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ORIGINAL RESEARCH COMMUNICATION

Folate and vitamin B-12 status in relation to anemia, macrocytosis, and cognitive impairment in older Americans in the age of folic acid fortification[1,2,3,4]

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Background: Historic reports on the treatment of pernicious anemia with folic acid suggest that high-level folic acid fortification delays the diagnosis of or exacerbates the effects of vitamin B-12 deficiency, which affects many seniors. This idea is controversial, however, because observational data are few and inconclusive. Furthermore, experimental investigation is unethical.

Objective: We examined the relations between serum folate and vitamin B-12 status relative to anemia, macrocytosis, and cognitive impairment (ie, Digit Symbol-Coding score <34) in senior participants in the 1999–2002 US National Health and Nutrition Examination Survey.

Design: The subjects had normal serum creatinine concentrations and reported no history of stroke, alcoholism, recent anemia therapy, or diseases of the liver, thyroid, or coronary arteries (n = 1459). We defined low vitamin B-12 status as a serum vitamin B-12 concentration <148 pmol/L or a serum methylmalonic acid concentration >210 nmol/L—the maximum of the reference range for serum vitamin B-12–replete participants with normal creatinine.

Results: After control for demographic characteristics, cancer, smoking, alcohol intake, serum ferritin, and serum creatinine, low versus normal vitamin B-12 status was associated with anemia [odds ratio (OR): 2.7; 95% CI: 1.7, 4.2], macrocytosis (OR: 1.8; 95% CI: 1.01, 3.3), and cognitive impairment (OR: 2.5; 95% CI: 1.6, 3.8). In the group with a low vitamin B-12 status, serum folate >59 nmol/L (80th percentile), as opposed to ≤59 nmol/L, was associated with anemia (OR: 3.1; 95% CI: 1.5, 6.6) and cognitive impairment (OR: 2.6; 95% CI: 1.1, 6.1). In the normal vitamin B-12 group, ORs relating high versus normal serum folate to these outcomes were <1.0 ($P_{interaction}$ < 0.05), but significantly <1.0 only for cognitive impairment (0.4; 95% CI: 0.2, 0.9).

Conclusion: In seniors with low vitamin B-12 status, high serum folate was associated with anemia and cognitive impairment. When vitamin B-12 status was normal, however, high serum folate was associated with protection against cognitive impairment.

Key Words: Aging • anemia • cognition disorders • folate • fortified food • nutrition surveys • vitamin B-12 deficiency

AJCN 2007 85: 3-5. [Full Text]

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[Abstract] [Full Text] [PDF]

Canadian Family Physician HOME

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Family Practice HOME

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Neurology HOME

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[Abstract] [Full Text] [PDF]

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[Abstract] [Full Text] [PDF]

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H. Refsum and A D. Smith
Are we ready for mandatory fortification with vitamin B-12?
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R. M Winkels, I. A Brouwer, R. Clarke, M. B Katan, and P. Verhoef
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Am. J. Clinical Nutrition, August 1, 2008; 88(2): 348 - 355.
[Abstract] [Full Text] [PDF]

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L. Hao, Q.-H. Yang, Z. Li, L. B Bailey, J.-H. Zhu, D. J Hu, B.-L. Zhang, J D. Erickson, L. Zhang, J. Gindler, *et al.*
Folate status and homocysteine response to folic acid doses and withdrawal among young Chinese women in a large-scale randomized double-blind trial
Am. J. Clinical Nutrition, August 1, 2008; 88(2): 448 - 457.
[Abstract] [Full Text] [PDF]

Journal of Nutrition HOME

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Plasma Homocysteine, but Not Folate or Vitamin B-12, Predicts Mortality in Older People in the United Kingdom
J. Nutr., June 1, 2008; 138(6): 1121 - 1128.
[Abstract] [Full Text] [PDF]

