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Abstract

Objective: To examine the prevalence of low serum folate and vitamin B12, in association with elevated serum homocysteine, in a representative sample of older Australians. Methods: During 1997-2000, 3,508 persons aged 50+ years were examined in a population-based cohort study conducted in two postcodes, west of Sydney, Australia. Of these, 2,901 participants (82.7%) provided fasting blood for estimates of serum folate, vitamin B12 and total homocysteine. Results: Low serum B12 (<185 pmol/L) was found in 22.9% of participants and low serum folate (<6.8 nmol/L) in 2.3% of participants. Among those people with very low serum vitamin B12 (<125 pmol/L) and low serum folate, 51% had elevated homocysteine. Conclusions: Low serum levels of vitamin B12 and elevated serum homocysteine are relatively frequent in older Australians. Implications: Appropriate public health action should be considered to reduce the prevalence of low serum vitamin B12 and elevated homocysteine in older Australians.

Keywords

folate, vitamin, b12, older, prevalence, australian, low, population, serum

Disciplines

Arts and Humanities | Life Sciences | Medicine and Health Sciences | Social and Behavioral Sciences

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Implications: Appropriate public health action should be considered to reduce the prevalence of low serum vitamin B12 and elevated homocysteine in older Australians.

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The prevalence of low blood levels of folate and vitamin B12 increases as people age.¹ Low serum levels of folate and vitamin B12 may lead potentially to several poor health outcomes. Low folate can cause gastrointestinal tract disturbances and eventual megaloblastic anaemia. Low vitamin B12 is of particular concern in the elderly, because it can cause megaloblastic anaemia and result in progressive neuropathy.² One of the most important effects of low blood folate and vitamin B12, however, is that this leads to elevated serum homocysteine, which may possibly carry a higher cardiovascular disease risk.³ Elevated

serum homocysteine has also been linked to other conditions affecting the elderly including cognitive dysfunction⁴ and vascular eye disease.⁵ Studies also indicate that elevated serum homocysteine in older people occurs at relatively higher serum vitamin B12 levels than in younger subjects,^{1,6} suggesting that the cut-points used to identify a 'low level' or deficiency state in older people may need to be higher than cut-points used for younger ages.

In recent years, folate fortification of commonly consumed foods has been introduced in several countries in order to increase folate intakes in women of

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child-bearing age, since numerous studies have shown that higher folate intake can prevent neonatal neural tube defects.⁷ However, to determine the public health impact of folate fortification on middle aged and older people, reliable prevalence estimates for both vitamin B12 and folate deficiency are required.⁸ Recent studies have been reported from United Kingdom, the Netherlands, United States of America and New Zealand,^{1,6,9,10} with prevalence estimates for vitamin B12 deficiency ranging from 10-40%, depending on the method and cut-points used to determine deficiency. No population-based studies of blood levels for folate, vitamin B12 and homocysteine have been conducted in Australia.

We report data from a representative population of older Australians to examine the prevalence of low serum folate and vitamin B12 and their effects on serum homocysteine.

Methods

Study population

A population cohort of 3,654 residents aged 49 years or older, living in two postcode areas of the Blue Mountains region, west of Sydney, was surveyed during 1992-94 for the Blue Mountains Eye Study (BMES1). The current study included 2,332 survivors from the cohort seen in BMES1 (response 75%, after excluding deaths) and a further 1,174 age-eligible residents not examined in BMES1 who had moved to the area over the five-year period since BMES1. These subjects had an age range of 50-98 years and were examined during the period 1997-2000, with an overall response of 83%. Of 3,508 total participants in the second cross-section, 2,963 provided blood for analysis (84.5%). This population had similar characteristics to older Australians in general,¹¹ with the exceptions that participants in BMES were slightly older, were more likely to have been born in the United Kingdom or Ireland and had a slightly higher socio-economic status (home ownership and higher educational level) than the Australian population of similar age range.¹²

Blood assays

Participants returned for fasting blood tests following their eye examinations, with biochemical estimations conducted at the Institute of Clinical Pathology and Medical Research (ICPMR) at Westmead Hospital. Serum vitamin B12, folate and red cell folate assays were performed using the competitive-binding assay method, conducted on a Beckman-Access analyzer. Total serum homocysteine assays were derived using a fluorescence polarisation immunoassay method on an IMx Analyzer. Serum folate, vitamin B12 and serum homocysteine were performed in assays for 2,901 subjects, while red cell folate assays were performed on a subsample of available fresh red cells (n=1,460). More details about the laboratory methods used are available on request.

