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Improvement in Stroke Mortality in Canada and the United States, 1990 to 2002

Quanhe Yang, PhD; Lorenzo D. Botto, MD; J. David Erickson, DDS, PhD; Robert J. Berry, MD; Christie Sambell, PhD; Helen Johansen, PhD; J.M. Friedman, MD, PhD

Background—In the United States and Canada, folic acid fortification of enriched grain products was fully implemented by 1998. The resulting population-wide reduction in blood homocysteine concentrations might be expected to reduce stroke mortality if high homocysteine levels are an independent risk factor for stroke.

Methods and Results—In this population-based cohort study with quasi-experimental intervention, we used segmented log-linear regression to evaluate trends in stroke-related mortality before and after folic acid fortification in the United States and Canada and, as a comparison, during the same period in England and Wales, where fortification is not required. Average blood folate concentrations increased and homocysteine concentrations decreased in the United States after fortification. The ongoing decline in stroke mortality observed in the United States between 1990 and 1997 accelerated in 1998 to 2002 in nearly all population strata, with an overall change from -0.3% (95% CI, -0.7 to 0.08) to -2.9 (95% CI, -3.5 to -2.3) per year ($P=0.0005$). Sensitivity analyses indicate that changes in other major recognized risk factors are unlikely to account for the reduced number of stroke-related deaths in the United States. The fall in stroke mortality in Canada averaged -1.0% (95% CI, -1.4 to -0.6) per year from 1990 to 1997 and accelerated to -5.4% (95% CI, -6.0 to -4.7) per year in 1998 to 2002 ($P\leq 0.0001$). In contrast, the decline in stroke mortality in England and Wales did not change significantly between 1990 and 2002.

Conclusions—The improvement in stroke mortality observed after folic acid fortification in the United States and Canada but not in England and Wales is consistent with the hypothesis that folic acid fortification helps to reduce deaths from stroke. (*Circulation*. 2006;113:1335-1343.)

Key Words: mortality ■ nutrition ■ population ■ prevention ■ stroke

Folic acid fortification of enriched grain products ($140\ \mu\text{g}$ folic acid per 100 g flour) was mandated by the Food and Drug Administration in the United States in 1996 and was fully in place by January 1, 1998.¹ The resulting population-wide increase in serum folate concentrations² produced a 20% decrease in the rate of neural tube defects^{3,4} and a population-wide reduction in blood homocysteine concentration.⁵

Clinical Perspective p 1343

Health Canada implemented mandatory folic acid fortification ($150\ \mu\text{g}$ of folic acid per 100 g of flour) in 1998.⁶ Mean red cell folate concentrations subsequently increased by 41% among women of reproductive age,⁷ and limited available data suggest that the expected concomitant reduction in average blood homocysteine concentration occurred.⁸

Blood homocysteine concentration appears to be an independent risk factor for stroke,^{9–12} so this population-wide

reduction of blood homocysteine concentrations could have important health benefits. Stroke is a major public health burden in the United States, Canada, and many other countries, although the associated mortality has slowly improved in recent years.^{13–15} Many factors have probably contributed to this improvement. We examined national stroke mortality data from the United States and Canada, where mandatory fortification has been in place since 1998, and compared the findings with similar data from England and Wales, where fortification is not mandatory, to see if accelerated improvement in stroke mortality occurred in association with folic acid fortification.

Methods

Mortality Data

Age-adjusted stroke mortality rates per 100 000-resident population were calculated for the United States with data from the National

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The online-only Data Supplement can be found at <http://circ.ahajournals.org/cgi/content/full/113/10/1335/DC1>.

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Center for Health Statistics Multiple Cause Mortality Files of the Centers for Disease Control and Prevention (CDC). Similar data were obtained from the Canadian Mortality Database at Statistics Canada and from the UK Office for National Statistics for England and Wales. We restricted our analysis to the period from 1990 through 2002 and to people ≥ 40 years of age, a group that experienced $>95\%$ of deaths associated with stroke.

The period of study included the time during which coding for cause of death was changed from the *International Classification of Diseases, 9th Revision* (ICD-9) to the *International Classification of Diseases, 10th Revision* (ICD-10). ICD-9 was used to code deaths in the United States from 1990 to 1998, in Canada from 1990 to 1999, and in England and Wales from 1990 to 2000. ICD-10 was used to code deaths in the United States from 1999 to 2002, in Canada from 2000 to 2002, and in England and Wales from 2001 to 2002. In the mortality analyses, we included all records with a code for stroke (ICD-9 codes 430.0 to 434.9 and 436.0 to 438.9 or ICD-10 codes I60-I69) as the underlying cause of death. To ensure comparability of the data throughout the entire period of study, we used comparability ratios to correct for the inclusiveness of ICD-10 codes relative to the corresponding ICD-9 codes.^{16–18} The comparability ratios were 1.059 (95% confidence interval [CI], 1.057 to 1.060) and 1.069 (95% CI, 1.053 to 1.085) for the United States and Canada and 1.090 (95% CI, 1.086 to 1.094) and 1.131 (95% CI, 1.125 to 1.136) for women and men from England and Wales, respectively.^{17–19}

