The Association of Dietary Folate, B_6, and B_{12} With Cardiovascular Mortality in Spain: An Ecological Analysis

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A B S T R A C T

Objectives. This study assessed the association of dietary folate, vitamin B_6, and vitamin B_{12} with cardiovascular mortality.

Methods. Poisson regression analyses assessed coronary/cerebrovascular mortality rates via nutrient data obtained from the National Nutrition Survey, which recorded 7-day food intakes from a national sample of 21 155 households.

Results. In regard to coronary mortality, male and female rate ratios (highest vs lowest quintile) were 0.83 (95% confidence interval [CI]=0.77, 0.91) and 0.95 (95% CI=0.86, 1.05), respectively, for folate and 0.74 (95% CI=0.65, 0.84) and 0.86 (95% CI=0.73, 0.99), respectively, for B_{12}. Intake of folate and B_6 (but not B_{12}) was significantly associated with cerebrovascular mortality.

Conclusions. B vitamins are associated with cardiovascular mortality in the general population. (*Am J Public Health.* 2000;90:1636–1638)

In Spain, coronary artery disease and stroke are the leading causes of death.[1] Marked geographical variations in mortality from these diseases have been described,[2,3] with the reasons for such differences as yet being unexplained.

Hyperhomocysteinemia is currently regarded as a possible cause of arteriosclerotic disease.[4] Hyperhomocysteinemia can result from deficiencies in folate, pyridoxine, and cyanocobalamin, and several recent studies have shown associations between dietary intake of these vitamins and vascular risk.[5–8] To our knowledge, however, no studies have focused on the extent to which these associations are reflected at a population level.

Geographical variations in dietary patterns in Spain are well documented.[9] The wide geographical differences in climate, cultural habits, economic activities, traditional cuisine, and food availability strongly condition provincial diets. We studied the effect of homocysteine metabolism–related nutritional factors on geographical patterns of cardiovascular mortality.

Methods

Baseline diet was assessed for each province in 1990. For the period 1990 to 1994, all coronary and cerebrovascular deaths were recorded, and age-specific mortality rates for each province were computed for the Spanish population aged 35 to 84 years. The association between provincial diet at baseline and provincial cardiovascular mortality was analyzed.

Province-level average dietary intakes of folate, vitamin B_6, and vitamin B_{12} were obtained from the National Nutrition Survey,[9] which recorded all food available in a household during the space of 1 week among a province-representative sample of 26 821 Spanish homes. The survey was conducted over 52 weeks to avoid seasonality. The response rate was 78.9% (21 155 units). Food quantities were recorded in units of weight or volume, and nutrient values were computed via Spanish food composition tables.[10]

All deaths due to coronary heart and cerebrovascular diseases (*International Classification of Diseases, Ninth Revision* codes 410–414 and 430–438) during 1990 to 1994 were computed from official death records.

Log-linear Poisson models were fitted with specific functions for computation of robust standard errors computation to allow for multivariate adjustments.[11] These models included the following control variables: prevalence of hypertension, diabetes, hypercholesterolemia, obesity, low physical activity, and use of vitamin supplements; tobacco (packs per year per inhabitant above the age of 16 years) and wine (grams per year per inhabitant above the age of 16 years) consumption; available family income per inhabitant; hospital beds per population; and dietary intake of othxxsxwer nutrients associated with cardiovascular risk (e.g., fats, proteins, vitamins E and C, and carotene).

The residual method was used in making energy adjustments.[12] The 3 B vitamins were modeled simultaneously to allow for individual estimations of vitamin effects.

Results

Mean (±SD) dietary intakes of folate, vitamin B_{12}, and vitamin B_6 were 203±17 μg, 8.86±1.77 μg, and 1.80±0.21 mg per person, respectively. Provincial values varied widely, ranging from 172 to 249 μg for folate, 4.33 to 12.30 μg for B_{12}, and 1.25 to 2.27 mg for B_6, partially as a result of variations in total amount of food consumed. When differences in amount of food consumed were taken into account, rates of provincial variation were 42% for folate and 109% for B_{12} but only 29% for B_6.

