Current Research

Diets Lower in Folic Acid and Carotenoids Are Associated with the Coronary Disease Epidemic in Central and Eastern Europe

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ABSTRACT

Objective To test our hypothesis that lower intakes of previously identified cardioprotective nutrients would be associated with the coronary epidemic in Central and Eastern Europe.

Design We conducted a survey of coronary mortality in 16 countries and diet in 19 countries.

Subjects/Setting Countries were placed in four groups with different cultural patterns (Central and Eastern Europe, including Russia; Western Europe and the United States; Mediterranean; and Asian).

Main Outcome Measures Independent predictors of coronary mortality.

Statistical Analyses Performed Means and standard deviations were calculated, and analysis of variance with Bonferroni post hoc tests and backward elimination regression analysis was conducted.

Results Coronary mortality was highest in Central and Eastern Europe followed by Western Europe and the United States, the Mediterranean countries, and Asia (Japan). The model with folate, fiber, and n-6/n-3 fatty acids explained the majority of variation in coronary mortality (men 86%, women 90%). Most of the variation was explained by folate (men 61%, women 62%). The picture is complicated by the fact that folate, lutein/zeaxanthin, and beta-carotene were highly intercorrelated (r=0.87 to 0.99).

Conclusions A diet low in foods containing folate and carotenoids (beta-carotene and lutein/zeaxanthin) may be a major contributing factor to increased coronary risk observed in the countries of Central and Eastern Europe.

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Life expectancy in many newly independent states of Central and Eastern Europe has declined dramatically (1,2) and is expected to remain unchanged or decrease even further (3). The major cause of this decline is a dramatic increase in coronary heart disease (CHD) (4,5). Traditional risk factors (abnormal plasma lipid and lipoprotein levels, smoking, hypertension, obesity, and high dietary saturated fat and cholesterol intake) do not explain this escalation (2,6).

New perspectives have modified traditional thinking about diet and CHD (7-12). Cardioprotective dietary factors, such as n-3 fatty acids, folate, and antioxidants (especially lutein/zeaxanthin), appear to reduce coronary risk by improving plaque stability and preventing thrombosis (13-17). There is also some indication that cardioprotective dietary factors may play a role in the CHD epidemic in Eastern Europe (6,8,18). To test our hypothesis that lower intakes of cardioprotective nutrients previously identified in other studies would be associated with the coronary disease epidemic in Central and Eastern Europe, we compared nutrients available for consumption and coronary mortality rates in four groups of countries with differing diets and differing CHD mortality rates.

METHODS

Selection of Countries

Nineteen countries with differing dietary patterns were selected for inclusion in the study. The countries were placed into four groups based on cultural patterns: Central (Czech Republic and Hungary) and Eastern Europe (Estonia, Lithuania, Poland, Romania, and the Russian Federation); Western Europe (Finland, Sweden, and the United Kingdom) and the United States; Mediterranean countries (France, Greece, Italy, and Spain); and Asia (China, Japan, Thailand, and Vietnam).

Dietary Assessment

Average food disappearance data for 1997 were collected for all 19 countries using Food Balance Sheets of the United Nations Food and Agriculture Organization (FAO) (19). The original plan was to use data for 1977 because coronary disease has a long time course. How-

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Table 1. Coronary heart disease (CHD) mortality and pathogenic dietary factors as reported for countries of Central and Eastern Europe and the Russian Federation, Western Europe and the United States, Mediterranean countries, and Asian countries[ab]