Statistical Analysis

Mortality rates were age-adjusted with 2000 population as standard in the United States, 2001 population as standard in Canada, and the European standard population in England and Wales. We computed rates by sex, age group (40 to 49, 50 to 59, 60 to 69, and ≥ 70 years), and, in the United States, race (white or black, the only groups with consistent definitions and large sample size in the National Health and Nutrition Examination Survey [NHANES] data sets). To document changes in trends concurrent with flour fortification, we used 1998, the year implementation was completed in the United States and Canada, as the boundary point and conducted simple segmented log-linear regression of age-adjusted mortality rates in 1990 through 1997 versus 1998 through 2002. We tested for a significant difference between the regression lines for the 2 segments using the *t* test.²⁰ We estimated the annual change in mortality rate before and after 1998 from the slope of the simple segmented log-linear regression. To estimate how many fewer deaths occurred each year after 1998, we used the 1990 to 1997 trend to predict 1998 to 2002 mortality rates and computed the difference between observed and predicted number of deaths.

Changes in Blood Values and Risk Factors in the United States

We conducted 2 additional analyses using NHANES data from the United States. We used data from NHANES III phase I (1988 to 1991), NHANES III phase II (1991 to 1994), and NHANES 1999 to 2000 to evaluate changes in blood folate and total homocysteine concentrations, as well as changes in the prevalence of major risk factors for stroke. We selected all participants except pregnant women who provided a blood sample and were ≥ 40 years of age and adjusted for the complex sampling design with SAS (SAS Institute, Cary, NC) or SUDAAN (Research Triangle Institute, Research Triangle Park, NC) statistical software. We estimated the geometric mean blood folate and total homocysteine concentrations by sex, race (white and black), and age group (40 to 59 and ≥ 60 years). Because blood homocysteine concentration was measured only during phase II of the NHANES III survey (1991–1994), we excluded phase I data from this analysis.

Serum folate concentrations were measured during the entire period of study using consistent methods, exhaustive quality control, and external proficiency testing.²¹ NHANES III phase II serum

homocysteine concentrations were measured by high-performance liquid chromatography at the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University.²² NHANES 1999 to 2000 plasma homocysteine concentrations were determined by a somewhat different high-performance liquid chromatography method at the CDC's NHANES Central Laboratory.²³

Sensitivity Analysis

To evaluate the extent to which changes in known risk factors for stroke could affect mortality rates during the study period, we conducted a sensitivity analysis using NHANES data for the United States. We used a single age group (≥ 40 years) to obtain stable estimates of 4 dichotomous risk factors: current cigarette smoking, hypertension, diabetes, and total serum cholesterol concentration ≥ 240 mg/dL, which together contribute to $>75\%$ of cardiovascular deaths.²⁴ The population was partitioned into 16 strata, depending on the presence or absence of each of the 4 dichotomous risk factors. We assumed that total mortality associated with stroke is partitioned among these 16 strata as a function of the size of each group.²⁰ We used NHANES data from before (NHANES III) and after (NHANES 1999 to 2000) fortification to obtain the joint distribution of risk factors, which were estimated from the published literature.^{25–29} When the relative risks differed among studies, we used the average risk (Appendix Table I found in the online Data Supplement).

Because interaction effects for multiple risk factors are not well understood, we assumed multiplicative effects in the sensitivity analysis. We used a fixed background risk for disease and relative risks for mortality rates 3 years before and 3 years after fortification (1994 to 1996 versus 1999 to 2001) and varied the joint distribution of risk factors according to the NHANES data. This way, we obtained estimates for the variation in stroke mortality that would have occurred after fortification (1999 to 2001) because of changes in these risk factors alone. We also varied the values of the joint distribution of risk factors through the range of their 95% CIs to account for the variability of estimated prevalence of the risk factors. We performed the sensitivity analysis with the @RISK program (Palisade Corp, Newfield, NY) with 10 000 Monte Carlo simulations.

To evaluate the extent to which changes from ICD-9 to ICD-10 affect the observed stroke mortality trends, we conducted a sensitivity analysis of different values of the comparability ratios. We estimated annual percent change and 95% CIs of the age-adjusted stroke mortality rate for 1990 to 1997 versus 1998 to 2002, assuming that the comparability ratio was 50% or 25% lower or higher than the point estimate.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Blood folate concentration increased and total homocysteine concentration decreased significantly ($P < 0.05$) among all population strata ≥ 40 years of age or older after folic acid fortification in the United States (Figures 1 and 2).

