming diets containing 200 ± 68 µg of folate per day

Time on unit	n	Serum folate ng/ml	RBC folate ng/ml
Admit	40	8.3 ± 2.7*	347 ± 134
1 mo	40	7.4 ± 2.3	328 ± 141
2 mo	37	7.1 ± 2.6	328 ± 137
3 mo	27	6.9 ± 2.3	308 ± 89
4 mo	23	6.5 ± 2.2	272 ± 114
6 mo	19	5.8 ± 1.4†	229 ± 44‡

血清葉酸値のカットオフ値は
7 nmol/L (=3.1 ng/ml)

赤血球葉酸値のカットオフ値は
300 nmol/L (=132 ng/ml)

* Mean ± SD.

† Significant difference from admit ($p < 0.03$) Scheffé contrasts.

‡ Significant difference from admit ($p < 0.05$) Scheffé contrasts.

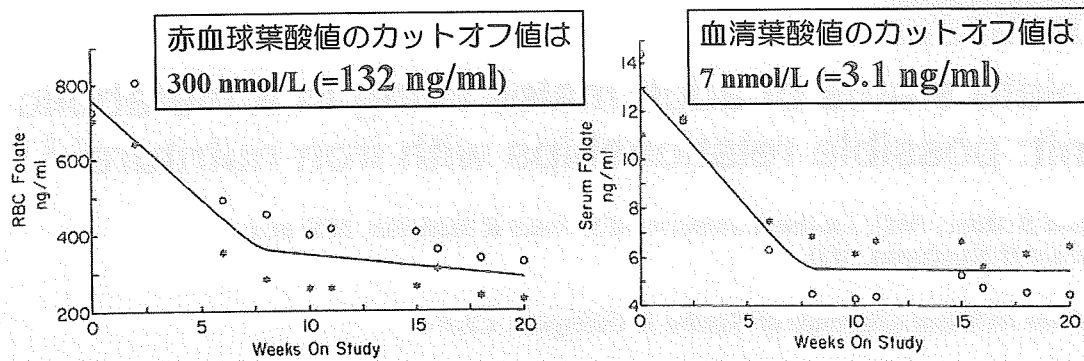


FIG 1. Changes with time of serum folate and erythrocyte folate in two volunteers consuming a diet containing 150 μg of folate per day. Estimated dietary intakes prior to start of study were 778 and 904 μg of folate as determined by a dietary interview.

赤血球葉酸値は実験最終日でも低下傾向を示していた。さらに実験を継続すると、カットオフ値以下になる危険性もあるが、直近の葉酸栄養状態を反映する血清葉酸値は平衡状態であることから、この2名の赤血球葉酸濃度も平衡状態に近づいていると推測される。

引用文献6から得られる結論

- DFEとして、200 μg /日の摂取があれば、男性成人は十分に葉酸栄養状態を維持することができる。
- EARはDFEとして200 μg /日以下である。

Controlled Dietary Folate Affects Folate Status in Nonpregnant Women^{1,2,3,4,5}

CAROLYN A. O'KEEFE, LYNN B. BAILEY,⁶ ELIZABETH A. THOMAS,
SARAH A. HOFER, BARBARA A. DAVIS, JAMES J. CERDA*
AND JESSE F. GREGORY III

*Food Science and Human Nutrition Department, University of Florida, Gainesville, FL 32611, and
*Division of Gastroenterology, Hepatology and Nutrition, Department of Medicine, College of Medicine,
University of Florida, Gainesville, FL 32610*