Country	CHD Mortality (per 100,000 Age-Standardized) Men	Women	Energy (kcal)	Cholesterol (mg/1,000 kcal)	SFA[c] (% kcal)	CSI[d] (1,000 kcal)	n-6/n-3
Central and Eastern Europe and the Russian Federation							
Czech Republic	224.3	118.8	3,360	116	9.6	16.6	4.5
Estonia	361.5	191.5	2,721	132	10.0	17.8	11.3
Hungary	258.9	139.4	3,213	112	11.8	18.8	16.8
Lithuania	350.4	211.4	3,280	97	8.0	13.8	6.4
Poland	126.8	45.8	3,146	105	10.6	17.1	4.5
Romania	243.4	150.9	3,546	70	6.0	10.2	17.8
Russian Federation	371.1	189.1	2,896	113	7.6	14.2	14.7
Mean	276.6[x]	149.6[x]	3,166[xy]	106	9.1[x]	15.5[xy]	10.9[x]
SD[e]	89.6	56.2	279	19	2.0	3.0	5.8
95% CI[f]	194-360	98-202	2,908-3,425	88-124	7-11	13-18	6-16
Western Europe and the United States							
Finland	213.8	94.9	2,953	128	11.2	19.0	3.4
Sweden	159.9	72.0	3,380	124	13.4	21.2	4.3
United Kingdom	174.4	81.7	3,181	111	10.3	17.1	4.8
United States	143.5	77.9	3,941	106	9.5	16.0	7.5
Mean	172.9[y]	81.6[x]	3,364[xy]	117	11.1[x]	18.3[x]	5.0[y]
SD	30.0	9.7	423	11	1.7	2.3	1.8
95% CI	125-221	66-97	2,691-4,036	100-134	8-14	15-22	2-8
Mediterranean countries							
France	60.4	23.9	3,687	151	14.1	23.3	9.5
Greece	98.8	42.2	3,768	96	9.1	15.0	12.3
Italy	92.9	43.7	3,810	105	9.9	16.3	8.7
Spain	78.2	34.3	3,238	121	9.2	16.4	10.6
Mean	82.6[z]	36.0[yz]	3,626[x]	118	10.5[x]	17.7[x]	10.3[xy]
SD	17.1	9.1	263	24	2.4	3.8	1.6
95% CI	55-110	22-50	3,207-4,045	80-157	7-14	12-24	8-13
Asian countries							
China			2,991	91	4.7	9.9	4.2
Japan	41.7[z]	21.1[z]	2,873	151	5.5	13.7	3.9
Thailand			2,473	95	9.4	15.3	5.5
Vietnam			2,530	37	3.6	5.8	5.1
Mean			2,717[y]	94	5.8[y]	11.2[y]	4.7[y]
SD			254	47	2.5	4.3	0.8
95% CI			2,312-3,121	19-168	2-10	4-18	4-6

[a]Values with unlike superscripts are significantly different, $P<.05$.
[b]Reprinted with permission (8).
[c]SFA=saturated fatty acids.
[d]CSI=cholesterol-saturated fat index.
[e]SD=standard deviation.
[f]CI=confidence interval.

ever, data for 1977 were not available for all of the countries.

A food balance sheet presents a comprehensive picture of the pattern of a country's food supply. The quantities of food listed as available for human consumption are the quantities of food reaching the consumer. Processed commodities are converted back to their primary equivalent. The amount of food actually consumed may be lower than the quantity shown in the food balance sheet, depending on the losses of edible food and nutrients in the household. Food disappearance data are useful in generating hypotheses about dietary factors associated with disease and have been widely used in epidemiologic comparisons (20). The FAO tables were used as the basis for determining dietary intakes of fish, vegetables, fruit, cereals, roots and legumes, meat, milk, and butterfat in grams per day. To gain information on cardioprotective and cardiopathogenic nutrients, daily nutrient intakes were computed using the Nutrition Data System for Research software (version 4.01, 1998 [unfortified folate] and 4.02, 1999 [all other nutrients], Nutrition Coordinating Center, University of Minnesota, Minneapolis) (21). All nutrients were

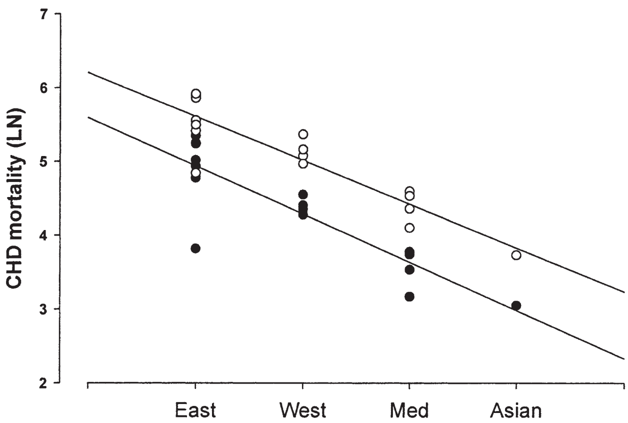

Figure 1. Coronary heart disease (CHD) mortality (log transformed [LN]) for four groups of countries: Central and Eastern Europe and the Russian Federation (East), Western Europe and the United States (West), Mediterranean countries (Med), and Asian (Japan). Open circles=men, closed circles=women. Adapted from reference (8).

expressed as a function of energy intake. Because the energy, fat, and protein intakes estimated using the Nutrition Coordinating Center database were similar to the intakes listed in the FAO tables for each country, we assumed that other nutrient intakes were reliable. The Cholesterol-Saturated Fat Index was computed for each country (22). A high Cholesterol-Saturated Fat Index indicates a high intake of saturated fat and cholesterol, the two dietary components that have the greatest elevating effect on plasma total and low-density lipoprotein cholesterol levels through their effects on low-density lipoprotein receptor activity in the liver (23). *Trans*-fatty acids were not included because the food disappearance data do not include processed foods, which are the source of the majority of dietary *trans*-fatty acids.