In the United States in 1990 to 2002, 1 963 024 records of whites or blacks listed stroke as the underlying cause of death. Whites accounted for 88% (1 734 766) of total stroke deaths. During this same period, 195 212 records listed stroke as the underlying cause of death among people in Canada, and 776 199 records listed stroke as the underlying cause of death among people in England and Wales.

Stroke mortality rates declined during this period in both men and women in all 3 countries (Figures 3 and 4). Simple segmented log-linear regression showed a clear pattern of acceleration of the rate of decline in age-adjusted stroke mortality rates after 1998, when folic acid

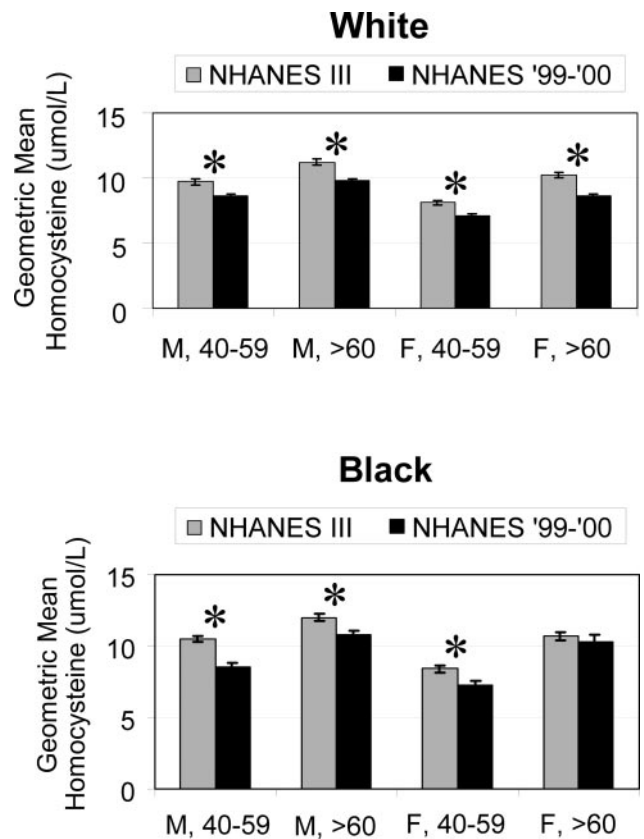
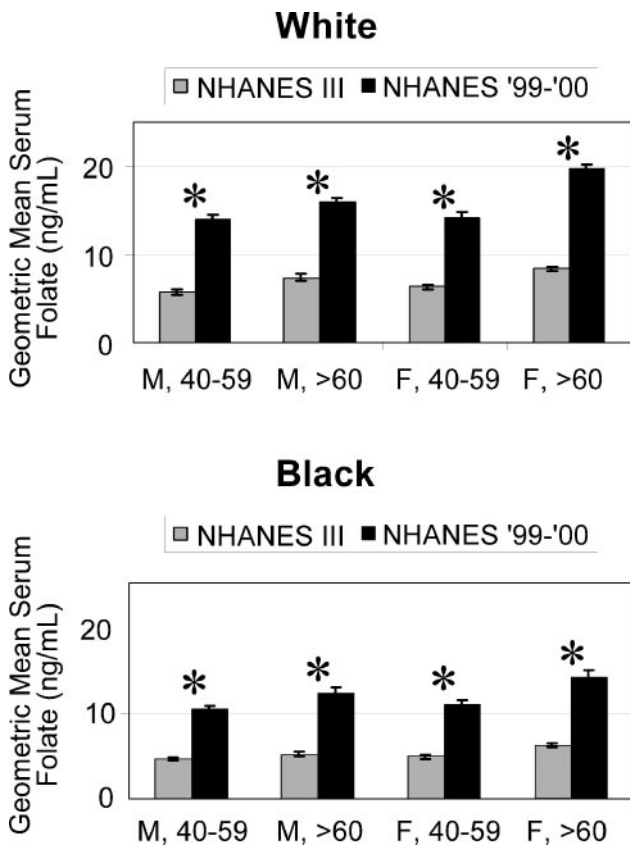


Figure 1. Serum folate concentrations among population ≥ 40 years of age by age, sex, and race in NHANES III 1991 to 1994 and NHANES 1999 to 2000, United States. Error bars indicate ± 1 SEM. *Significant difference ($P < 0.05$).

Figure 2. Blood homocysteine concentrations among population ≥ 40 years of age by age, sex, and race in NHANES III 1991 to 1994 and NHANES 1999 to 2000, United States. Error bars indicate ± 1 SEM. *Significant difference ($P < 0.05$).

fortification was implemented, compared with the previous 8 years in nearly all of the groups studied in the United States and Canada (Table 1 and Figures 3 and 4). In the United States, the estimated annual percent decline in stroke-related mortality rates among whites in all age and sex groups was $\leq 1.0\%$, with 1 exception, before fortification and increased to $\geq 2.7\%$ after fortification. A similar effect was seen among blacks, with the annual decline increasing from 1.4% among men and 0.7% among women before fortification to 2.9% among men and 2.7% among women after fortification. These percentages translate into $\approx 12\,900$ fewer stroke deaths per year among people ≥ 40 years of age in the United States than if the trend established in 1990 to 1997 had continued without change (Table 1).