In univariate analyses, a significant inverse association was found between age-adjusted coronary mortality and both folate and B_{12}, and there was an evident dose–response effect as mortality rates decreased linearly with increases in intake of these vitamins (see Figure 1). Cerebrovascular mortality was associated only with intake of B_{12}. No significant association was found between mortality and B_6 intake.

Multivariate modeling results showed that adjustments for total energy, age, income, and

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TABLE 1—Adjusted Effects of Dietary Folate, B_{12}, and B_6 (Quintiles) on Cardiovascular Mortality: Spain, 1990–1994

		Ischemic Heart Disease				Cerebrovascular Disease			
		Men		Women		Men		Women	
	No. of Provinces (Population Aged 35–84 y)	Age-Adjusted Mortality Rate,[a] Mean ± SD	Multivariate-Adjusted RR[b] (95% CI)	Age-Adjusted Mortality Rate,[a] Mean ± SD	Multivariate-Adjusted RR[b] (95% CI)	Age-Adjusted Mortality Rate,[a] Mean ± SD	Multivariate-Adjusted RR[b] (95% CI)	Age-Adjusted Mortality Rate,[a] Mean ± SD	Multivariate-Adjusted RR[b] (95% CI)
Folate, μg									
<187.2	11 (2 026 341)	121.9 ± 24	1.00	55.8 ± 14	1.00	99.7 ± 22	1.00	86.4 ± 18	1.00
187.2–199.7	9 (1 342 817)	106.2 ± 19	0.93 (0.87, 1.00)	49.6 ± 12	0.91 (0.83, 0.99)	96.4 ± 17	0.87 (0.81, 0.94)	83.4 ± 19	0.85 (0.78, 0.94)
199.8–209.5	10 (2 183 149)	88.1 ± 17	0.83 (0.77, 0.89)	39.7 ± 11	0.84 (0.78, 0.91)	74.8 ± 20	0.85 (0.78, 0.92)	63.3 ± 19	0.89 (0.80, 0.98)
209.6–221.2	10 (2 121 680)	88.8 ± 14	0.82 (0.76, 0.88)	41.0 ± 6	0.88 (0.81, 0.95)	85.3 ± 14	0.75 (0.70, 0.80)	74.2 ± 15	0.76 (0.67, 0.87)
>221.3	10 (1 013 530)	90.1 ± 14	0.83 (0.77, 0.91)	42.3 ± 9	0.95 (0.86, 1.05)	83.6 ± 15	0.84 (0.76, 0.93)	76.4 ± 15	0.84 (0.71, 0.99)
B_{12}, μg									
<7.35	10 (1 759 474)	120.1 ± 23	1.00	56.4 ± 14	1.00	91.3 ± 16	1.00	79.8 ± 14	1.00
7.35–8.49	10 (3 706 580)	112.7 ± 20	0.96 (0.89, 1.04)	54.2 ± 10	1.04 (0.96, 1.12)	105.8 ± 22	1.11 (1.03, 1.21)	92.3 ± 19	1.14 (1.03, 1.26)
8.50–9.39	11 (1 283 351)	94.7 ± 14	0.89 (0.81, 0.97)	44.0 ± 7	0.98 (0.87, 1.09)	86.3 ± 18	1.04 (0.94, 1.14)	77.7 ± 19	1.03 (0.90, 1.18)
9.40–10.81	10 (1 285 691)	87.4 ± 13	0.84 (0.75, 0.94)	38.5 ± 6	0.97 (0.88, 1.08)	81.6 ± 13	1.08 (0.96, 1.20)	68.9 ± 15	1.04 (0.90, 1.20)
>10.81	9 (652 421)	80.4 ± 11	0.74 (0.65, 0.84)	35.1 ± 3	0.86 (0.73, 0.99)	73.9 ± 15	1.02 (0.88, 1.17)	63.8 ± 15	0.92 (0.76, 1.11)
B_6, mg									
<1.49	10 (2 845 211)	107.0 ± 25	1.00	48.9 ± 13	1.00	98.9 ± 25	1.00	81.3 ± 22	1.00
1.49–1.55	9 (1 085 431)	89.4 ± 19	0.90 (0.82, 0.99)	39.6 ± 7	0.91 (0.81, 1.02)	77.3 ± 14	0.86 (0.78, 0.96)	63.4 ± 16	0.93 (0.82, 1.05)
1.56–1.67	11 (2 146 525)	105.0 ± 29	0.90 (0.84, 0.97)	48.2 ± 16	0.98 (0.88, 1.09)	85.4 ± 21	0.85 (0.79, 0.92)	74.1 ± 20	0.88 (0.80, 0.97)
1.68–1.82	10 (1 215 172)	99.4 ± 19	0.92 (0.85, 0.99)	49.4 ± 12	0.92 (0.81, 1.03)	93.8 ± 19	0.88 (0.82, 0.96)	86.9 ± 17	0.97 (0.87, 1.09)
>1.82	10 (1 395 178)	94.5 ± 14	0.93 (0.87, 1.01)	42.1 ± 8	0.95 (0.87, 1.04)	83.9 ± 10	0.86 (0.79, 0.93)	77.1 ± 11	0.93 (0.85, 1.03)