CHD Mortality

For mortality rates, we used World Health Organization reports. The category "ischaemic heart diseases" expressed as age-standardized death rates per 100,000 for men and for women for 1997 or the closest year for which there were data available (24). Because no mortality data were available for China, Thailand, or Vietnam, the analyses of Asian countries were limited to Japan.

Statistical Analyses

Dietary variables were screened by computing means and standard deviations. Groups of countries were compared using analysis of variance with Bonferroni post hoc tests for detection of pairwise differences (version 10.0, 2000, SPSS, Inc, Chicago, IL). Backward elimination multiple regression analysis was used to identify independent predictors of mortality (JMP, version 5.1, 2002, SAS Institute, Cary, NC). When variables were highly intercorrelated ($r \geq 0.6$), one variable was selected to be included in the regression analysis. The n-6/n-3 and n-3 were highly correlated ($r=-0.89$); the ratio was selected. The Cholesterol-Saturated Fat Index was highly correlated with cholesterol ($r=0.63$) and saturated fat ($r=0.95$); the Cholesterol-Saturated Fat Index was selected because it is a single number that takes into account both cholesterol and saturated fat. Folate, lutein/zeaxanthin, and beta-carotene were highly intercorrelated ($r=0.87$ to 0.99); separate models were run using each of these variables and folate was selected for inclusion in the final model because scientific evidence suggests a possible mechanism for folate being protective against CHD. Other variables included in the regression analyses were vitamin C, vitamin E, and n-6 fatty acids (n-6 was not highly correlated with n-6/n-3, $r=0.31$ or with n-3 fatty acids, $r=-0.45$). The residuals in the final regression model did not significantly deviate from normal.

RESULTS

CHD Mortality

As shown in Table 1 and Figure 1, coronary mortality in Central and Eastern Europe was six to seven times higher than in Japan, three to four times higher than in the Mediterranean countries, and one and one-half times higher than in Western Europe and the United States. Coronary mortality for men differed significantly between the Central and Eastern Europe, Western Europe and the United States, and Mediterranean groups. Coronary mortality was not significantly different between men of Mediterranean countries and Japan. Similar trends were noted for women with the exception that coronary mortality in the Central and Eastern Europe and Western Europe and the United States groups was not significantly different because of the very low coronary mortality in Polish women. In all geographic groups, women had approximately one half the CHD mortality of men in the same countries.

Pathogenic Dietary Factors for CHD

Energy available for consumption was lower in the Asian countries, but similar for the other three groups of countries (Table 1). The primary reason for providing the energy available for consumption was to provide clarity for the nutrient data that were expressed as a function of energy (% kcal or unit/1,000 kcal).

There were no significant differences in dietary cholesterol among the four groups of countries, with all countries having cholesterol available for consumption of approximately 100 mg/1,000 kcal (total cholesterol intake of 300 to 400 mg/day). The goal of the National Cholesterol Education Program Therapeutic Lifestyle Changes Diet is a cholesterol intake of <200 mg/day (25).

Saturated fat available for consumption was significantly higher in Central and Eastern Europe and the Russian Federation, Western Europe and the United States, and the Mediterranean countries (9% to 11% of total energy) than in the Asian countries (6% of total energy). The goal of the National Cholesterol Education Program Therapeutic Lifestyle Changes Diet is a saturated fat intake of <7% of total energy (25).

The Cholesterol-Saturated Fat Index was significantly lower in the Asian countries than in Western Europe and the United States and the Mediterranean countries (15.5 [Eastern and Central Europe], 18.3 [Western Europe and

Table 2. Coronary heart disease (CHD) mortality and protective dietary factors as reported by Central and Eastern Europe and the Russian Federation, Western Europe and the United States, Mediterranean countries, and Asian countries[ab]