ABSTRACT In a study designed to estimate the requirement for dietary folate in nonpregnant women, 17 women (21–27 y) consumed 200, 300, or 400 $\mu\text{g}/\text{d}$ of total folate for 70 d which was provided by low folate conventional foods (30 μg) plus supplemental folic acid. Group means for initial serum and erythrocyte folate and plasma homocysteine concentrations were not significantly different. Serum and erythrocyte folate decreased relative to the initial value in the 200 $\mu\text{g}/\text{d}$ group ($43.4 \pm 12.1\%$, $13.6 \pm 16.6\%$, respectively; mean \pm sd), in contrast to an increase in the 400 $\mu\text{g}/\text{d}$ group ($16.8 \pm 52.0\%$, $10.2 \pm 18.5\%$, respectively). The final serum folate in the 200 and 300 $\mu\text{g}/\text{d}$ groups (6.4 ± 0.8 nmol/L, 7.3 ± 1.1 nmol/L, respectively) was significantly lower than that of the 400 $\mu\text{g}/\text{d}$ group (14.3 ± 2.0 nmol/L), with evidence in the 200 $\mu\text{g}/\text{d}$ and 300 $\mu\text{g}/\text{d}$ groups of low (<6.8 nmol/L) serum folate concentrations. Differences in final erythrocyte folate did not reach statistical significance, although low values (<362 nmol/L) were frequent in subjects with 200 $\mu\text{g}/\text{d}$ intake. In the 200 $\mu\text{g}/\text{d}$ group, plasma homocysteine was negatively correlated with serum and erythrocyte folate, and final mean plasma homocysteine (12.6 ± 1.7 $\mu\text{mol}/\text{L}$) was significantly higher than that of the 300 or 400 $\mu\text{g}/\text{d}$ groups. Elevated plasma homocysteine levels (>16 $\mu\text{mol}/\text{L}$) were observed in the 200 $\mu\text{g}/\text{d}$ group only. Data from this study indicate that 200 $\mu\text{g}/\text{d}$ of folate was not sufficient to maintain folate status of these women and suggest that the current RDA of 180 $\mu\text{g}/\text{d}$ may not be adequate to meet the dietary folate intake needs of nonpregnant women. *J. Nutr.* 125: 2717–2725, 1995.

PGAを70日間付加：200, 300, あるいは400 $\mu\text{g}/\text{日}$ 。
被験者：非妊娠女性（21～27歳, 47～67kg）

TABLE 1
Nutrient composition of 3-d cycle menus¹

	Day 1	Day 2	Day 3
Energy, kJ	1838	1841	1853
Protein, g	80.7	74.1	79.1
Fat, g	57.2	83.8	74.1
Folate, μg	29.5	29.6	27.5

¹ Supplementation was provided by the following: Fos Free[®]—1500 USPU retinyl acetate, 150 USPU vitamin D₃, 50 mg ascorbic acid, 5 mg thiamin mononitrate, 2 mg riboflavin, 10 mg niacinamide, 1 mg D-calcium pantothenate, 3 mg pyridoxine HCl, 2 μg cyanocobalamin, 175.5 mg Ca, 14.5, mg Fe.

Solgar[®] Chelated Solamins Multimineral—333 mg Ca, 133 mg P, 100 μg I, 7 mg Fe, 166 mg Mg, 166 μg Cu, 7 mg Zn, 66 mg K, 13 μg Cr, 33 μg Se, 40 μg Mo.

Albertsons[®]—600 mg Ca.

実験最終日の血清葉酸値

今回の策定では血清葉酸値は指標とはしない。その理由は、直近の栄養状態しか反映しないから。

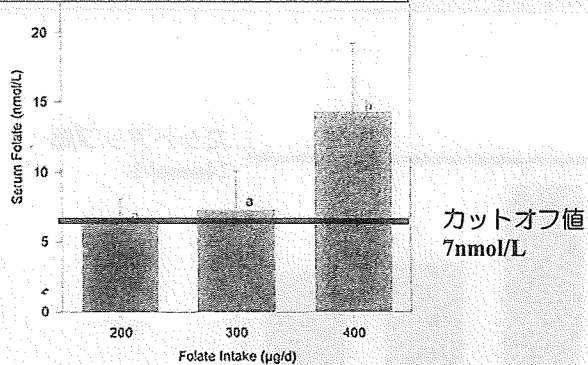


FIGURE 1 Serum folate concentration (mean \pm SD) ($n = 5$ for the 200 $\mu\text{g}/\text{d}$ group and $n = 6$ for the 300 and 400 $\mu\text{g}/\text{d}$ groups) at the end of the 70-d experimental period. Bars designated by the same letter were not significantly different [$P = < 0.05$].

実験最終日の赤血球葉酸値

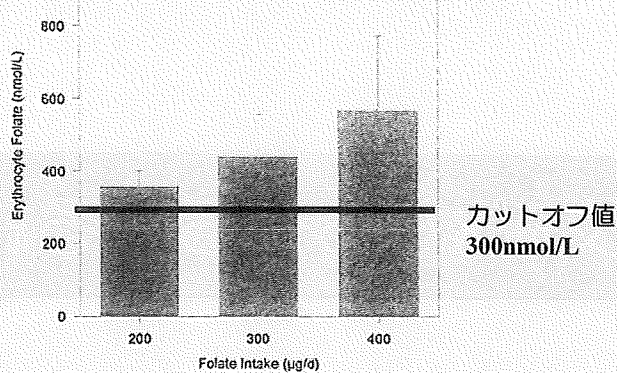


FIGURE 3 Erythrocyte folate concentration (mean \pm SD) ($n = 5$ for the 200 $\mu\text{g}/\text{d}$ group and $n = 6$ for the 300 and 400 $\mu\text{g}/\text{d}$ groups) at the end of the 70-d experimental period. Values were not significantly different [$P > 0.05$].