Note. RR = rate ratio; CI = confidence interval.

[a]Per 100 000 person-years.

[b]Adjusted for age, income, total energy, no. of hospital beds, prevalence of cardiovascular risk factors (smoking, hypertension, hypercholesterolemia, obesity, diabetes, and low physical activity), percentage of moderate wine consumers, percentage of vitamin supplement consumers, and other nutrient (total fat, saturated fat, protein, fiber, vitamin E, vitamin C, carotene) content of familiy diet.

established risk factors did not modify the crude effects of folate and B_6; however, B_{12} was no longer associated with cerebrovascular mortality (Table 1). Folate showed a protective effect on coronary and cerebrovascular mortality in men and a weaker but still significant effect in women. Protection increased proportionately with intake of folate. Similarly, B_{12} intake was significantly and inversely associated with coronary mortality. Finally, B_6 evinced a limited protective effect that reached statistical significance only with respect to cerebrovascular mortality in men.

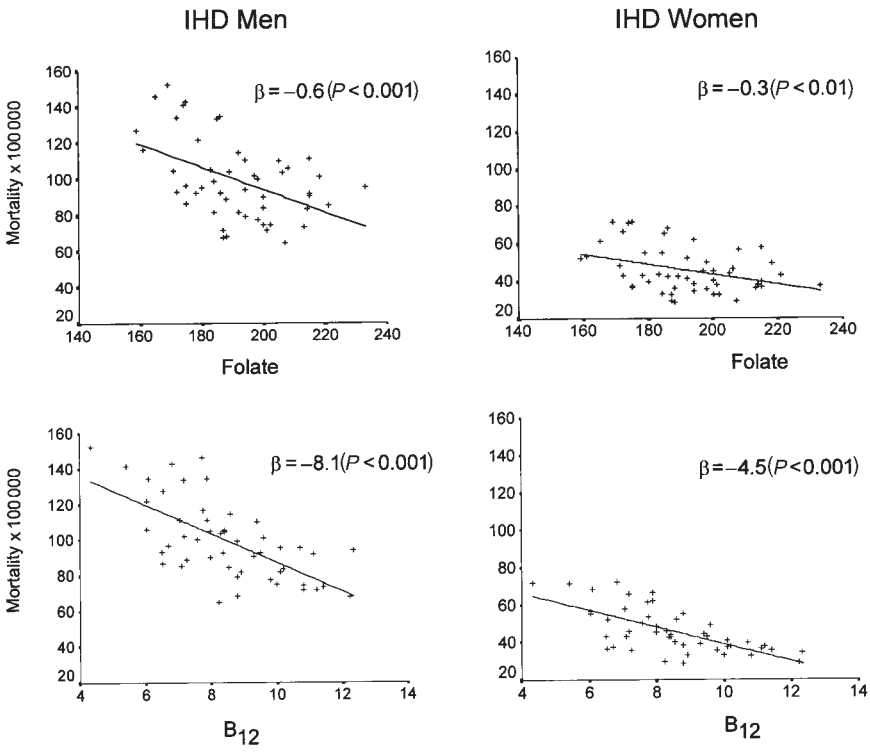
Discussion

Our results show that residents of provinces where diets are richer in folate exhibit lower cardiovascular mortality, irrespective of variations in socioeconomic levels, cardiovascular risk, and use of vitamin supplements and other dietary factors, and that this association is evident for both coronary and cerebrovascular diseases and among both men and women. These findings support the associations reported at an individual level.[5–7] Folic acid is present in leafy vegetables, the intake of which has been related to cardiovascular disease,[13] and folic acid supplements have been shown to reduce hyperhomocysteinemia.[14]

Similarly, higher intake of B_{12} was associated with a significant reduction in coronary disease mortality. In contrast, the apparent association with cerebrovascular mortality disappeared when adjustment was made for confounders. Previous studies that focused on B_{12} intake as a cardiovascular risk factor could not demonstrate significant associations with carotid stenosis,[5] myocardial infarction,[6] or ischemic heart disease.[7,8]

Our study failed to produce a definitive result in regard to the putative association of B_6 with cardiovascular mortality. Published studies have yielded contradictory results, and only the Nurses' Health Study registered a significant decrease in coronary heart disease risk in association with higher B_6 intake.[7] Studies examining B_6 plasma levels consistently produce positive results. In particular, results from the ARIC study indicate a strong relation of plasma B_6, but not dietary B_6, with vascular disease.[8] In our results, although statistical significance was not attained, all point estimates were below unity. It is therefore feasible that a protective effect, albeit not as strong as that of folate, might exist.

