Did national folic acid fortification reduce socioeconomic and racial disparities in folate status in the US?

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Background	The purpose of this study is to determine the impact of the 1998 US Food and Drug Administration folic acid fortification policy on disparities in folate status in the United States.
Methods	We use repeated cross-sectional data from the U.S. National Health and Nutrition Examination Surveys (NHANES), a nationally representative sample of over 14 000 participants ages 25 and older. We calculate pre-fortification (1991–94) and post-fortification (1999–2002) absolute differences and relative prevalence ratios of low red blood cell (RBC) folate status (<362.6 nmol), by race/ethnicity and income quartile. We also estimate kernel density plots and relative and absolute concentration curves pre- and post-fortification.
Results	The excess prevalence of low RBC folate status associated with the lowest income quartile and black race declined by 67% and 48%, respectively, following fortification. Despite these absolute gains, the relative ratio of low folate status increased after fortification for the lowest compared with the highest income groups (from 1.27 to 2.08) and among whites compared with blacks (from 1.64 to 3.75).
Conclusions	The effects of the fortification policy highlight the importance of distinguishing absolute from relative differences when evaluating interventions to reduce health disparities. Targeting of high risk populations is likely needed to eliminate remaining folate disparities.
Keywords	Folate, folic acid, fortification, socioeconomic factors, ethnic groups

Introduction

Differences in health status by socioeconomic status (SES), whether measured by mortality, chronic disease or self-reported health, are consistently observed in the United States.[1] The U.S. Department of Health and Human Services declared as one of the two major goals of the *Healthy People 2010* initiative 'to eliminate health disparities among different segments of the population'.[2] Unfortunately, knowledge regarding the effectiveness of policy interventions that might reduce these health disparities is lacking. The Food and Drug Administration (FDA) first authorized folic acid fortification of all enriched cereal-grain products in the US in March 1996 with the primary purpose of decreasing the number of pregnancies affected by neural tube defects, and the policy became mandatory by January 1998.[3] This article examines racial/ethnic and income disparities in folate status in the US before and after enactment of mandatory fortification.

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In addition to neural tube defects, low folate status has been suggested as a risk factor for some types of cancer.[4] Low folate also contributes to higher concentrations of homocysteine, an amino acid that has been implicated in ischaemic heart disease, stroke, physical functioning, hip fractures and dementia.[5–10] A recent randomized, double-blind study found that 3 years of folic acid supplementation improved cognitive function in a sample of 50- to 70-year-olds with raised plasma homocysteine levels.[11] The causality of the association between homocysteine and cardiovascular disease, as well as the efficacy of folic acid in preventing cardiovascular disease, is still a matter of on-going debate.[9,12–14] Given the potential connections between folate and chronic illnesses, the folic acid fortification policy of the FDA provides a unique opportunity to evaluate how a population-level, non-targeted intervention influences the distribution of risk factors that may contribute to health disparities.

Several studies have documented group differences in folate status in the US prior to fortification. For example, non-Hispanic whites were found to have significantly higher levels of serum and red blood cell (RBC) folate compared with non-Hispanic blacks for the period 1988–91, with only weak associations found between education and serum and RBC folate.[15] Additional work has documented an increase in the levels of serum folate and RBC folate concentrations, since the implementation of the FDA folic acid fortification policy across race/ethnic and socioeconomic groups in the US.[16–19] Overall, mean RBC folate concentrations were 57% higher in 1999–2000 compared with 1988–94, and mean folate intake increased 28%.[19] The prevalence of low RBC folate (<362.2 nmol/l) fell from 45.8% to 7.3% over this time period.[17] While these studies described general trends by certain subgroups, to our knowledge no study has explicitly examined the magnitude of relative and absolute disparities in folate status by income and race/ethnicity before and after fortification.