Country	CHD Mortality (per 100,000 Age-Standardized) Men	Women	% Total Energy (% kcal) n-6	n-3	Lutein/ zeaxanthin (μg/1,000 kcal)	β-carotene (mg/1,000 kcal)	Vitamin E (mg/1,000 kcal)	Vitamin C (mg/1,000 kcal)	Folate (μg/1,000 kcal)	Fiber (g/1,000 kcal)
Central and Eastern Europe and the Russian Federation										
Czech Republic	224.3	118.8	5.3	1.2	5,869	3,007	5.5	43	159	11
Estonia	361.5	191.5	6.6	0.6	4,771	2,566	6.4	37	140	14
Hungary	258.9	139.4	8.9	0.5	6,838	3,605	7.3	45	161	9
Lithuania	350.4	211.4	4.7	0.7	6,675	3,219	4.3	28	157	15
Poland	126.8	45.8	5.0	1.1	10,504	5,086	5.4	49	226	11
Romania	243.4	150.9	5.1	0.3	6,630	3,413	4.9	43	167	12
Russian Federation	371.1	189.1	5.8	0.4	6,228	3,106	5.7	39	162	12
Mean	276.6[x]	149.6[x]	5.9[xy]	0.7[x]	6,788	3,429	5.6[x]	41[x]	167[x]	12
SD[c]	89.6	56.2	1.4	0.3	1,783	801	1.0	7	27	2
95% CI[d]	194-360	98-202	5-7	0.4-1	5,139-8,436	2,689-4,169	5-7	34-47	148-187	10-14
Western Europe and the United States										
Finland	213.8	94.9	4.3	1.2	6,142	3,089	4.9	45	162	10
Sweden	159.9	72.0	6.0	1.4	4,720	2,542	5.5	47	137	9
United Kingdom	174.4	81.7	6.7	1.4	6,079	3,090	6.3	47	165	10
United States	143.5	77.9	9.6	1.3	5,586	3,067	5.8	56	154	9
Mean	172.9[y]	81.6[x]	6.6[x]	1.3[y]	5,632	2,947	5.6[x]	49[x]	155[x]	10
SD	30.0	9.7	2.2	0.1	657	270	0.6	5	13	1
95% CI	125-221	66-97	3-10	1.2-1.4	4,587-6,677	2,517-3,378	5-7	41-56	129-180	8-11
Mediterranean countries										
France	60.4	23.9	9.3	1.0	8,311	4,309	8.4	56	202	9
Greece	98.8	42.2	6.6	0.5	11,417	6,060	8.3	87	259	12
Italy	92.9	43.7	6.7	0.8	9,699	4,976	7.1	107	223	12
Spain	78.2	34.3	9.8	0.9	9,673	4,931	9.2	65	219	10
Mean	82.6[z]	36.0[yz]	8.1[x]	0.8[xy]	9,750	5,069	8.2[y]	79[y]	226[y]	11
SD	17.1	9.1	1.7	0.2	1,275	727	0.9	23	24	2
95% CI	55-110	22-50	5-11	0.5-1.1	7,721-11,779	3,912-6,227	7-10	42-115	200-251	8-13
Asian countries										
China			4.6	1.1	17,523	10,790	6.1	64	343	13
Japan	41.7[z]	21.1[z]	5.8	1.5	11,156	5,973	6.2	49	244	11
Thailand			2.8	0.5	4,070	2,692	3.3	45	126	7
Vietnam			1.9	0.4	7,116	5,095	2.4	39	219	7
Mean			3.8[y]	0.9[xy]	9,966	6,138	4.5[x]	49[x]	219[xy]	10
SD			1.8	0.5	5,814	3,397	2.0	11	97	3
95% CI			1-7	0.03-1.7	716-19,218	732-11,544	1-8	32-67	124-314	5-14

[a]Values with unlike superscripts are significantly different, $P<.05$.
[b]Reprinted with permission (8).
[c]SD=standard deviation.
[d]CI=confidence interval.

United States], 17.7 [Mediterranean], and 11.2 [Asian]). The Cholesterol-Saturated Fat Index of a diet containing 300 mg cholesterol and 10% saturated fat is 19/1,000 kcal. The Cholesterol-Saturated Fat Index of a diet containing 200 mg cholesterol and <7% saturated fat is 13/1,000 kcal, the goal of the National Cholesterol Education Program Therapeutic Lifestyle Changes Diet (25).

The n-6/n-3 was significantly higher in Central and Eastern Europe than in Western Europe and the United States, and the Asian countries. The n-6/n-3 for Estonia, Hungary, Romania, and the Russian Federation was 11.3, 16.8, 17.8, and 14.7, respectively [an n-6/n-3 >10 has been associated with CHD (10,26)]. The only other countries with n-6/n-3 >10/1,000 kcal were Greece (12.3) and Spain (10.6).

