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－

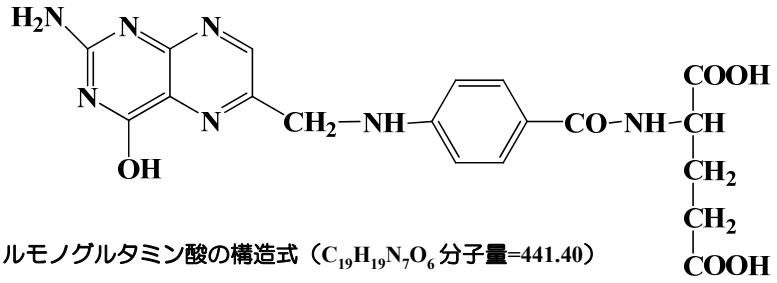
主任研究者　　柴田　克己　　滋賀県立大学　　教授

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（$C_{19}H_{19}N_7O_6$ 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
B1	67±20	
B2	64±16	
B6	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中に含まれる水溶性ビタミンの遊離型ビタミンに対売る相対利用率．
日本家政学会誌，60，57-63 (2009)．

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 Sauberlich 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)	200		↓ (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)	570		↑	
	Food 30+PGA370 (N=6)	670		↑	
11 Venn 2003	Food 241 (N=50)	241	24w	→	→
	Food 241+5MTHF100 (N=53)	441		↑	↓
	Food 241+PGA100 (N=52)	441		↑	↓
10 Brouwer 1999	Food 210 (N=22)	210	4w	→	→
	Food 560 (N=23)	560		↑	↓
	Food 210+PGA250 (N=22)	560		↑	↓
9 Cuskelly 1996	Food 200 (N=9)	200	3m	→	-
	Food 268 (advice, N=7)	268		→	-
	Food 400 (N=10)	400		→	-
	Food 186+PGA269 (N=6)	724		↑	-
	Food 200+PGA400 (N=9)	1000		↑	-

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

引用文献5

Folate requirement and metabolism in nonpregnant women[1–3]

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	Height	Weight	Race
	y	*cm*	*kg*	
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.

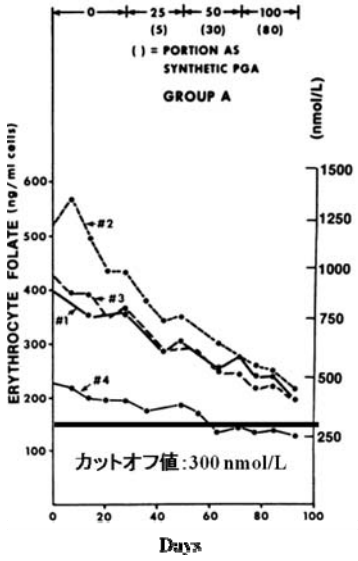


TABLE 2
Summary of the experimental design of the study

Period	Duration	Groups	Diets	Folate content: Natural	Folate content: PGA*
				μg/d	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.

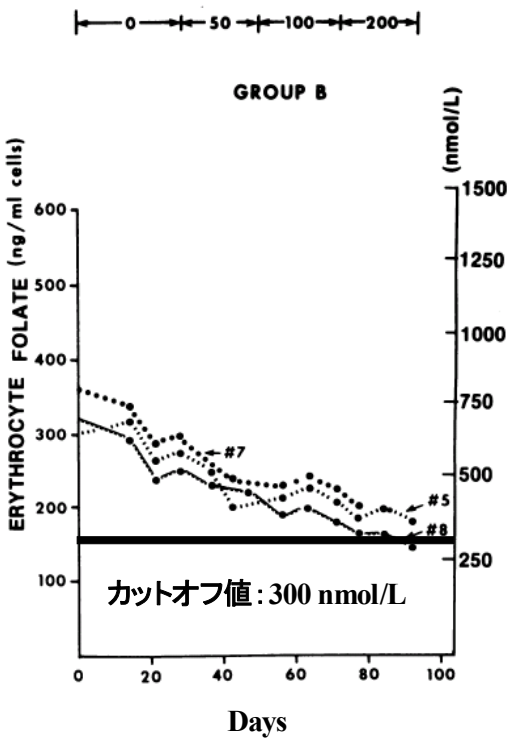
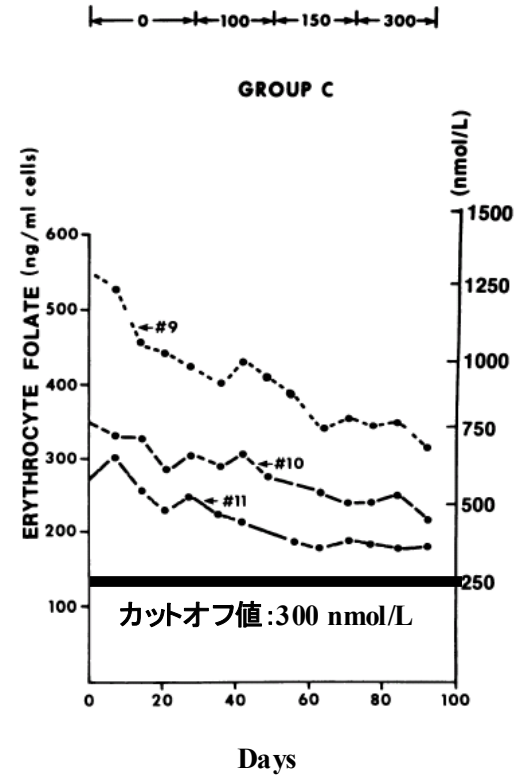