Consideration must be given to several limitations of our study. The primary limitation is the ecologic nature of the study, indicating that ecologic fallacy cannot be ruled out.[15,16] Statistical limitations entailed by ecologic studies[17] have been minimized by in-



Note. IHD = ischemic heart disease; CVD = cerebrovascular disease.

FIGURE 1—Crude scatterplots and regression fitting of age-adjusted ischemic heart disease mortality vs intake of folate and vitamin B_{12}: Spain, 1990–1994.

cluding homogeneous strata of sufficient sizes,[18,19] but there may be residual confounding. Therefore, no inference can be extrapolated to the individual level. However, this study is valuable in that it provides estimates of effect magnitudes at the national level, information that is not obtainable in individual-based studies.

Death certificate quality in Spain in regard to cardiovascular codes has been validated with good results, especially in the age ranges covered by this study.[20] Dietary data were drawn from a survey of foods available at the household level only; thus, real diets were underestimated. Nevertheless, although our values seem low in comparison with those of studies conducted elsewhere, data from 4 large-scale Spanish surveys conducted by means of 24-hour-recall methods were almost identical.[21] Other methods, such as food-frequency questionnaires, may overestimate vitamin consumption.

In conclusion, our results suggest that intake of dietary folate, vitamin B_6, and vitamin B_{12} is associated with cardiovascular mortality in Spain. These findings not only support the hypothesis that B vitamins/homocysteine can be linked to cardiovascular risk but highlight their public health importance. □

Contributors

M. J. Medrano designed the study, identified data sources and methodological tools, revised and selected relevant bibliographical references, and wrote drafts of the paper. M. T. Olalla and J. Almazán collected the data, prepared the files, and designed the presentation of results. M. J. Sierra and M. J. Medrano conducted the epidemiological analyses, and G. López-Abente conducted the advanced statistical work.

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