Dietary Factors Protective Against CHD

n-6 fatty acids as a percent of total energy were significantly higher in Western Europe and the United States and the Mediterranean countries than in the Asian countries (Table 2). n-3 fatty acids as a percent of total energy were significantly lower in Central and Eastern Europe and the Russian Federation than in Western Europe and

Table 3. Multiple regression of coronary heart disease (CHD) mortality data from 16 countries in Central and Eastern Europe and the Russian Federation, Western Europe and the United States, Mediterranean countries, and Asian Countries[a]						
	Coefficient		**% of Variation in CHD Explained (r^2)**		***P***	
Dietary variable	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
Folate, μg/1,000 kcal	−0.01	−0.01	61	62	.0014	.0001
Fiber, g/1,000 kcal	0.16	0.19	20	22	.0023	.0374
Fatty acids, n-6/n-3	0.03	0.04	5	6	.0103	.0280
Total			86	90		

[a]Adapted from reference (8).

the United States. There were no significant pairwise differences in lutein/zeaxanthin, beta-carotene, or fiber among the four groups of countries. Vitamins C and E were significantly higher in the Mediterranean countries than in the other three groups of countries. Dietary folate was significantly higher in the Mediterranean countries than in Central and Eastern Europe and the Russian Federation and Western Europe and the United States.

Dietary Determinants of CHD Mortality

Pathogenic and protective dietary factors were regressed on coronary mortality data from all 16 countries, separated by sex. The model that included folate, fiber, and n-6/n-3 fatty acids was selected for inclusion because scientific evidence suggests a possible mechanism for folate being protective against CHD (Table 3).

The full model explained the majority of the variation in mortality from CHD (86% for men and 90% for women). Most of that variation was explained by folate (61% for men and 62% for women). To further explore the association of folate with coronary mortality we carried out a regression of folate on CHD mortality (Figure 2). Japan and the Mediterranean countries, with the highest folate available for consumption, had the lowest rates of CHD mortality (Table 2). The countries of Western Europe and the United States and of Central and Eastern Europe and the Russian Federation had a lower amount of dietary folate available for consumption and higher rates of CHD mortality.

Fiber explained 20% of CHD mortality for men and 22% for women. In the presence of the other variables, the relationship of the fiber to CHD mortality was positive. The ratio of n-6 to n-3 fatty acids explained 5% (men) and 6% (women) of the variation in CHD mortality.

It is important to note that folate, lutein/zeaxanthin, and beta-carotene were highly intercorrelated (r=0.87 to 0.99). When folate was in the model, neither lutein/zeaxanthin nor beta-carotene was independently related to CHD mortality. However, when either lutein/zeaxanthin or beta-carotene was entered in place of folate, the model explained 91% to 93% of the variation in CHD mortality with most of the variation being accounted for by lutein/zeaxanthin or beta-carotene (inversely associated with CHD mortality). For men, fiber and the n-6/n-3 fatty acids were also significant in these models and were positively associated with CHD mortality. In the model that included lutein/zeaxanthin, vitamin C was significantly and negatively associated with CHD mortality. For women only the n-6/n-3 was significant in these models and was positively associated with CHD mortality.

DISCUSSION

These results point to an important role of foods that are rich in folate and carotenoids in understanding the very