TABLE 2
Summary of the experimental design of the study

Period	Duration	Groups	Diets	Folate content: Natural	Folate content: PGA*
				μg/d	*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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		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.

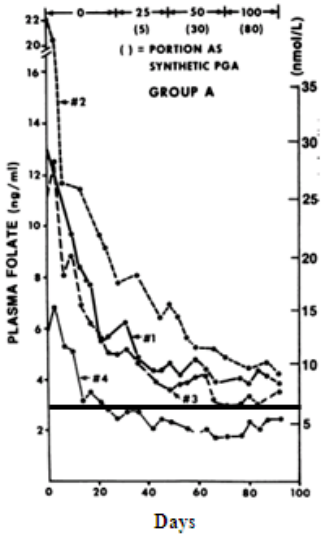
赤血球中葉酸濃度の変動

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180μg/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の血漿中の葉酸濃度の変動

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，180μg/日がEARに近い値であると判断した．

引用文献6

Folate status of adult males living in a metabolic unit: possible relationships with iron nutriture[1,2]

David B Milne, PhD, LuAnn K Johnson, MS, Janet R Mahalko, MS, and Harold H Sandstead, 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 8 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 481 ng/ml also exhibited a highly significant ($p < 0.001$) decline in red blood cell folate. Men with erythrocyte folate below 480 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

血清葉酸値のカットオフ値は
7 nmol/L (=**3.1 ng/ml**)

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	RBC folate
		ng/ml	*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‡

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.

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

血清葉酸値のカットオフ値は
7 nmol/L (=3.1 ng/ml)

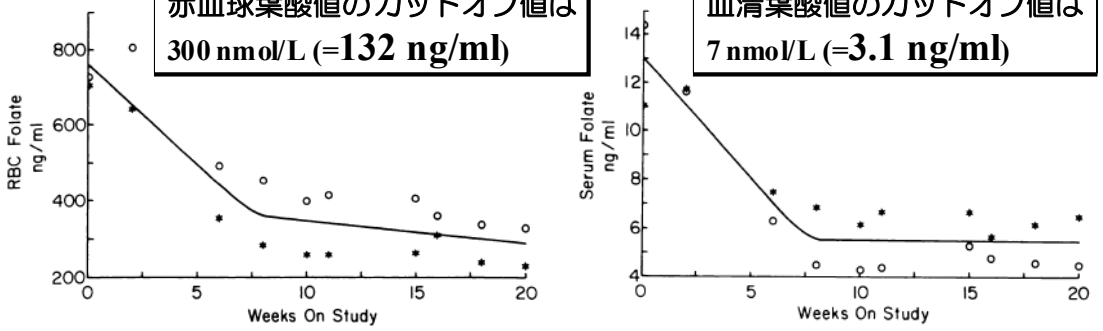


FIG 1. Changes with time of serum folate and erythrocyte folate in two volunteers consuming a diet containing 150 μg of folate per day. Estimated dietary intakes prior to start of study were 778 and 904 μg of folate as determined by a dietary interview.

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，200μg/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200μg/日以下である.