Given the large reduction in the prevalence of low folate status for all groups following fortification, we expected that paying attention to changes in both absolute and relative differences across groups would be important in evaluating the impact of fortification on disparities in low RBC folate status. In this study, we examined both the absolute and relative prevalence ratios of low RBC folate status by race/ethnicity and income quartile before and after implementation of the FDA's national fortification policy. As other countries continue to debate mandatory fortification,[20,21] this analysis can shed light on the ability of such a far-reaching policy to reach the highest risk groups in a population.

Methods

Study population

Data for this study come from three waves of the National Health and Nutrition Examination Surveys (NHANES), which were conducted by the National Center for Health Statistics and the Centers for Disease Control and Prevention to assess the health, dietary practices and nutritional status of the civilian, non-institutionalized population of the US 2 months and older. Details on the survey design and sampling methods of the NHANES III and NHANES 1999–2000 and 2001–02 surveys have been published elsewhere.[22,23] The NHANES III survey was conducted in two phases, each individually designed to be nationally representative. We use data from the second phase of NHANES III, covering the years 1991–94, to represent the period prior to fortification. Folic acid fortification was mandated by the FDA in March 1996, requiring full implementation by January 1998.[24] We use NHANES surveys from 1999–2000 and 2001–02 to represent the period post-fortification. We do not use data from the first phase of NHANES III, 1988–91 in order to focus on the before and after periods that are closest in time to implementation of the fortification policy. Using temporally proximate periods is likely to reduce error associated with varying trends in diet, supplement use or health behaviours.

Physical examinations for the NHANES surveys are conducted in Mobile Exam Centers (MEC), at which time blood samples are obtained by venipuncture. We limit our sample to adults aged 25 and older in order to reduce the measurement error associated with income in early adulthood. Of the 8699 individuals participating in the physical examination in NHANES III, 357 (4%) are missing values for RBC folate. Those missing were more likely to be non-Hispanic Black or Mexican-American, but do not significantly differ by age, income or sex. Of the remaining 8342 respondents, 671 (8%) were missing data for income. Those missing income data did not significantly differ in RBC folate status. In the combined 1999–02 data, 8252 individuals participated in the exam. Of this group, 262 (3%) were missing data on RBC folate. Of the remaining 7990 respondents, 804 (10%) were missing data on income, but those missing did not differ significantly in RBC folate status. Our final samples consists of 7671 individuals in NHANES III 1991–94, and 7288 individuals in the combined NHANES 1999–2000 and 2001–02 surveys.

Measures

RBC, also known as erythrocyte, folate is a marker of long-term folate status. RBC folate concentrations were assessed in NHANES III using two different methods. Prior to November 1993, RBC concentrations were assayed using the Quanta Phase I Folate Radioassay Kit (Bio-Rad Laboratories, Hercules, CA, USA), while from December 1993 onward the Quanta Phase II Folate Radioassay Kit (Bio-Rad Laboratories, Hercules, CA, USA) that was also used by NHANES 1999–2000 and 2001–02 surveys. The CDC has applied a correction factor to the earlier NHANES III assays to account for incorrect calibration, and detailed

laboratory procedures for the two surveys are available elsewhere.[25–27]

We used a dichotomous measure for whether the individual has low RBC folate using a previously established cut-point of <362.6 nmol (160 μg/l).[17,28] Continuous values of RBC folate were used to examine distributions of RBC folate before and after fortification. Income was divided into quartiles based on the poverty income ratio (PIR), defined as the ratio of a family's income to their appropriate threshold income based on household size. Since the NHANES surveys do not disclose the year in which an individual was interviewed within a wave, using the PIR ensures comparable inflation-adjusted measures across survey years. Race–ethnicity was represented in three categories: non-Hispanic white, non-Hispanic black and Mexican-American.