Because functional folate and vitamin B12 deficiency are not well defined, and the vitamin B12 cut-off for the diagnosis of deficiency in older people may need to be increased,¹ we applied a number of cut-points for serum vitamin B12: <125 pmol/L (ICPMR laboratory guide), 125-<185 pmol/L,¹³ 185-<220 pmol/L¹⁴ and \geq 220 pmol/L. Serum folate cut-points were: <6.8 nmol/L (ICPMR lab guide), 6.8-<11 nmol/L,^{13,15} and \geq 11 nmol/L. Cut-points for red cell folate were: <370 nmol/L (ICPMR lab guide), 370-<513 nmol/L.¹⁶ Red cell folate was included because it may be a better measure of long-term folate intake than serum folate.¹⁵

Statistical analyses

The proportion of persons with serum folate, serum vitamin B12 and red cell folate at various cut-points were estimated and those with elevated serum homocysteine (>15 μ mol/L) are indicated by each category. Significant differences between genders were calculated using z-ratios. Figures present the proportion of people considered as likely to be deficient or at risk of deficiency in folate (red cell folate) or vitamin B12, by gender and age categories (*p* for trend calculated using the Mantel-Haenszel chi-square statistic). The maximum number for each table and figure

Table 1: Prevalence of various cut-points for low serum vitamin B12, serum folate and red cell folate, and proportion who had elevated serum homocysteine (>15 μ mol/L) in 2,901 older Australians.

Variable	n (%)			Homocysteine >15 μ mol/L (n, % of those in blood category)		
	Total	Women	Men	Total	Women	Men
Serum vitamin B12 (pmol/L)						
1. 'very low' <125	184 (6.3)	101 (6.1)	83 (6.7)	95 (51.6)	44 (43.6)	51 ^b (61.4)
2. 'low' 125-<185	481 (16.6)	263 (15.9)	218 (17.5)	124 (25.8)	59 (22.4)	65 ^a (29.8)
3. 'moderately low' 185-<220	359 (12.4)	178 (10.8)	181 ^b (14.5)	69 (19.2)	26 (14.6)	43 ^a (23.8)
4. 'normal' \geq 220	1,877 (64.7)	1,113 (67.2)	764 ^b (61.3)	198 (10.5)	97 (8.7)	101 ^b (13.2)
Serum folate (nmol/L)						
1. 'very low' <6.8	66 (2.3)	32 (1.9)	34 (2.7)	34 (51.5)	13 (40.6)	21 ^a (61.8)
2. 'moderately low' 6.8-<11	471 (16.2)	255 (15.4)	216 (17.3)	176 (37.4)	92 (36.1)	84 (38.9)
3. 'normal' \geq 11	2,364 (81.5)	1,367 (82.6)	997 (80) ^a	276 (11.7)	121 (8.9)	155 ^b (15.5)
Red cell folate (nmol/L)						
1. 'very low' <370	20 (1.4)	12 (1.5)	8 (1.3)	13 (65)	6 (50)	7 (87.5)
2. 'moderately low' 370-<513	82 (5.8)	51 (6.5)	31 (4.5)	37 (45)	22 (43.1)	15 (48.4)
3. 'normal' \geq 513	1,313 (92.8)	718 (91.9)	595 (93.8)	163 (12.4)	68 (9.5)	95 (16) ^b

Notes:

(a) *p* for significant difference by gender <0.05 (calculated using the z-ratio for significance of difference between independent proportion).

(b) *p* for significant difference by gender <0.01.

is presented, so that subject number may vary between tables. All analyses used SAS version 8.0 (SAS Institute, Inc. Cary, NC). *P*-values <0.05 were considered statistically significant.

