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A cost-effectiveness analysis of folic acid fortification policy in the United States

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Abstract

Objective: To quantify the health and economic outcomes associated with changes in folic acid consumption following the fortification of enriched grain products in the USA.
Design: Cost-effectiveness analysis.
Setting: Annual burden of disease, quality-adjusted life years (QALY) and costs were projected for four steady-state strategies: no fortification, or fortifying with 140, 350 or 700 μg folic acid per 100 g enriched grain. The analysis considered four health outcomes: neural tube defects (NTD), myocardial infarctions (MI), colon cancers and B_{12} deficiency maskings.
Subjects: The US adult population subgroups defined by age, gender and race/ethnicity, with folate intake distributions from the National Health and Nutrition Examination Surveys (1988–1992 and 1999–2000), and reference sources for disease incidence, utility and economic estimates.
Results: The greatest benefits from fortification were predicted in MI prevention, with 16 862 and 88 172 cases averted per year in steady state for the 140 and 700 μg fortification levels, respectively. These projections were between 6261 and 38 805 for colon cancer and 182 and 1423 for NTD, while 15–820 additional B_{12} cases were predicted. Compared with no fortification, all post-fortification strategies provided QALY gains and cost savings for all subgroups, with predicted population benefits of 266 649 QALY gained and $3·6 billion saved in the long run by changing the fortification level from 140 μg/100 g enriched grain to 700 μg/100 g.
Conclusions: The present study indicates that the health and economic gains of folic acid fortification far outweigh the losses for the US population, and that increasing the level of fortification deserves further consideration to maximise net gains.

Keywords
Cost-effectiveness analysis
Folic acid fortification
Prenatal and maternal nutrition
Health policy

Increasing the intake of folate or folic acid during preconception and early in pregnancy can significantly reduce the risk of neural tube defects (NTD) in newborns[1,2]. Increased intake may also reduce the risk of myocardial infarction (MI) and colon cancer[3–16] and increase the risk that symptoms of vitamin B_{12} deficiency are masked[4,5,7,12], thereby allowing the neurological manifestations of the disease to progress[4].

In 1998, the US Food and Drug Administration mandated that manufacturers add 140 μg of folic acid per 100 g of enriched cereal-grain product[11,13,14], and several studies have shown that such fortification provides substantial health and economic benefits[6,8,9,13,14,17–21]. However, the potential economic and health effects of this and alternative fortification policies have not been evaluated using national post-policy data adjusted for measurement error, while considering all four relevant health outcomes among population subgroups.

Accordingly, the present analysis quantifies the projected health and economic outcomes for NTD, MI, colon cancers and B_{12} maskings associated with the changes in folic acid consumption following fortification in the USA, as well as for alternative fortification levels.

Methods

Overview

Population-wide disease burden and the associated costs and quality-adjusted life years (QALY) were projected under four scenarios: no fortification, or fortification with

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140, 350 or 700 μg of folic acid per 100 g enriched grain. The no-fortification strategy reflects the pre-fortification levels of folate intake, the 140 μg strategy reflects the current post-fortification intake in the USA, and fortifying with 350 and 700 μg are hypothetical scenarios[13,19,20]. The four scenarios differ only in terms of the distribution of folate intake in the population, which we model in four categories: ≤200, 201–300, 301–400 and >400 μg/d.

For each scenario, we projected the steady-state number of NTD, MI, colon cancers and B_{12} maskings among a US population of non-institutionalised, non-Hispanic white (heretofore referred to as 'white'), non-Hispanic black ('black') and Mexican-American persons aged 15 years or older. Other racial/ethnic subgroups were not included because of insufficient sample size on which to base folate intake estimates. For each folate intake category, we estimated age-, gender- and race/ethnicity-specific risks of developing each of the four health outcomes. We then assigned lifetime QALY losses and disease-related net costs for each health outcome, using either published estimates or a Markov modelling approach, to calculate the population-wide impact of each strategy.