In Canada, the estimated annual percent decline in stroke-related mortality rates was 1.2% for men and 0.9% for women ≥ 40 years of age before fortification and increased to 5.6% for men and 5.4% for women after fortification. These percentages translate into ≈ 2800 fewer stroke deaths per year than if the trend established in 1990 to 1997 had continued without change (Table 1).

In contrast, there was no consistent change in the ongoing decline of age-adjusted stroke mortality in England and Wales after 1998 (Table 1 and Figures 3 and 4). In fact, there were ≈ 1890 more stroke deaths in 1999 to 2002 than if the trend established in 1990 to 1997 had continued (Table 1).

Impact of Changes in Risk Factors in the United States

Sensitivity analysis based on changes in the prevalence of smoking, hypertension, diabetes, and serum total cholesterol concentration ≥ 240 mg/dL in the United States during the period of study predicted a 0.1% increase (2.5th to 97.5th centile, 5.2% decline to 5.3% increase) in stroke mortality after 1998 (Table 2). A 9.3% decline actually was observed.

Discussion

The slowly declining trend in stroke mortality rates observed since at least 1990 in the United States and Canada accelerated significantly after 1998, when mandatory folic acid fortification was implemented. This improvement in stroke mortality paralleled the reduction in occurrence rates observed for neural tube defects, which are known to be prevented by folic acid.^{3,30} In contrast, no improvement in the decline of stroke mortality or in the occurrence of neural tube defects^{31,32} was seen in England and Wales, where folic acid fortification is not mandatory.

The improvement in stroke mortality we observed in the United States and Canada appears to be largely independent of changes in all-cause mortality (Appendix Table II) and seems unlikely to be related to the change in coding from ICD-9 to ICD-10 (Appendix Table III). Chance is an unlikely explanation for our findings, given the statistical testing results.