実験最終日の血清ホモシステイン値

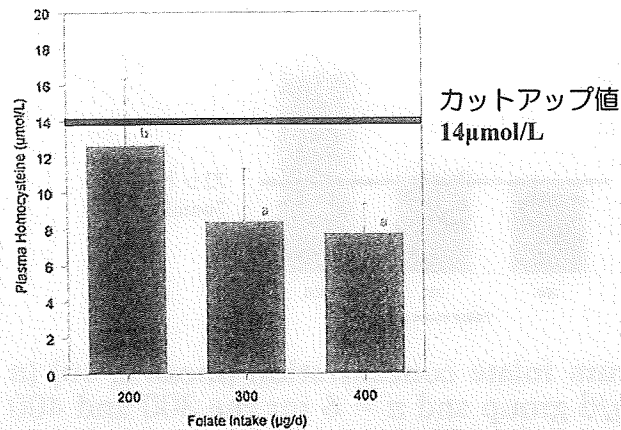


FIGURE 4 Plasma homocysteine concentration (mean \pm SD) ($n = 5$ for the 200 $\mu\text{g}/\text{d}$ group and $n = 6$ for the 300 and 400 $\mu\text{g}/\text{d}$ groups) at the end of the 70-d experimental period. Bars designated by the same letter were not significantly different ($P < 0.05$)

引用文献8から得られる結論

- PGAとして200 $\mu\text{g}/\text{日}$ (DFEとしては300 $\mu\text{g}/\text{日}$) の摂取があれば、女性成人は十分に葉酸栄養状態を維持することができる。
- EARはDFEとしては300 $\mu\text{g}/\text{日}$ 以下である

Effect of increasing dietary folate on red-cell folate: implications for prevention of neural tube defects

Geraldine J Cuskelly, Helene McMillin, John M Scott

Interpretation We have shown that compared with supplements and fortified food, consumption of extra folate as natural food folate is relatively ineffective at increasing folate status. We believe that advice to women to consume folate-rich foods as a means to optimise folate status is misleading.

Lancet 1996; **347**: 657-59

Summary

Background Recommendations by the UK Department of Health suggest that protection from neural tube defects (NTD) can be achieved through intakes of an extra 400 µg daily of folate/folic acid as natural food, foods fortified with folic acid, or supplements. The assumption is that all three routes of intervention would have equal effects on folate status.

Methods We assessed the effectiveness of these suggested routes of intervention in optimising folate status. 62 women were recruited from the University staff and students to take part in a 3-month intervention study. Participants were randomly assigned to one of the following five groups: folic acid supplement (400 µg/day; I); folic-acid-fortified foods (an additional 400 µg/day; II); dietary folate (an additional 400 µg/day; III); dietary advice (IV), and control (V). Responses to intervention were assessed as changes in red-cell folate between preintervention and postintervention values.

Findings 41 women completed the intervention study. Red-cell folate concentrations increased significantly over the 3 months in the groups taking folic acid supplements (group I) or food fortified with folic acid (group II) only ($p < 0.01$ for both groups). By contrast, although aggressive intervention with dietary folate (group III) or dietary advice (group IV) significantly increased intake of food folate ($p < 0.001$ and $p < 0.05$, respectively), there was no significant change in folate status.