Results

Table 1 shows the prevalence of low B12 and folate using various cut-points. Very low levels of serum vitamin B12, indicating deficiency (<125 pmol/L) were observed in 6.3% of BMES participants (6.1% of women and 6.7% of men). Low serum vitamin B12 (<185 pmol/L) was present in 22.9% of persons (22.0% of women and 24.2% of men), and 35.3% when moderately low serum B12 level was defined as <220 pmol/L. Very low serum folate (<6.8 nmol/L) was present in only 2.3% of persons in this age range (2.0% of women and 2.7% of men), but 18.5% were low using the higher cut-point of <11.0 nmol/L. Based on red cell folate assays, 1.4% of persons (1.5% of women and 1.3% of men) had very low levels of folate, indicating a high likelihood of folate deficiency (<370 nmol/L) and 7.2% had moderately low folate levels (<513 nmol/L). In persons with very low serum vitamin B12 and very low serum folate, about 51% had elevated homocysteine levels. In persons with very low and moderately low red cell folate, approximately 65% and 45%, respectively, had elevated homocysteine levels. Men were more likely to have elevated serum homocysteine levels with very low concentrations of serum vitamin B12 and serum folate ($p=0.008$, $p=0.04$, respectively). Overall, elevated serum homocysteine (>15 $\mu\text{mol/L}$) was found in 16.7% of participants (20.8% men and 13.7% of women, $p<0.0001$) in this population.

The proportion of people with low serum vitamin B12 increased with age as shown in Figure 1 and this trend was more marked in men (p for trend in men ≤ 0.0001). Among persons aged 80 years or older, 9.5% of women and 13.6% of men had very low serum

B12, indicating a high likelihood of vitamin B12 deficiency. Approximately 30% of men aged 70 years and over and women aged 80 years and over had low serum B12 values, and were thus at risk of vitamin B12 deficiency.

The prevalence of very low red cell folate increased with age for both women and men, and the trend was particularly marked for men (p for trend in men = 0.001), with the prevalence increasing to 9.4% in men aged 80 years or older. Using a higher cut-point (<513 nmol/L), relatively similar proportions of older men and women were at risk of folate deficiency, rising with age to around 16% among persons aged 80 years or older.

Discussion

This study provides evidence that a relatively high proportion of older Australians have low vitamin B12 levels (22.9%). Although low blood folate levels were uncommon, the proportion with low levels of folate increased with age, up to 10% among males 80 years and over. In addition, about half of those with very low serum vitamin B12, very low serum folate and moderately low red cell folate demonstrated a likelihood of having a functional deficiency, as they had elevated serum homocysteine. Increased evidence suggests that the measurement of serum methylmalonic acid (MMA) and/or serum total homocysteine should be included in the tools to diagnose vitamin B12 or folate deficiency,^{1,17,18} especially in cases of borderline concentrations. MMA is a more expensive measure and therefore less practical to include in regular clinical assessments. Overall, we found an elevated serum homocysteine in a relatively high proportion (16.7%) of the study population. This is an important finding, not only in terms of the associated increased risk with vitamin B12 and folate deficiency, but because it is a possible independent risk factor for vascular disease.³

Figure 1: Prevalence of low serum vitamin B12, by age categories, in 1,690 women and 1,273 men. Vitamin B12 deficiency is likely for serum B12 <125 pmol/L; persons are considered at risk of vitamin B12 deficiency for serum B12 <185 pmol/L.