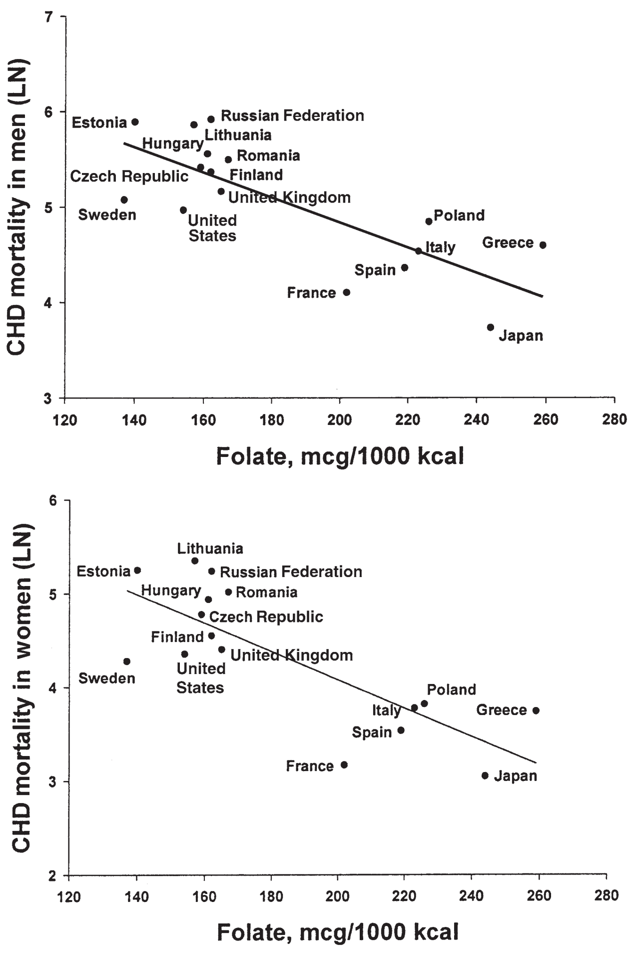

Figure 2. Regression of coronary heart disease (CHD) mortality (log transformed [LN]) on folate intake. Adapted from reference (8).

high rate of CHD in Central and Eastern Europe. Because one role of folate is to interconvert homocysteine to methionine, an inadequate intake of folate can lead to elevation of plasma homocysteine. Homocysteine may be the coronary-inducing factor that is produced by a lack of dietary folate. The relative risk of developing an acute coronary event over a 10-year period was 0.45 and 0.53 for high-risk Finnish men in the two highest quintiles of folate intake compared to men in the lowest quintile (27). It was not possible to determine the individual contribution of folate, lutein/zeaxanthin, and beta-carotene as protectors against coronary disease. All three nutrients tend to be present in the same foods derived from plants; they could even play a synergistic role in the protection against coronary disease.

The association of higher fiber with higher CHD mortality is the opposite one would expect. This finding was tempered by the fact that when either lutein/zeaxanthin or beta-carotene replaced folate in the model, fiber was not a predictor of CHD mortality in women. It is also important to keep in mind that food available for consumption is representative of food before processing and fiber is removed in the processing of some foods.

A higher ratio of n-6 to n-3 fatty acids being associated with a higher CHD mortality is consistent with current thinking that this ratio is too high in Western countries (10,25). A low intake of fish and a high intake of n-6 rich vegetable oils and meat from grain-fed rather than grass-fed animals would contribute to a higher n-6/n-3. When n-6 fatty acids are disproportionately high compared with n-3 fatty acids, more thromboxane A_2, a procoagulant, is produced (28). A higher vitamin C intake being associated with a lower CHD mortality might be explained by its strong antioxidant properties.

Another aspect of this discussion relates to prevention. If dietary intake of foods rich in folate were to be increased in countries with high CHD mortality, would there be a decrease in the coronary epidemic in both men and women? The unique situation in Poland, where coronary mortality is low and dietary intake of folate and other protective nutrients is high, is also suggestive. Interestingly, compared to other Eastern European countries, Poland's rates of coronary mortality have decreased over the past few years and resemble the rates in Mediterranean countries. This has been attributed to the increased consumption of fruits and vegetables, rich sources of folate, and other protective nutrients (29).

In the Seven Countries Study, the lowest 25-year CHD mortality rates were found in the Mediterranean countries of Southern Europe and in Japan compared with countries with high CHD mortality rates such as the United States and Finland (30). The Mediterranean diet is low in saturated fat and high in monounsaturated fatty acids; high in antioxidants, especially vitamins C and E; and high in folic acid and fiber (31). Other studies have shown that high intakes of fruits and vegetables were associated with a lower risk of cardiovascular disease (32-35). Likewise, in this study folic acid, the carotenoids, and vitamin C, the richest sources being fruits and vegetables, were associated with lower CHD mortality.

It is important to note two limitations of this study. One, because food disappearance data are useful in generating hypotheses about dietary factors associated with disease and cannot be used to evaluate causal relationship, the data from this study should be used to stimulate research that will establish whether folate and/or carotenoids do contribute to lower coronary risk (36). Two, because of necessity we had to use food disappearance data and CHD mortality data from the same year. This is not ideal because coronary heart disease develops over a long time period.

Whereas our findings implicate the role of cardioprotective nutrients in addressing the CHD epidemic in Central and Eastern Europe, a single factor, dietary or otherwise, could never explain this coronary epidemic. The terrible toll from sudden death that is particularly striking in men aged 30 to 50 years is likely the result of a combination of many factors (2). Still, the diets in these countries that are high in pathogenic dietary factors and low in protective dietary factors, especially folate and carotenoids, may help explain the very high death rate from coronary disease in both men and women in Central and Eastern Europe.

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