引用文献8

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. HOFLER, 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 μg/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 μg/d group (43.4 ± 12.1%, 13.6 ± 16.6%, respectively; mean ± SD), in contrast to an increase in the 400 μg/d group (16.8 ± 52.0%, 10.2 ± 18.5%, respectively). The final serum folate in the 200 and 300 μg/d groups (6.4 ± 0.8 nmol/L, 7.3 ± 1.1 nmol/L, respectively) was significantly lower than that of the 400 μg/d group (14.3 ± 2.0 nmol/L), with evidence in the 200 μg/d and 300 μg/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 μg/d intake. In the 200 μg/d group, plasma homocysteine was negatively correlated with serum and erythrocyte folate, and final mean plasma homocysteine (12.6 ± 1.7 μmol/L) was significantly higher than that of the 300 or 400 μg/d groups. Elevated plasma homocysteine levels (>16 μmol/L) were observed in the 200 μg/d group only. Data from this study indicate that 200 μg/d of folate was not sufficient to maintain folate status of these women and suggest that the current RDA of 180 μg/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400μg/日．
被験者：非妊娠女性（21～27歳，47～67kg）

TABLE 2

Nutrient composition of 3-d cycle menus[1]

	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

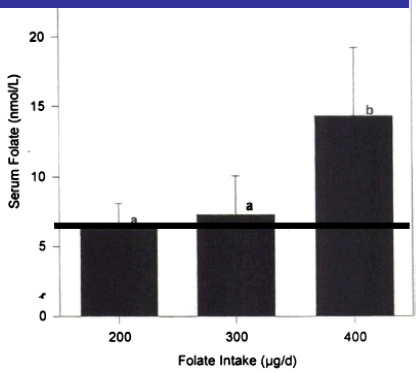
[1] Supplementation was provided by the following: Fos Free®—1500 USPU retinyl acetate, 150 USPU vitamin D_3, 50 mg ascorbic acid, 5 mg thiamin mononitrate, 2 mg riboflavin, 10 mg niacinamide, 1 mg D-calcium pantothenate, 3 mg pyridoxine HCl, 2 μg cyanocobalamin, 175.5 mg Ca, 14.5, mg Fe.

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

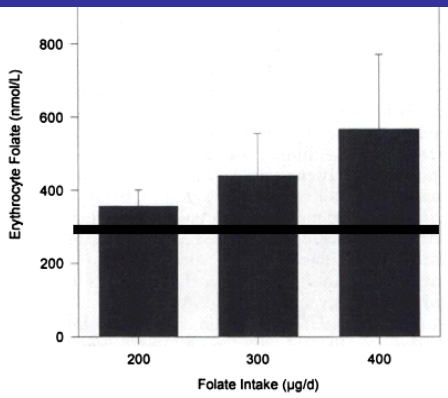
今回の策定では
血清葉酸値は
指標とはしない．
その理由は，直近の
栄養状態しか反映
しないから．



カットオフ値
7nmol/L

FIGURE 1 Serum folate concentration (mean ± SD) (n = 5 for the 200 µg/d group and n = 6 for the 300 and 400 µg/d groups) at the end of the 70-d experimental period. Bars designated by the same letter were not significantly different (P = < 0.05).

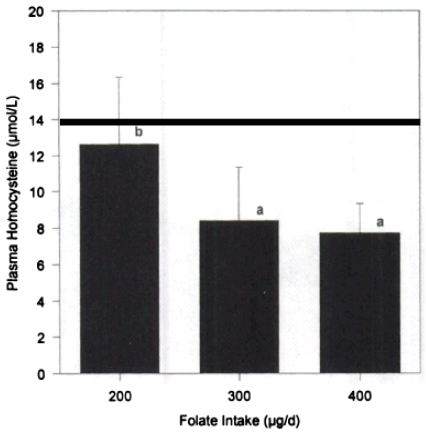
実験最終日の赤血球葉酸値



カットオフ値
300nmol/L

FIGURE 3 Erythrocyte folate concentration (mean ± SD) (n = 5 for the 200 µg/d group and n = 6 for the 300 and 400 µg/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



カットアップ値
14μmol/L

FIGURE 4 Plasma homocysteine concentration (mean ± SD) (n = 5 for the 200 μg/d group and n = 6 for the 300 and 400 μg/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200μg/日（DFEとしては300μg/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300μg/日以下である**