Clinical Chemistry HOME

P. M. Ueland and S. Hustad
Homocysteine and Folate Status in an Era of Folic Acid Fortification: Balancing Benefits, Risks, and B-vitamins
Clin. Chem., May 1, 2008; 54(5): 779 - 781.
[Full Text] [PDF]

The American Journal of CLINICAL NUTRITION HOME

A D. Smith, Y.-I. Kim, and H. Refsum
Is folic acid good for everyone?
Am. J. Clinical Nutrition, March 1, 2008; 87(3): 517 - 533.
[Abstract] [Full Text] [PDF]

Journal of Nutrition HOME

A. H. Lichtenstein, H. Rasmussen, W. W. Yu, S. R. Epstein, and R. M. Russell
Modified MyPyramid for Older Adults
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[Abstract] [Full Text] [PDF]

Proceedings of the National Academy of Sciences HOME

J. Selhub, M. S. Morris, and P. F. Jacques
In vitamin B12 deficiency, higher serum folate is associated with increased total homocysteine and methylmalonic acid concentrations
PNAS, December 11, 2007; 104(50): 19995 - 20000.
[Abstract] [Full Text] [PDF]

The American Journal of CLINICAL NUTRITION HOME

R. Clarke, J. Birks, E. Nexo, P. M Ueland, J. Schneede, J. Scott, A. Molloy, and J. G. Evans
Low vitamin B-12 status and risk of cognitive decline in older adults
Am. J. Clinical Nutrition, November 1, 2007; 86(5): 1384 - 1391.
[Abstract] [Full Text] [PDF]

The American Journal of CLINICAL NUTRITION HOME

L. Hoey, H. McNulty, N. Askin, A. Dunne, M. Ward, K. Pentieva, J. Strain, A. M Molloy, C. A Flynn, and J. M Scott
Effect of a voluntary food fortification policy on folate, related B vitamin status, and homocysteine in healthy adults
Am. J. Clinical Nutrition, November 1, 2007; 86(5): 1405 - 1413.
[Abstract] [Full Text] [PDF]

The American Journal of CLINICAL NUTRITION HOME

I. Brouwer and P. Verhoef
Folic acid fortification: is masking of vitamin B-12 deficiency what we should really worry about?
Am. J. Clinical Nutrition, October 1, 2007; 86(4): 897 - 898.
[Full Text] [PDF]

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L. B Bailey
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[Full Text] [PDF]

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C. M Pfeiffer, C. L Johnson, R. B Jain, E. A Yetley, M. F. Picciano, J. I Rader, K. D Fisher, J. Mulinare, and J. D Osterloh
Trends in blood folate and vitamin B-12 concentrations in the United States, 1988 2004
Am. J. Clinical Nutrition, September 1, 2007; 86(3): 718 - 727.
[Abstract] [Full Text] [PDF]

BMJ HOME

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BMJ, July 28, 2007; 335(7612): 171 - 171.
[Full Text] [PDF]

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Reduction in Neural-Tube Defects after Folic Acid Fortification in Canada
N. Engl. J. Med., July 12, 2007; 357(2): 135 - 142.
[Abstract] [Full Text] [PDF]

Proceedings of the National Academy of Sciences HOME

W. He, H. Wang, L. C. Hartmann, J.-X. Cheng, and P. S. Low
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PNAS, July 10, 2007; 104(28): 11760 - 11765.
[Abstract] [Full Text] [PDF]

The American Journal of CLINICAL NUTRITION HOME

R. J Berry, H. K Carter, and Q. Yang
Cognitive impairment in older Americans in the age of folic acid fortification
Am. J. Clinical Nutrition, July 1, 2007; 86(1): 265 - 267.
[Full Text] [PDF]

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M. S. Morris, P. F Jacques, I. H Rosenberg, and J. Selhub
Reply to RJ Berry et al
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[Full Text] [PDF]

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A D. Smith
Reply to RJ Berry et al
Am. J. Clinical Nutrition, July 1, 2007; 86(1): 268 - 269.
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