被験者：非妊娠女性（17～40歳），3か月間

	Supplement (Group I, n=9)	Ferriect loads (Group II, n=6)	Dietary folate (Group III, n=20)	Dietary advice (Group IV, n=7)	Control (Group V, n=9)
Folate/folic acid intake (μg/day)					
Preintervention	203 (37)	186 (55)	209 (17)	175 (79)	191 (56)
Postintervention	651 (143)*	427 (176)*	410 (214)†	265 (51)*	215 (66)
of which folic acid	456 (10)	203 (9)	0	0	0
Post minus preintervention	448 (31)*	241 (55)	201 (117)	90 (73)	24 (51)
Mean ± change (CI)	194 (125, 253)	127 (72, 179)	111 (59, 163)	55 (-13, 196)	22 (-51, 65)
Red cell folate (ng/L)					
Preintervention	354 (66)	326 (95)	326 (92)	345 (41)	355 (72)
Postintervention	452 (115)†	406 (135)†	334 (101)	352 (74)	335 (50)
Post minus preintervention	148 (65)	173 (124)	28 (104)	7 (75)	17 (44)
Mean ± change (CI)	49 (27, 70)	57 (12, 101)	11 (-6, 28)	14 (-1, 29)	21 (-5, 48)

Values are mean (SD). Differences between pre and postintervention: *p<0.05, †p<0.05, ‡p<0.01 (paired t-test).

拡大化

	Dietary advice (Group IV, n=7)	Control (Group V, n=9)
DFE摂取量 μg/日	175 (46) 229 (67)* 51 (93) 92 (73) 59 (-13, 196)	191 (50) 210 (68) 0 33 (57) 31 (-59, 95)
μg/L		
実験前のRCF値	345 (41)	326 (72)
終了時のRCF値	352 (74) 53 (75) 13 (-1, 33)	335 (60) 9 (44) 5 (-5, 16)

赤血球葉酸値のカットオフ値は
300 nmol/L (=132 μg/L)

Dietary Folate from Vegetables and Citrus Fruit Decreases Plasma Homocysteine Concentrations in Humans in a Dietary Controlled Trial^{1,2}

Ingeborg A. Brouwer,^{1,3} Marijke van Dusseldorp,⁴ Clive E. West,⁵ Saskia Meyboom,⁶ Chris M. G. Thomas,^{1,2} Marinus Duran,⁹ Karin H. van het Hof,⁵ Tom K.A.B. Eskes,⁷ Joseph G.A.J. Hautvast⁸ and Régine P. M. Steegers-Theunissen^{1,2*}

¹Division of Human Nutrition and Epidemiology, Wageningen Agricultural University, 6700 EV Wageningen; ²Department of Obstetrics and Gynaecology, ³Department of Epidemiology, and ⁴Department of Chemical Endocrinology, University Hospital St. Radboud, 6500 HB Nijmegen; ⁵Laboratory of Metabolic Diseases, Wilhelmina Children's Hospital, 3501 CA Utrecht and ⁶Unilever Research Vlaardingen, 3130 AC Vlaardingen, the Netherlands.

ABSTRACT Elevated total plasma homocysteine (tHcy) concentrations are considered a risk factor for neural tube defects (NTD) and cardiovascular disease. Supplementation with folic acid decreases the risk of women having children with NTD. In both sexes, it decreases tHcy levels. We investigated the efficacy of natural dietary folate in improving folate and homocysteine status. We performed a 4-wk dietary controlled, parallel design intervention trial with 88 healthy subjects (18–45 y) divided into 3 treatment groups: the dietary folate group, the folic acid group and the placebo group. Each day each group was fed a different diet. The dietary folate group received a diet high in vegetables and citrus fruit (total folate content ~560 µg) plus a placebo tablet. The folic acid group received a diet naturally low in folate (~210 µg) plus 500 µg folic acid and placebo tablet on alternate days, i.e., 250 µg folic acid/d. And the placebo group received the same low-folate diet as the folic acid group plus a placebo tablet. After 4 wk of intervention, folate status improved, and tHcy concentrations decreased in both the dietary folate and the folic acid groups. From the amount of additional folate (350 µg/d) and folic acid (250 µg/d) consumed, the relative bioavailability of dietary folate compared to folic acid was calculated to be 60–88%, depending on the endpoint used. In conclusion, increasing the consumption of vegetables and citrus fruit, both good sources of folate, will improve folate status and decrease tHcy concentrations. This may contribute to the prevention of cardiovascular disease and NTD in the general population. *J. Nutr.* 129: 1135–1139, 1999.