Statistical analysis

We calculated crude absolute differences in prevalence and relative prevalence ratios directly from tabulation of prevalence rates across income quartiles and separately for race/ethnic groups. We used a multivariable poisson regression model to calculate the prevalence ratio and adjusted absolute differences for low RBC folate status by income quartile and race/ethnicity, adjusting for age and sex. Income and race/ethnicity are simultaneously adjusted in the poisson models. Since robust error variance is not compatible with adjustment for complex survey design, we used the more conservative (wider) confidence intervals provided by STATA's survey commands. Kernel density estimates were used to examine smoothed distributions of continuous RBC folate by income groups and race/ethnicity before and after fortification. Relative and absolute concentration curves and indices for income were created by plotting the cumulative proportion of the sample ranked by income quartile on the *X*-axis against the cumulative proportion of cases of low RBC folate status on the *Y*-axis. All analyses were carried out using STATA statistical software version 10.0 adjusting for complex survey design (StataCorp, College Station, TX, USA).

Results

Figure 1 displays the changes in the continuous distribution of RBC folate in different groups before and after fortification. Here, we see a significant population shift in exposure following folic acid fortification. While the distributions for RBC folate have universally shifted to the right, it is clear that income and racial/ethnic differentials in low folate status still remain following fortification. Figure 2 shows relative and absolute concentration curves for income and low RBC folate status before and after fortification. Similarly, these calculations show that low RBC folate status became relatively more concentrated among the poor following fortification, reflected by a 179% increase in the
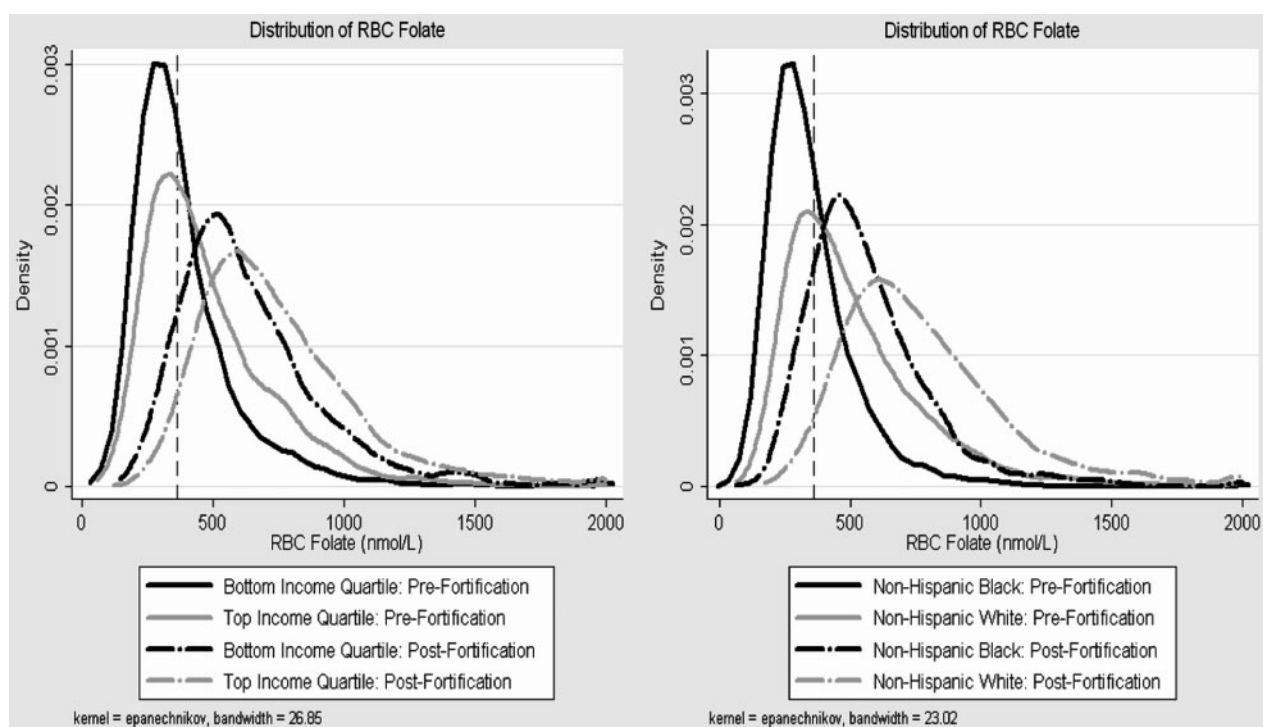
Figure 1 Distributions of RBC folate by income quartile (left) and race/ethncity (right) before (1991–94) and after (1999–2002) FDA mandated fortification. Vertical dotted line indicates cut-off for low folate status = 362.2 nmol/l. National Health and Nutrition Examination Survey, United States
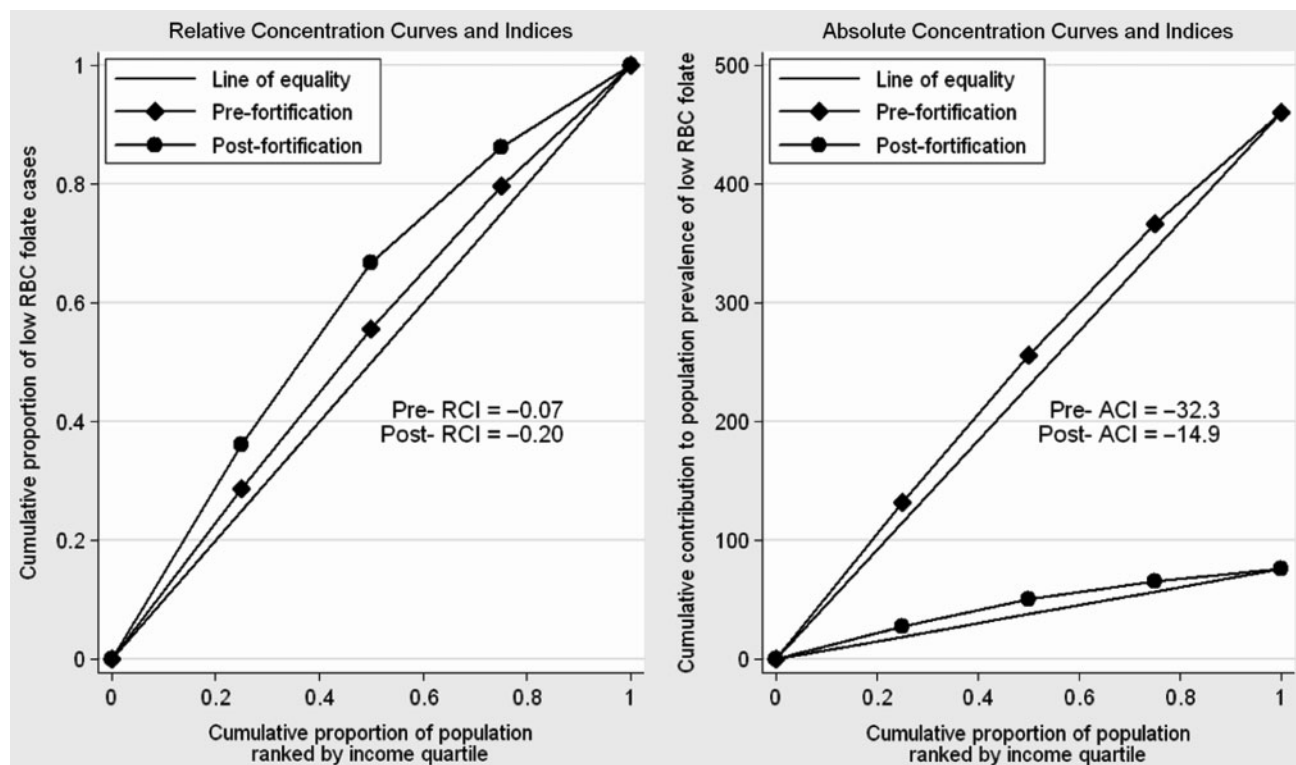
Figure 2 Relative and absolute concentration curves and indices for low RBC folate status by income quartile before and after fortification. National Health and Nutrition Examination Survey, United States, 1991–94 and 1999–2002

Relative Concentration Index (RCI). The Absolute Concentration Index (ACI), on the other hand, declined by 53.9%, reflecting the dramatic decreases in low RBC folate status for all income groups.