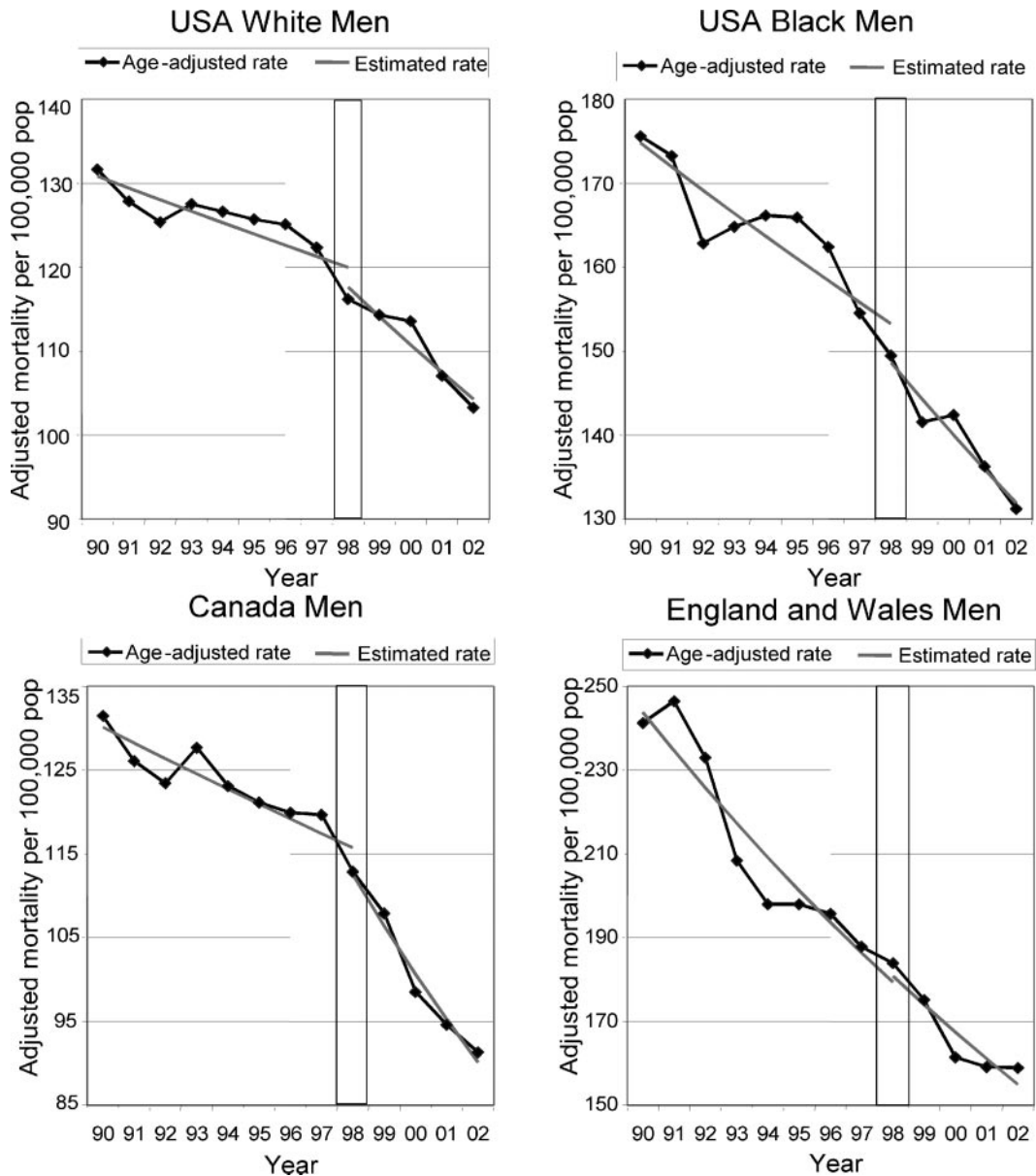


Figure 3. Actual and estimated age-adjusted stroke mortality per 100 000 men in the United States and Canada and in England and Wales, 1990 to 2002. The estimates are based on simple segmented log-linear regression analysis of the observed data.

It is unclear how much of the decline in stroke mortality is due to reduced incidence and how much to reduced case-fatality rate. Population-based data from the United States and Canada that would be helpful in assessing this are very limited. Age-adjusted rates of stroke hospitalization in the United States increased significantly from 1988 to 1997,³³ and a Canadian study found stable age-adjusted stroke hospitalization rates in the Calgary Health Region from 1994 to 2002.³⁴ The prevalence of nonfatal stroke was estimated from NHANES data to be 1.87% among noninstitutionalized 25- to 74-year-old people in the United States in 1991.³⁵ A similar calculation based on 1999 to 2002 NHANES data yields a prevalence of 2.01% (SE=0.21). Thus, we find no evidence that stroke incidence decreased in the United States and Canada during the period studied. If this is true, the decline in stroke mortality we observed may be largely attributable to a reduced case-fatality rate.³⁶

Our study is based on aggregate rather than individual data, but the setting makes it considerably more robust than a typical ecological study. Our analysis can be considered a national, population-based cohort study with quasi-experimental intervention because virtually the entire population was exposed to folic acid fortification, the biochemical effect of this exposure was demonstrated through population-based measurement of blood folate and homocysteine concentrations, and every death in the population was collected through national records. A similar approach has been used to demonstrate other population-wide changes associated with universal exposures.^{3,37,38}

There is considerable evidence that elevated blood homocysteine concentration is an independent risk factor for stroke and that reduced blood homocysteine concentration is associated with a reduced risk for stroke.⁹⁻¹² In a