被験者：18歳～45歳，女性66名，男性28名
4週間

Daily intake of nutrients and energy during dietary intervention period¹

Energy/Nutrient	Intervention		
	Dietary folate group	Folic acid group ²	Placebo group
Folate, µg/d ³			
Calculated	594 ± 27	226 ± 9	226 ± 9
Analyzed	560 ± 184	210 ± 49	210 ± 49
Folic acid, µg/d	0	250 ²	0
Protein, energy%	14.1	13.7	13.6
Fat, energy%	31.7	30.7	30.5
Carbohydrates, energy%	53.6	55.6	55.9
Alcohol, energy%	1.3	1.5	0.5
Dietary fiber, g/d	4.8	4.2	4.1
Energy, MJ/d	9.89 ± 2.53	9.61 ± 2.57	9.85 ± 2.47
Energy, kcal/d	2364 ± 605	2297 ± 614	2354 ± 590

¹ Values are based on the analysis of six complete duplicate diets (one for each day of the menu cycle) plus its calculated contribution from the free-choice items (see Methods section).
² The folic acid group received one 500 µg folic acid tablet and one placebo tablet on alternate days.
³ The folate content represents the daily amount for a subject receiving 11 MJ/d. Differences in folate content were similar for all energy levels.

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² The folic acid group received one 500 µg folic acid tablet and one placebo tablet on alternate days.
³ The folate content represents the daily amount for a subject receiving 11 MJ/d. Differences in folate content were similar for all energy levels.

	Placebo group (no additional folate or folic acid) (n = 22)
Plasma folate, nmol/L	
Week 0	13.2 ± 3.4
Week 2	12.9 ± 3.6
Week 4	12.7 ± 2.9
Change from baseline	-0.6 ± 1.7
Red blood cell folate, nmol/L	
Week 0	347 ± 76
Week 4	345 ± 68
Change from baseline	-1.2 ± 38.6
Plasma homocysteine, μmol/L	
Week 0	10.2 ± 2.5
Week 2	9.8 ± 2.3
Week 4	10.7 ± 2.6
Change from baseline	0.6 ± 1.5

引用文献10から得られる結論

- DFEとしては226μg/日の摂取があれば、成人は十分に葉酸栄養状態を維持することができる。
- EARはDFEとしては226μg/日以下である。

Comparison of the effect of low-dose supplementation with L-5-methyltetrahydrofolate or folic acid on plasma homocysteine: a randomized placebo-controlled study¹⁻³

Bernard J Venn, Timothy J Green, Rudolf Moser, and Jim I Mann

Am J Clin Nutr, 2003;77:658-662.

ABSTRACT

Background: Food fortification with folic acid has been introduced in several countries for the prevention of neural tube defects. Fortification has lowered total homocysteine (tHcy) concentrations in the US population, a consequence that may have health benefits. However, folic acid fortification could mask vitamin B-12 deficiency. Synthetic L-5-methyltetrahydrofolate (L-MTHF) may be more appropriate than folic acid as a fortificant because it is unlikely to mask the hematologic indicators of vitamin B-12 deficiency.

Objective: The objective of the study was to compare the effectiveness of 100 µg folic acid/d with that of equimolar L-MTHF in lowering tHcy in healthy volunteers.

Design: The study was designed as a 24-wk, randomized, placebo-controlled intervention. Free-living healthy volunteers ($n = 167$) were randomly assigned to receive a daily supplement containing folic acid (100 µg), L-MTHF (113 µg), or placebo. Blood collected at baseline and at 8, 16, and 24 wk was analyzed for tHcy, plasma folate, and red blood cell folate (RBCF) concentrations.

Results: At 24 wk, after adjustment for baseline values, mean (95% CI) tHcy was 14.6% (9.3, 19.5%) and 9.3% (3.7, 14.6%) lower, mean plasma folate was 34% (14, 56%) and 52% (30, 78%) higher, and mean RBCF was 23% (12, 35%) and 31% (19, 44%) higher in the L-MTHF and folic acid groups, respectively, than in the placebo group. L-MTHF was more effective than was folic acid in lowering tHcy ($P < 0.05$). At 24 wk, the increases in plasma folate and RBCF concentrations did not differ significantly between the 2 supplemented groups.

Conclusion: Low-dose L-MTHF is at least as effective as is folic acid in reducing tHcy concentrations in healthy persons. *Am J Clin Nutr* 2003;77:658-662.