Table 1 shows both the crude relative and absolute inequalities in low folate status by income and race/ethnicity before and after fortification. Following fortification, the prevalence of low folate status dropped from 528 to 110/1000 for the lowest income quartile while the change in the highest income quartile was from 374 to 42/1000. The excess prevalence for the lowest income quartile thus dropped from 155 to 67/1000 following fortification, a drop of 57%. Prior to fortification, the prevalence ratio of low folate status for the lowest vs highest income groups was 1.41 (95% CI: 1.32–1.52). Post-fortification, this prevalence ratio increased to 2.59 (95% CI: 2.01–3.32), despite the 57% decrease in absolute excess prevalence.

The bottom portion of Table 1 illustrates similar results by race/ethnicity. The prevalence of low folate status in non-Hispanic blacks dropped by 476/1000 following fortification. For Hispanics, the crude risk fell by 426/1000 and for non-Hispanic whites the risk fell by 289/1000. In absolute terms, the excess prevalence for non-Hispanic blacks compared with non-Hispanic whites fell 58%. Despite these absolute gains, the prevalence ratio for non-Hispanic blacks compared with non-Hispanic whites *increased* following fortification from 1.98 (95% CI: 1.86–2.10) to 4.54

(95% CI: 3.76–5.50). For Hispanics, excess prevalence compared with non-Hispanic whites fell a dramatic 87% from 158 to 20/1000, while the prevalence ratio remained fairly constant at 1.53 (95% CI: 1.22–1.92) vs 1.48 (95% CI: 1.38–1.59) prior to fortification.

Table 2 shows the relative prevalence ratio of low RBC folate status adjusted for age, sex, race/ethnicity and income quartile based on a poisson regression model. These models confirm our unadjusted results, showing that the prevalence ratio of low RBC folate status increased for non-Hispanic blacks vs non-Hispanic whites and the lowest vs the highest income quartile following fortification. For non-Hispanic blacks compared with non-Hispanic whites, the prevalence ratio for low folate status increased from 1.64 (95% CI 1.42–1.89) to 3.75 (95% CI 2.83–4.98) after fortification. For the bottom income quartile compared with the top, the relative ratio increased from 1.27 (95% CI 1.12–1.43) to 2.08 (95% CI 1.60–2.70).

Table 2 also shows absolute prevalence differences before and after fortification adjusted for age, sex, race/ethnicity and income quartile. We see a similar pattern to the unadjusted results, whereby absolute differences in the prevalence of low RBC folate status decline steeply after fortification. The estimated excess prevalence for non-Hispanic blacks compared with non-Hispanic Whites fell 48%, and the excess prevalence for the lowest vs highest income quartile fell 67%.

Table 1 Distribution of cases of low RBC folate (<362.2 nmol/l) by income and race/ethnicity before and after fortification, National Health and Nutrition Examination Survey 1991–94 and 1999–2001, United States, ages 25 and older

	Rate per 1000 (95% CI)	Excess prevalence per 1000 (95% CI)	Crude relative ratio (95% CI)
Income			
Pre-fortification (1991–1994)			
Bottom income quartile	528 (507–549)	155 (124–186)	1.41 (1.32–1.52)
3rd income quartile	496 (472–520)	123 (90–156)	1.33 (1.23–1.44)
2nd income quartile	442 (418–467)	69 (36–102)	1.18 (1.09–1.29)
Top income quartile	374 (351–396)	0	1
Post-fortification (1999–2001)			
Bottom income quartile	110 (91–128)	67 (47–87)	2.59 (2.01–3.32)
3rd income quartile	93 (79–107)	51 (35–66)	2.19 (1.73–2.79)
2nd income quartile	59 (48–69)	16 (3–29)	1.38 (1.07–1.79)
Top Income Quartile	42 (34–50)	0	1
Race/ethnicity			
Pre-fortification (1991–1994)			
Non-hispanic black	647 (626–667)	320 (293–346)	1.98 (1.86–2.10)
Hispanic	484 (461–507)	158 (129–186)	1.48 (1.38–1.59)
Non-hispanic white	327 (310–344)	0	1
Post-fortification (1999–2001)			
Non-hispanic black	171 (152–190)	134 (114–153)	4.54 (3.76–5.50)
Hispanic	58 (48–67)	20 (9–31)	1.53 (1.22–1.92)
Non-hispanic white	38 (32–44)	0	1