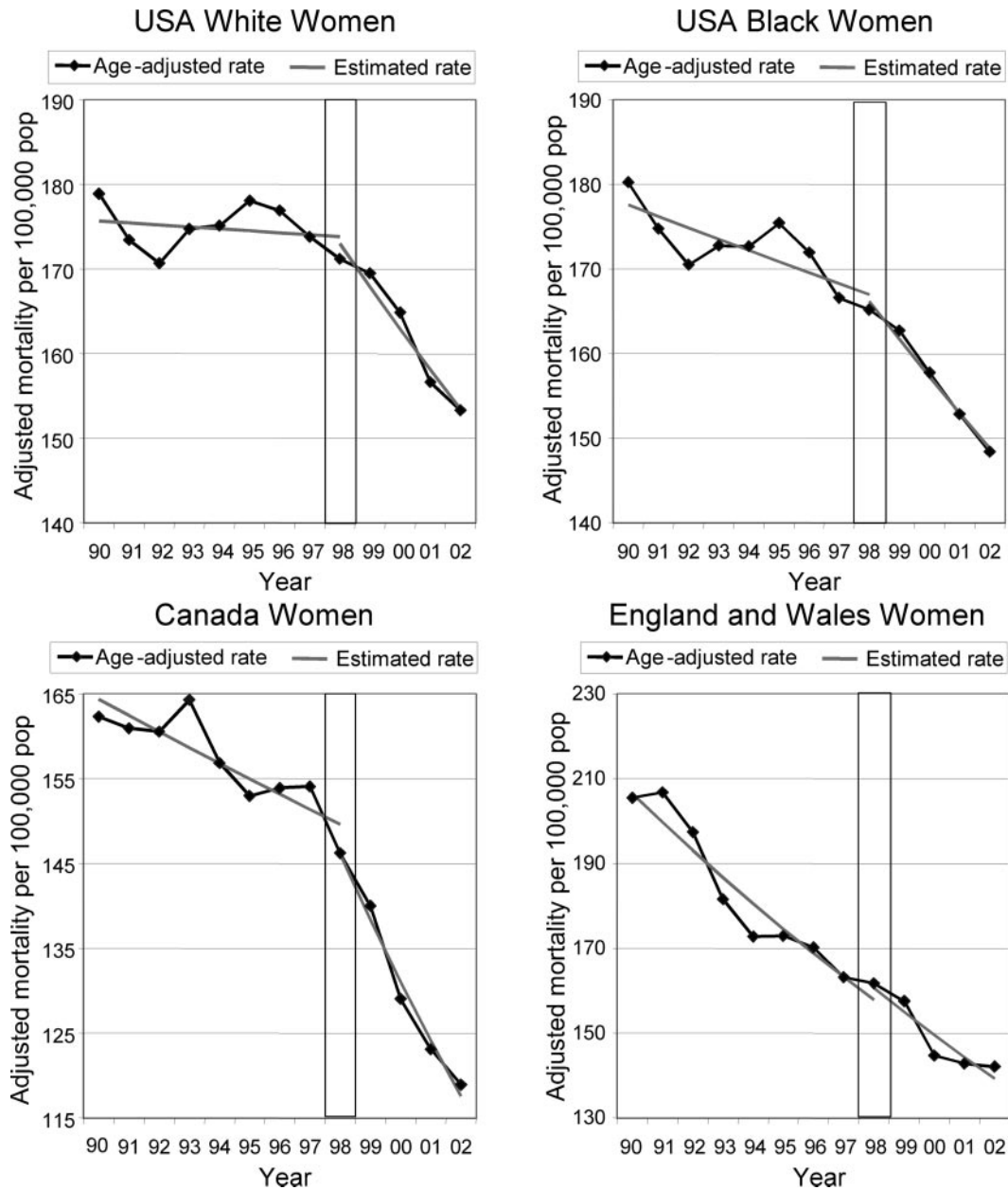


Figure 4. Actual and estimated age-adjusted stroke mortality per 100 000 women in the United States and Canada and in England and Wales, 1990 to 2002. The estimates are based on simple segmented log-linear regression analysis of the observed data.

recent meta-analysis of 111 studies examining the association between the *MTHFR* C677T polymorphism and stroke, Casas and colleagues¹¹ found that T-allele homozygotes, who have a greater mean homocysteine concentration than homozygotes for the C (wild-type) allele, also have a significantly increased risk for stroke. The authors of another recent meta-analysis of *MTHFR* C677T polymorphism studies stratified their analysis by continent to approximate folate status.¹² The findings were consistent with the possibility that population-wide folic acid fortification helps to prevent stroke.¹² Such “mendelian randomization” studies are largely free from confounding effects and support a causal link between blood homocysteine concentration and the risk for stroke.

A clinical trial that randomized 3318 adults to a folate-containing multivitamin supplement or placebo showed a 58% reduction in stroke-associated deaths among men (but not women) who took the supplements.³⁹ Another randomized clinical trial in 3680 patients assessed the effect on stroke recurrence and other vascular end points of lowering blood homocysteine concentration by 2 $\mu\text{mol/L}$ with high-dose B-vitamin (folate, B12, B6) treatment.⁴⁰ No reduction in recurrent stroke was observed, but, as the authors noted,⁴⁰ the study’s statistical power was only 31% to detect a significant reduction of the combined number of stroke and coronary events because almost all patients were enrolled after folic acid fortification had occurred. A recent re-analysis of these data showed a 21% reduction in the risk for the combined end

TABLE 1. Estimated Annual Percent Change and 95% CIs of Stroke Age-Adjusted Mortality Rate by Age Group and Sex in the United States and Canada and in England and Wales, 1990–1997 and 1998–2002