Characteristics of study participants in each treatment group at baseline^a

Characteristic	Placebo group (n = 50)	L-MTHF group (n = 53)	Folic acid group (n = 52)
Age (yr) ^b	47 ± 13.5	41 ± 13.5	46 ± 16.7
Women [n (%)]	36 (72)	43 (81)	34 (73)
Plasma vitamin B-12 (pmol/L)	279 (249, 312) ^c	256 (228, 287)	270 (239, 304)
Plasma total cholesterol (mmol/L)	5.8 (5.5, 6.1)	5.3 (5.1, 5.6)	5.5 (5.2, 5.8)
Plasma creatinine (µmol/L)	96 (92, 101)	95 (90, 100)	98 (94, 103)
Dietary folate (µg/d)	241 (215, 276)	244 (217, 275)	211 (182, 244)
<i>MTHFR</i> 677C→T (n)			
CC	24	30	27
CT	22	18	22
TT	4	5	3

付加はなし
241µgのDFE

256µgのDFE
+ 113µg
(227 nmol)
のL-MTHF-Ca

270µgのDFE
+ 100µg
(227 nmol)
のPGA

Plasma total homocysteine (tHcy), plasma folate, and red blood cell folate (RCF) concentrations in the intervention groups at each time point^a

Treatment	Baseline ^b	Week 8	Week 16	Week 24	Percentage difference from baseline at week 24 ^c
Plasma tHcy (µmol/L)					
Placebo (n = 50)	8.5 (8.0, 9.1)	8.8 (8.2, 9.4)	8.8 (8.2, 9.4)	8.5 (7.9, 9.1)	
L-MTHF (n = 53)	8.8 (8.0, 9.6)	8.3 (7.7, 9.1)	8.1 (7.4, 8.8)	7.4 (6.9, 8.0)	-14.6 (-9.3, -19.5) ^d
Folic acid (n = 52)	8.4 (7.7, 9.1)	8.1 (7.5, 8.7)	7.8 (7.2, 8.4)	7.6 (7.1, 8.2)	-9.3 (-3.7, -14.6) ^d
Plasma folate (nmol/L)					
Placebo (n = 50)	19.7 (17.4, 22.3)	19.0 (16.4, 22.0)	18.5 (15.9, 21.5)	20.5 (17.6, 24.0)	
L-MTHF (n = 53)	17.5 (15.4, 20.0)	22.3 (19.7, 25.3)	23.5 (19.8, 26.7)	25.6 (22.6, 28.9)	34 (14, 56) ^d
Folic acid (n = 52)	23.3 (20.5, 26.5)	28.9 (25.8, 32.4)	28.5 (24.6, 33.1)	34.5 (30.5, 39.0)	52 (30, 78) ^d
RCF (nmol/L)					
Placebo (n = 50)	884 (804, 972)	866 (781, 959)	884 (789, 991)	848 (752, 956)	
L-MTHF (n = 53)	814 (739, 897)	899 (822, 983)	1053 (926, 1087)	984 (910, 1064)	23 (12, 33) ^d
Folic acid (n = 52)	915 (838, 999)	999 (924, 1079)	1057 (959, 1164)	1137 (1053, 1227)	31 (19, 44) ^d

Placebo = 付加はなし。241µgのDFE

L-MTHF = 256µgのDFE + 113µg(227 nmol)のL-MTHF-Ca

Folic acid = 270µgのDFE + 100µg(227 nmol)のPGA

Treatment	Baseline ^b	Week 24
Plasma tHcy (µmol/L)	カットアップ値: 14µmol/L	
Placebo (n = 50)	8.5 (8.0, 9.1)	<u>8.5 (7.9, 9.1)</u>
L-MTHF (n = 53)	8.8 (8.0, 9.6)	7.4 (6.9, 8.0)
Folic acid (n = 52)	8.4 (7.7, 9.1)	7.6 (7.1, 8.2)
Plasma folate (nmol/L)		
Placebo (n = 50)	19.7 (17.4, 22.3)	20.5 (17.6, 24.0)
L-MTHF (n = 53)	17.5 (15.4, 20.0)	25.6 (22.6, 28.9)
Folic acid (n = 52)	23.3 (20.5, 26.5)	34.5 (30.5, 39.0)
RCF (nmol/L)	カットオフ値: 300 nmol/L	
Placebo (n = 50)	884 (804, 972)	<u>848 (752, 956)</u>
L-MTHF (n = 53)	814 (739, 897)	984 (910, 1064)
Folic acid (n = 52)	915 (838, 999)	1137 (1053, 1227)

引用文献11から得られる結論

- DFEとしては241 μg /日の摂取があれば、成人は十分に葉酸栄養状態を維持することができる。
- EARはDFEとしては241 μg /日以下である。

結論

- 男女成人の葉酸のEARは食事性葉酸として、200 μg /日とした。