引用文献9

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

Geraldine J Cuskelly, Helene McNulty, 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)	Fortified foods (group II, n=6)	Dietary folate (group III, n=10)	Dietary advice (group IV, n=7)	Control (group V, n=9)
Folate/folic acid intake (μg/day)					
Preintervention	209 (37)	186 (35)	209 (73)	175 (40)	191 (50)
Postintervention	601 (43)*	407 (76)†	410 (121)‡	268 (67)*	210 (68)
of which folic acid	400 (0)	269 (93)	0	51 (53)	0
Post minus preintervention	392 (31)	221 (95)	201 (117)	92 (73)	23 (57)
Mean % change (CI)	196 (159, 233)	127 (72, 370)	111 (59, 343)	59 (−13, 198)	21 (−50, 95)
Red-cell folate (μg/L)					
Preintervention	351 (60)	328 (46)	366 (92)	345 (41)	326 (72)
Postintervention	492 (118)†	498 (135)†	394 (101)	399 (74)	335 (60)
Post minus preintervention	141 (88)	173 (102)	28 (104)	53 (75)	9 (44)
Mean % change (CI)	40 (21, 59)	52 (31, 73)	11 (−6, 28)	16 (−1, 33)	5 (−5, 16)

Values are mean (SD). Differences between pre and postintervention: *p<0·05, †p<0·01, ‡p<0·001 (paired *t* test).

拡大化

	Dietary advice (group IV, n=7)	Control (group V, n=9)
	175 (40)	191 (50)
DFE摂取量	268 (67)*	210 (68)
μg/日	51 (53)	0
	92 (73)	23 (57)
	59 (−13, 198)	21 (−50, 95)
μg/L		
実験前のRCF値	345 (41)	326 (72)
終了時のRCF値	399 (74)	335 (60)
	53 (75)	9 (44)
	16 (−1, 33)	5 (−5, 16)

赤血球葉酸値のカットオフ値は
300 nmol/L (=132 μg/L)

引用文献10

Dietary Folate from Vegetables and Citrus Fruit Decreases Plasma Homocysteine Concentrations in Humans in a Dietary Controlled Trial[1,2]

Ingeborg A. Brouwer,*†[3] Marijke van Dusseldorp,* Clive E. West,*
Saskia Meyboom,* Chris M. G. Thomas,†‡ Marinus Duran,§ Karin H. van het Hof,¶
Tom K.A.B. Eskes,† Joseph G.A.J. Hautvast* and Régine P. M. Steegers-Theunissen†**

*Division of Human Nutrition and Epidemiology, Wageningen Agricultural University, 6700 EV Wageningen; †Department of Obstetrics and Gynaecology, **Department of Epidemiology, and ‡Department of Chemical Endocrinology, University Hospital St. Radboud, 6500 HB Nijmegen; §Laboratory of Metabolic Diseases, Wilhelmina Children's Hospital, 3501 CA Utrecht and ¶Unilever 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 66 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 60–98%, 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 period[1]

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%	53.0	55.6	55.9
Alcohol, energy%	1.3	1.5	0.5
Dietary fiber, g/MJ	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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Fat, energy%	31.7	30.7	30.5
Carbohydrates, energy%	53.0	55.6	55.9
Alcohol, energy%	1.3	1.5	0.5
Dietary fiber, g/MJ	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.

	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 ± 79
Week 4	345 ± 69
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 ± 2.8
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.

引用文献11

Comparison of the effect of low-dose supplementation with L-5-methyltetrahydrofolate or folic acid on plasma homocysteine: a randomized placebo-controlled study[1–3]

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 (RCF) 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 RCF 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 RCF 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;77:658–62.

Characteristics of study participants in each treatment group at baseline[1]

Characteristic	Placebo group (n = 50)	L-MTHF group (n = 53)	Folic acid group (n = 52)
Age (y)[2]	47 ± 13.5	41 ± 13.5	46 ± 16.7
Women [n (%)]	36 (72)	43 (81)	38 (73)
Plasma vitamin B-12 (pmol/L)	279 (249, 312)[3]	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, 270)	244 (217, 275)	211 (182, 244)
MTHFR 677C→T (n)			
C/C	24	30	27
C/T	22	18	22
T/T	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[1]

Treatment	Baseline[2]	Week 8	Week 16	Week 24	Percentage difference from baseline at week 24[3]
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)[4]
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)[4,5]
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, 25.2)	23.0 (19.8, 26.7)	25.6 (22.6, 28.9)	34 (14, 56)[4]
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)[4]
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)	1003 (926, 1087)	984 (910, 1064)	23 (12, 35)[4]
Folic acid (n = 52)	915 (838, 999)	999 (924, 1079)	1057 (959, 1164)	1137 (1053, 1227)	31 (19, 44)[4]

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[2]	Week 24
Plasma tHcy (μmol/L)	カットアップ値: 14μmol/L	
Placebo (n = 50)	8.5 (8.0, 9.1)	8.5 (7.9, 9.1)
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)	848 (752, 956)
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241μg/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241μg/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，200μg/日とした.