Population and Age Group (in years)	Estimated Annual Percent Change in Mortality Rate Before and After 1998 (95% CI)			Yearly Deaths Observed in 1999–2002 vs Expected Based on 1990–1997 Trends		
	1990–1997	1998–2002	<i>P</i> for 2 Slopes*	Expected	Observed	Difference
United States						
Black men						
40–49	–2.4 (–3.3––1.5)	–7.9 (–9.9––5.9)	0.0019	853	675	178
50–59	–0.1 (–0.9–0.8)	–4.4 (–6.0––2.8)	0.0056	1459	1126	334
60–69	–1.8 (–2.5––1.1)	–2.0 (–3.8––0.2)	0.8821	1582	1526	55
≥70	–1.4 (–2.1––0.7)	–2.1 (–3.5––0.6)	0.4812	4418	4345	73
All black men	–1.4 (–1.9––0.8)	–2.9 (–3.7––2.2)	0.0514	8311	7671	640
Black women						
40–49	–0.8 (–2.4–0.9)	–3.6 (–5.7––1.5)	0.1721	783	682	101
50–59	–1.8 (–2.5––1.0)	–4.5 (–6.5––2.6)	0.0480	957	920	37
60–69	–2.1 (–2.9––1.4)	–2.0 (–3.9–0.02)	0.9208	1408	1342	67
≥70	–0.2 (–0.8–0.4)	–2.6 (–3.5––1.6)	0.0117	8324	7865	459
All black women	–0.7 (–1.1––0.2)	–2.7 (–3.0––2.4)	0.0028	11 472	10 808	664
White men						
40–49	0.5 (–0.2–1.1)	–2.7 (–4.9––0.5)	0.0282	1763	1427	336
50–59	–1.0 (–1.4––0.5)	–4.8 (–6.1––3.4)	0.0009	3274	2832	442
60–69	–0.7 (–1.0––0.4)	–4.0 (–4.8––3.1)	<0.0001	6585	5724	861
≥70	–0.8 (–1.1––0.4)	–2.8 (–3.7––1.7)	0.0066	46 349	43 476	2873
All white men	–0.7 (–1.1––0.4)	–2.9 (–3.7––2.1)	0.0012	57 970	53 459	4512
White women						
40–49	–1.7 (–2.3––1.1)	–0.4 (–1.6–0.9)	0.1384	1250	1246	4
50–59	–0.9 (–1.6––0.2)	–4.9 (–6.7––3.1)	0.0070	2751	2326	425
60–69	–0.7 (–1.2––0.1)	–4.5 (–5.8––3.0)	0.0016	5470	4893	577
≥70	0.1 (–0.3–0.6)	–2.8 (–3.4––2.2)	0.0004	85 522	78 367	6156
All white women	0.03 (–0.4–0.5)	–2.9 (–3.5––2.4)	0.0003	94 992	87 831	7162
Canada						
Men						
40–49	–4.0 (–6.7––1.2)	–8.8 (–11.0––6.5)	0.1528	134	136	–2
50–59	–2.1 (–4.1–0.01)	–5.2 (–7.4––2.9)	0.2606	363	293	70
60–69	–1.6 (–2.5––0.8)	–5.4 (–6.3––4.5)	0.0030	885	719	166
≥70	–1.0 (–1.3––0.7)	–5.4 (–6.2––4.6)	<0.0001	6115	5177	938
All men	–1.2 (–1.8––0.6)	–5.6 (–7.3––3.8)	<0.0001	7498	6325	1173
Women						
40–49	–2.4 (–4.4––0.4)	–5.8 (–10.1––1.3)	0.2677	147	131	16
50–59	–1.9 (–3.3––0.4)	–8.6 (–11.2––5.8)	0.0112	277	242	36
60–69	–0.9 (–2.1–0.3)	–7.2 (–9.2––5.1)	0.0046	641	494	147
≥70	–0.9 (–1.3––0.4)	–5.1 (–5.6––4.6)	<0.0001	9630	8137	1494
All women	–0.9 (–1.6––0.3)	–5.4 (–6.8––4.0)	<0.0001	10 696	9002	1693
England and Wales†						
Men						
40–49	–2.8 (–3.7––1.8)	–5.6 (–6.4––4.8)	0.0289	399	357	43
50–59	–3.8 (–4.8––2.9)	–6.9 (–8.3––5.5)	0.0372	983	915	68
60–69	–4.4 (–5.2––3.7)	–6.7 (–7.6––5.8)	0.0282	2333	2313	21
≥70	–4.2 (–5.2––3.2)	–3.8 (–5.2––2.4)	0.7048	16 802	17 448	–647
All men	–4.1 (–5.1––3.1)	–3.9 (–5.2––2.6)	0.8550	20 517	21 032	–516
Women						
40–49	–2.2 (–3.0–1.4)	–6.0 (–7.7––4.4)	0.2392	354	333	21
50–59	–3.1 (–3.7––2.5)	–6.9 (–8.5––5.3)	0.0036	750	716	36
60–69	–4.0 (–4.6––3.3)	–7.2 (–8.1––6.3)	0.0020	1802	1743	59
≥70	–3.7 (–4.4––3.0)	–3.4 (–4.5––2.2)	0.7260	30 800	32 289	–1490
All women	–3.6 (–4.3––2.9)	–3.6 (–4.7––2.4)	0.9639	33 706	35 081	–1375

*Probability value for testing differences of the 2 slopes (1990–1997 vs 1998–2002) of the estimated stroke mortality rate changes.

†We used year 2000 England and Wales population as standard in estimating expected and observed number of stroke deaths.