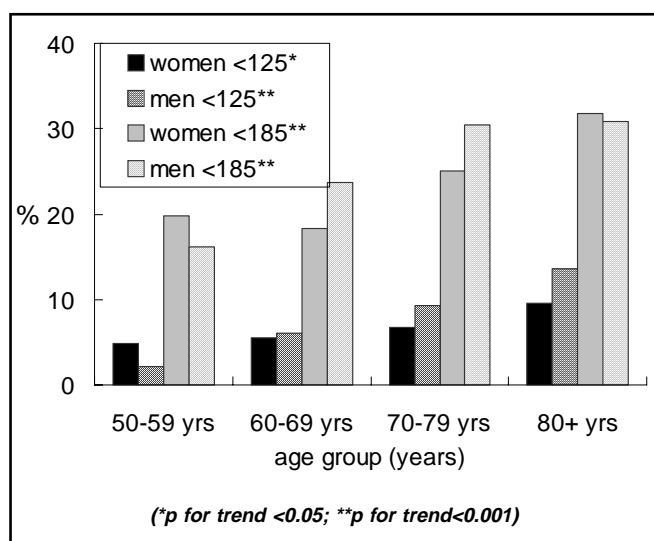
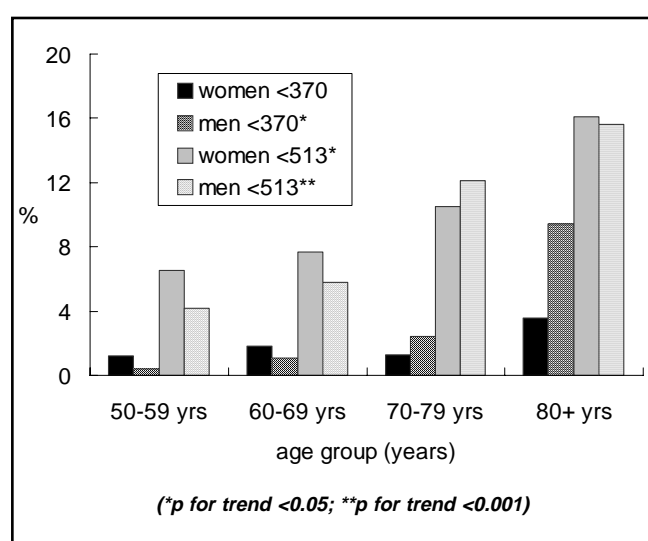


Figure 2: Prevalence of low red cell folate, by age categories, in 805 women and 655 men. Folate deficiency is likely for red cell folate <370 nmol/L; persons are considered at risk of folate deficiency for red cell folate <513 nmol/L.



In Australia, folate fortification of food is voluntary, and breakfast cereals are the main products fortified. In previous research,⁸ we examined the potential impact on folate intake in older people if folate fortification became mandatory in Australia. Under this scenario, our results showed that only 0.5% of the study population would be likely to consume levels greater than 1000 µg per day from synthetic folic acid, the intake considered by the Institute of Medicine (IOM) as the tolerable upper intake level.¹⁹ Concern has been expressed in the literature that mandatory folate fortification may adversely affect people with B12 deficiency by masking the deficiency,²⁰ although this risk is considered very low if clinicians routinely diagnose B12 deficiency with appropriate tests, including serum B12 levels and homocysteine.¹ Evidence concerning relevant clinical practice could not be located in the literature, but the results of a recent United States (US) study of the prevalence of megaloblastic anaemia before and after mandatory folate fortification are reassuring. Although folate fortification may be expected to reduce the prevalence of anaemia in people with vitamin B12 deficiency, Mills and others (2003)²¹ observed no significant change in anaemia prevalence among groups of older people with low serum B12 prior to and after mandatory folate fortification was introduced. Because our study suggests that a large proportion of older Australians could be at risk of B12 deficiency, this should be considered in current revisions to food regulations relating to food fortification. Some researchers have suggested that vitamin B12 should be added to any folate-fortified foods.^{22,23} Because our earlier research showed that most older people who would be likely to consume high levels of folate are those who take supplements containing folic acid,⁸ it is recommended that vitamin B12 be included in any vitamin supplements containing folate.

Consideration should also be given to identifying those older people at risk of low serum vitamin B12 and elevated homocysteine, among whom early intervention with the use of appropriate supplements may be valuable. In a recent small intervention trial, Bjorkegren (2004)¹⁸ observed an improvement in not only haematological parameters but also neurological symptoms (indicative of B12 deficiency) and oral mucosal symptoms (indicative of folate deficiency), among older people receiving folate and B12 supplements who had been identified with low serum B12 and elevated homocysteine or MMA. Other studies have shown no or little improvement in clinical symptoms or health-related quality of life with lowering MMA or homocysteine.^{24,25} These studies, however, were conducted on younger adults.

This paper provides the first population-based data about the status of folate, vitamin B12 and homocysteine levels among older people in Australia. Of particular concern is the substantial pool of older people at risk of vitamin B12 deficiency and the prevalence of elevated serum homocysteine levels, for which evidence indicates is an independent risk factor for vascular disease.³ An understanding of the modifiable determinants of serum homocysteine and serum vitamin B12 will be important in determining future public health recommendations.

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