母乳中の葉酸含量

発表年	第一著者名	被験者の人種	試料数	成熟乳の葉酸含量 （葉酸塩酸塩としてmg / L）
1996	井戸田正	日本人	2727	54μg/L
2005	Sakurai T	日本人	114	62± 29μg/L[14]
2008	柴田克己	日本人	282	46±22μg/L

井戸田正，菅原牧裕，矢賀部隆史，佐藤則文，前田忠夫（1996)最近の日本人人乳組成に関する全国調査（第十報），水溶性ビタミン含量について．*日本小児栄養消化器病学会雑誌*10:11-20
Sakurai T, Furukawa M, Asoh M, Kanno T, Tadsashi Kojima T, Yonekubo A (2005) Fat-soluble and Water-Soluble Vitamin Contents of Breast Milk from Japanese Women. *J Nutr Sci Vitaminol* 51:239-247
柴田克己，遠藤美佳，廣瀬潤子，他．日本人の母乳中（1～5か月）の水溶性ビタミン含量の分布（資料）日本栄養食糧学会誌　印刷中.

6～１１月の目安量

表．　年齢区分体位基準値

年齢	身長(cm)	身長(cm)	体重(kg)	体重(kg)
	男	女	男	女
0～5(月)	62.2	61.0	6.6	6.1
6～11(月)	71.5	69.9	8.9	8.2
1～2	85.0	84.0	11.7	11.0
3～5	103.4	103.2	16.2	16.2
6～7	120.0	119.6	22.0	22.0
8～9	130.0	130.2	27.5	27.2
10～11	142.9	141.4	35.5	34.5
12～14	159.6	155.0	48.0	48.0
15～17	170.0	157.0	58.4	50.6
18～29	171.4	158.0	63.0	50.6
30～49	170.5	158.0	68.5	53.0
50～69	165.7	153.0	65.0	53.6
70以上	161.0	147.5	59.7	49.0

葉酸	男	女
母乳中の濃度	54.00	54.00
0～5月の目安量	42.12	42.12
成人の推奨量(/1000kcal)		
成人の推奨量(/日)	200.00	200.00
乳児からの外挿値		
成人からの外挿値	52.26	52.58
平均	99.11	99.61
6～11月の目安量	78.89	

1. 男について，乳児からの外挿値と成人からの外挿値を求め，平均値を算出した
2. 女について，乳児からの外挿値と成人からの外挿値を求め，平均値を算出した
3. 1と2の値の平均値を6～11月の目安量とした

妊婦の付加量

・ 要因加算法から算定するデータはない.

代謝特性に基づいて算定.
葉酸要求量は胎児要求量に応じて増大する

通常の適正な食事摂取時に100μg/日のプテロイルモノグルタミン酸を補足 すると妊婦の赤血球の葉酸レベルを適正量に維持することができたというデータがあるのでこの値を採用した. この値を食事性葉酸の値に換算すると200μg/日 (100÷0.5)となる. 相対生体利用率を50%とした. この値を妊娠時の付加量(EAR)とした。

RDA=EAR×1.2

授乳婦の付加量

(哺乳量×葉酸濃度) ÷相対生体利用率から算定

哺乳量=0.78L
葉酸濃度=54μg/L
相対生体利用率=50%

(0.78×54) ÷0.5= 84μg

EARは平滑化して80μg

RDA=EAR×1.2

耐容上限量

妊娠可能な女性において，神経管閉鎖障害の発症および再発を予防するために，受胎前後の３ヶ月以上の間，0.36～5mg/日のプテロイルモノグルタミン酸が投与されているが,副作用の報告はない．そこで，これらの報告から，NOAELを5 mg/日とし，文献値の体重の値から，80μg/kg体重/日とし，UFを3として，

ULを27μg/kg体重/日とした.