TABLE 2. Sensitivity Analysis of Stroke Age-Adjusted Mortality Rates Based on Changes in Prevalence of Current Cigarette Smoking, Hypertension, Diabetes, and Total Serum Cholesterol Concentration ≥ 240 mg/dL 3 Years Before (1994–1996) and 3 Years After (1999–2001) Folic Acid Flour Fortification in the United States

	Age-Adjusted Mortality Rate per 100 000, 1994–1996	Age-Adjusted Mortality Rate per 100 000, 1999–2001	Estimated Annual Percent Change in Mortality Rate Before and After 1998 (95% CI)		Simulated Median (2.5th and 97.5th Centiles) of Mortality Rate per 100 000 for 1999–2001
			1990–1997	1998–2002	
			Stroke mortality	151.4	

points in the high-dose group after exclusion of the subset of patients who were unlikely a priori to respond to B-multivitamin therapy.⁴¹

The Norwegian Vitamin (NORVIT) Study presented at the European Society of Cardiology in September 2005 randomized 3749 patients who had experienced an acute myocardial infarction within the previous 7 days into groups that received 4 different folic acid and B-vitamin combinations. After an average of 3.5 years follow-up, the study found no significant effect of folic acid treatment on cardiovascular disease risk despite producing a 25% reduction in average serum homocysteine concentration. This study cannot be fully assessed until it has been peer reviewed and its data are published, but it has already engendered considerable controversy because of its complex design and limited statistical power. Clearly, additional investigations of the effect of reducing blood homocysteine concentration on cardiovascular disease risk are needed.

Many factors, including large public health programs promoting heart disease and stroke prevention (see http://www.cdc.gov/cvh/state_program/index.htm), have probably contributed to the long-term decline of stroke mortality observed in the United States and Canada.^{14,15,42} Many lifestyle changes and treatments operate on stroke mortality through their effects on major established risk factors such as smoking, hypertension, and diabetes. These factors explain >75% of stroke mortality, but most showed little improvement or actually worsened during the 1990s (Appendix Table IV), so they are unlikely to be primary factors in the marked improvement in stroke mortality centered around the time of folic acid fortification.^{14,43–51} Our sensitivity analysis is consistent with this assessment (Table 2). More widespread use of aspirin, statins, β -blockers, ACE inhibitors, and revascularization procedures, as well as a decline in cigarette smoking, may also have affected stroke mortality in the late 1990s,^{14,15,42,51–55} but such changes are likely to produce a gradual decline in the mortality rate, as was seen in England and Wales, rather than an abrupt population-wide improvement. The substantial improvement in stroke mortality we observed in the United States and Canada after 1998 in almost all racial, sex, and age groups studied, including those that traditionally benefit less or later from therapeutic advances and public health campaigns, also argues against an effect that operated solely through better treatment or amelioration of conventional risk factors.

In contrast, a population-wide impact could be expected from a population-based intervention such as folic acid fortification of enriched grain products. After fortification,

we observed the expected changes in serum folate and homocysteine concentrations in all US population strata studied (Figures 1 and 2). The timing of the accelerated decline in stroke mortality in our study is generally consistent with the timing of fortification, and the degree of decline is consistent with what was predicted⁹ for the change in blood homocysteine concentrations observed in the US population (Figures 1 and 2).⁵ For example, the predicted improvements in stroke mortality based on the observed changes in homocysteine concentration were 9.0% for white men, 10.9% for white women, 12.8% for black men, and 8.4% for black women in the 3 years after fortification (1999 to 2001) in the United States. The observed average improvements were 11.3% for white men, 7.4% for white women, 15.0% for black men, and 9.0% for black women.

The epidemiological analysis presented here certainly does not establish causality, but the trends we observed are consistent with the hypothesis that folic acid fortification is contributing to a reduction in stroke deaths. Stroke and cardiovascular disease cause an extraordinary societal burden, and all effective prevention and treatment strategies ought to be implemented. If folic acid fortification is responsible for even a fraction of the accelerated improvement we observed, this public health benefit is an important bonus to the reduction in neural tube defect rates previously demonstrated.³ Moreover, these benefits accrue to all members of the population, regardless of ethnic, social, and economic barriers that have mitigated the benefits of many advances in prevention and treatment for women, ethnic minorities, the poor, and the uninsured.⁵⁶

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Disclosures

None.

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CLINICAL PERSPECTIVE

Mandatory folic acid fortification of enriched grain products was implemented in the United States and Canada in 1996 to 1998 to reduce the occurrence of neural tube defects. This intervention increased the average serum folate concentration on a population-wide basis and would be expected to produce a consequent reduction of the average homocysteine concentration. If high serum homocysteine concentration is an independent risk factor for stroke, as has been suggested by several previous studies, folic acid fortification would also be expected to improve stroke mortality. We evaluated trends in stroke-related mortality before and after folic acid fortification was implemented in the United States and Canada and, as a comparison, during the same period in England and Wales, where folic acid fortification is not required. Average blood folate concentrations increased and homocysteine concentrations decreased in the United States after fortification. Stroke mortality improved overall and in almost all population subgroups studied after mandatory folic acid fortification was implemented in the United States and Canada, but not in England and Wales, during this period. Changes in other major recognized risk factors do not appear to account for the reduction in stroke-related deaths in the United States. Our findings are consistent with the possibility that mandatory folic acid fortification of enriched grain products helps to reduce deaths from stroke.