Table 2 Adjusted relative and absolute differences in prevalence of low RBC folate (<362.6 nmol) pre- and post-folic acid fortification by race/ethnicity and income quartile, National Health and Nutrition Examination Surveys, 1991–94 and 1999–2002

	Pre-fortification (1991–94) Prevalence ratio (95% CI)	Post-Fortification (1999–2002) Prevalence ratio (95% CI)	Pre-fortification (1991–94) Absolute difference (per 1000) (95% CI)	Post-fortification (1999–2002) Absolute difference (per 1000) (95% CI)
White	Reference	Reference	Reference	Reference
Black	1.64 (1.42–1.89)	3.75 (2.83–4.98)	233 (180–286)	121 (96–146)
Hispanic	1.21 (0.99–1.49)	1.18 (0.89–1.76)	73 (−13–160)	8 (−9–26)
Top income quartile	Reference	Reference	Reference	Reference
2nd income quartile	1.12 (1.01–1.23)	1.28 (1.0–1.64)	48 (15–80)	6 (−4–18)
3rd income quartile	1.22 (1.09–1.37)	2.07 (1.59–2.71)	89 (46–133)	36 (17–55)
Bottom income quartile	1.27 (1.12–1.43)	2.08 (1.60–2.70)	124 (77–170)	41 (20–61)
Observations	7671	7288	7671	7288

Also adjusted for age and gender.

Discussion

Few public health interventions are as far reaching as fortification of the national food supply. While previous work has documented general trends in folate status following FDA mandated fortification,[16–18] this study explicitly examined changes in relative and absolute disparities in folate status by race/ethnicity and income following fortification. The results of this study confirm that all income and racial/ethnic groups in the US benefited in absolute terms from the FDA mandated

folic acid fortification policy that took affect January 1998. Mean levels of RBC folate increased dramatically in all groups, with a consequent drop in the percentage of individuals classified as having low RBC folate. This large overall improvement lead to a dramatic decline in absolute income and racial inequalities in low RBC folate status following fortification. Nonetheless, those individuals remaining with low RBC folate status following fortification were more concentrated in groups with lower income and non-Hispanic black race.

Lynch et al.[29] have recently highlighted the importance of examining social disparities based on absolute risk measures such as the excess risk difference, since relative measures can emphasize differences in risk across groups that do not necessarily account for the majority of cases of the outcome of interest. This can occur when the risk factor accounting for a majority of cases of a particular outcome does not vary significantly by subgroup. When the major risk factor is eliminated or greatly reduced, any remaining group differences in risk may appear large on the relative scale, even though those risk factors account for very few total cases in the populations.[29] This scenario parallels our pre- and post-fortification population, where the fortification intervention has broadly reduced the largest risk of low RBC folate status, namely low dietary intake of folic acid. Because risk has dropped so precipitously for all groups, remaining risk differences across income or race can look large on the relative scale even when the total number of cases has been greatly reduced.

Recent work by Keppel employed a relative measure of disparity to identify the 10 largest racial and ethnic health disparities in the US.[30] Keppel acknowledges the limitations of such a relative approach, since the absolute differences and thus the true public health impact are not revealed from such a perspective. While relative measures such as those used by Keppel are necessary to compare inequalities in outcomes measured on different scales, our study further highlights the risk in assuming that the size of a relative association provides information on the public health significance. The strength of a relative measure depends upon the distribution of complementary causal components in a population and is population dependent, therefore.

Despite the large improvements in overall levels of folate following fortification, disparities, whether measured by an absolute or relative metric, still persist. What factors might account for the remaining racial/ethnic and income differences in folate status? Apart from enriched grains, legumes and vegetables (especially leafy greens) are important dietary sources folate.[19] There is some evidence of socioeconomic differences in diet and nutrition. Lower income, lower educational attainment and non-Hispanic black ethnicity are associated with lower intake of fruits, vegetables and essential nutrients, and higher intake of total fat in the US.[31–34] Similar patterns have been found in other developed countries such as Britain, Australia, Denmark, Switzerland and The Netherlands.[35–41] A growing literature is examining the role that neighbourhoods and access to healthy foods might play in these disparities.[31,42,43] Studies of racial and ethnic differences in folate intake from different sources suggests that differences in folic acid supplement intake account for a majority of racial/ethnic disparities in folate levels in the US. These studies show that food folate intake means and medians are quite similar across racial/ethnic groups both before and after fortification, while intake from supplements is dramatically higher for non-Hispanic whites.[18,44]

Recent work has shown that despite fortification, most women still do not consume enough folic acid to meet the Institute of Medicine's recommendation of 400 µg/day to reduce the risk of neural tube defects and these rates vary significantly by race/ethnicity.[44] Since clinically relevant disparities in folic acid and folate levels still persist, should public health researchers push for fortification levels to be increased? There is evidence that many products may contain higher levels of folic acid than required by FDA regulation, leading to a higher increase in folic acid intake from fortified foods than was expected by the FDA.[19,45] This has contributed to concern that fortification could raise intake above safe limits for some individuals, which can mask B12 deficiency and lead to irreversible neurological damage, especially in the elderly.[46,47] Currently, no database exists in the US that contains information on the amount of folic acid contained in foods, and manufacturer food labels have been found to be unreliable.[19,45] This makes estimating the potential effects of higher fortification levels difficult, and higher levels of mandated fortification would likely be controversial. Remaining income and racial/ethnic disparities will likely need to be addressed by health care professionals and public health approaches that encourage targeted consumption of folic acid supplements, especially for women of child-bearing ages and those in high risk socioeconomic and race/ethnic groups.

There are several considerations regarding the interpretation of our study findings. First, our analysis does not examine changes in other trends such as dietary or supplement intake by subgroup that might also have contributed to changes in folate disparities over the time period examined. Nevertheless, our goal was to examine the potential for a far-reaching policy such as folic acid fortification to reduce disparities in folate status above and beyond the influence of other concurrent changes in behaviours or other risk factors over this period. Recent work has examined specific sources of racial/ethnic differences in folate intake such as supplement use before and after fortification, and future work could do the same for income differences. Another limitation is that a one-time measurement of economic status, such as income, may be measured with error and/or not reflect broader dimensions of SES such as wealth, thus underestimating the relationship

between SES and folate status both before and after fortification.

The 1998 FDA folic acid fortification policy was a successful example of Geoffrey Rose's goal of improving population health by shifting the entire distribution of a health risk rather than exclusively targeting high risk individuals.[48] Nonetheless, it is notable that even with an intervention as aggressive as fortifying the food supply, neither absolute levels of population prevalence or disparities in the prevalence of low folate status have been completely eliminated. Given the difficulty in reducing disparities to zero even with such a large-scale intervention, it is important for public health officials to track absolute as well as relative disparities when prioritizing the health disparities that should receive the greatest attention and resources.

Acknowledgements

KEY MESSAGES

- In the period following folic acid fortification in the US, the absolute prevalence of low RBC folate fell dramatically for all racial/ethnic and income groups.

- While absolute disparities in low RBC folate status by race/ethnicity and income fell following fortification, relative measures of inequality increased as the prevalence of low RBC folate status became concentrated in more disadvantaged groups.

- Targeting of high risk populations is likely needed to eliminate remaining folate disparities in the US.

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