Folate intake distributions

Estimates of population-based folate intake distributions were previously derived using food and dietary supplement data from two periods of the National Health and Nutrition Examination Surveys (NHANES)[22]. Briefly, data from NHANES III (1988–1994) were used to estimate pre-fortification food folate intake, and those from NHANES 1999–2000 were used to estimate both dietary supplement intake and post-fortification food folate intake. Because nutrient intake data are based primarily on one 24 h dietary recall measure, which does not represent an individual's average long-term daily intake, population distribution estimates of dietary folate intake were corrected for measurement error using a sub-sample of NHANES III subjects who had provided two 24 h recalls. Total folate intake distributions before and after the fortification policy, corrected for measurement error, are shown in Fig. 1 and in the Appendix. Folate intake for the two hypothetical scenarios was estimated as the product of the pre–post differences in corrected food folate intake and the ratio of the higher to the current levels (e.g. 350/140 for the 350 μg strategy), plus the post-fortification supplement intake.

Disease incidence

Annual incidence of the four disease outcomes prior to fortification was estimated as a function of age range, gender and race/ethnicity (Table 1). When data were not available for the Mexican-American population, the rates for the Hispanic population were used.

All women between the ages of 15 and 44 years[23–26] were considered at risk for an NTD-affected pregnancy. NTD incidence as a function of race/ethnicity was based on estimates from the Centers for Disease Control and Prevention (CDC) of 10·6 cases of spina bifida and anencephaly per 10 000 live births[9,27]. Live birth rates from the National Center for Health Statistics[28] were used to calculate NTD incidence per 100 000 women aged 15–44 years.

MI incidence was based on calculations by gender and age from the Framingham Risk Equations[29]. The relative racial/ethnic distribution of MI incidence was assumed to be the same as that of CHD-specific death among each age and gender-specific subgroup[30]. Subgroup-specific annual colon cancer incidence rates were derived from the Surveillance, Epidemiology, and End Results Program (SEER) of the National Cancer Institute[31–33].

Vitamin B_{12} masking was defined as the delayed diagnosis of B_{12} deficiency followed by the development of neurological complications. Estimates of masking risk incorporated the probability of consuming greater than 1000 μg folate/d[22] – the 'tolerable upper intake level' for folic acid[10,11] – and the risk of pernicious anaemia (PA) – a common cause of B_{12} deficiency[19,34,35].

Folate-specific incidence of each disease was calculated by using data on the percentage of the population in each folate intake category (Fig. 1) and the relative risks of disease by folate intake to split out the subgroup-specific disease rates. The risk of NTD was reduced by 50 % for women with folate intake levels of greater than 400 μg/d[1,2,13,14,19,20], and the relative reduction of MI risk for individuals with folate intake greater than 400 μg/d was 24 %[36]. The risk ratios for colon cancer diagnosis by folate intake were 0.92, 0·79 and 0·69 for 201–300, 301–400 and >400 μg/d, respectively, compared with ≤200 μg/d[37]. Relative risks for MI and colon cancer were assumed to be the same for men and women.

Valuing outcomes

The number of disease events associated with each strategy were estimated as the product of incidence and national population estimates for each subgroup[38]. The numbers of events were multiplied by the associated QALY lost and net costs per event (Table 2) to estimate the net health and economic impact of each fortification strategy. All QALY and cost estimates were discounted by 3 % per year.

Health related quality-of-life

Estimates of QALY lost for NTD and B_{12} masking outcomes were based on a CDC cost-effectiveness analysis[20] that used the Quality of Well-Being Index[39]. To estimate the QALY lost associated with MI and colon cancer we used a Markov modelling approach in which we incorporated disease-specific mortality, health-related quality-of-life weights and mortality from other causes[40–42]. For MI, we assumed the same utility for patients with coronary artery disease (CAD) of 0·84, calculated from previous analyses as the mean of mild and severe angina, weighted by the proportion of angina patients with CAD[43–45]. For colon cancer, life expectancy after

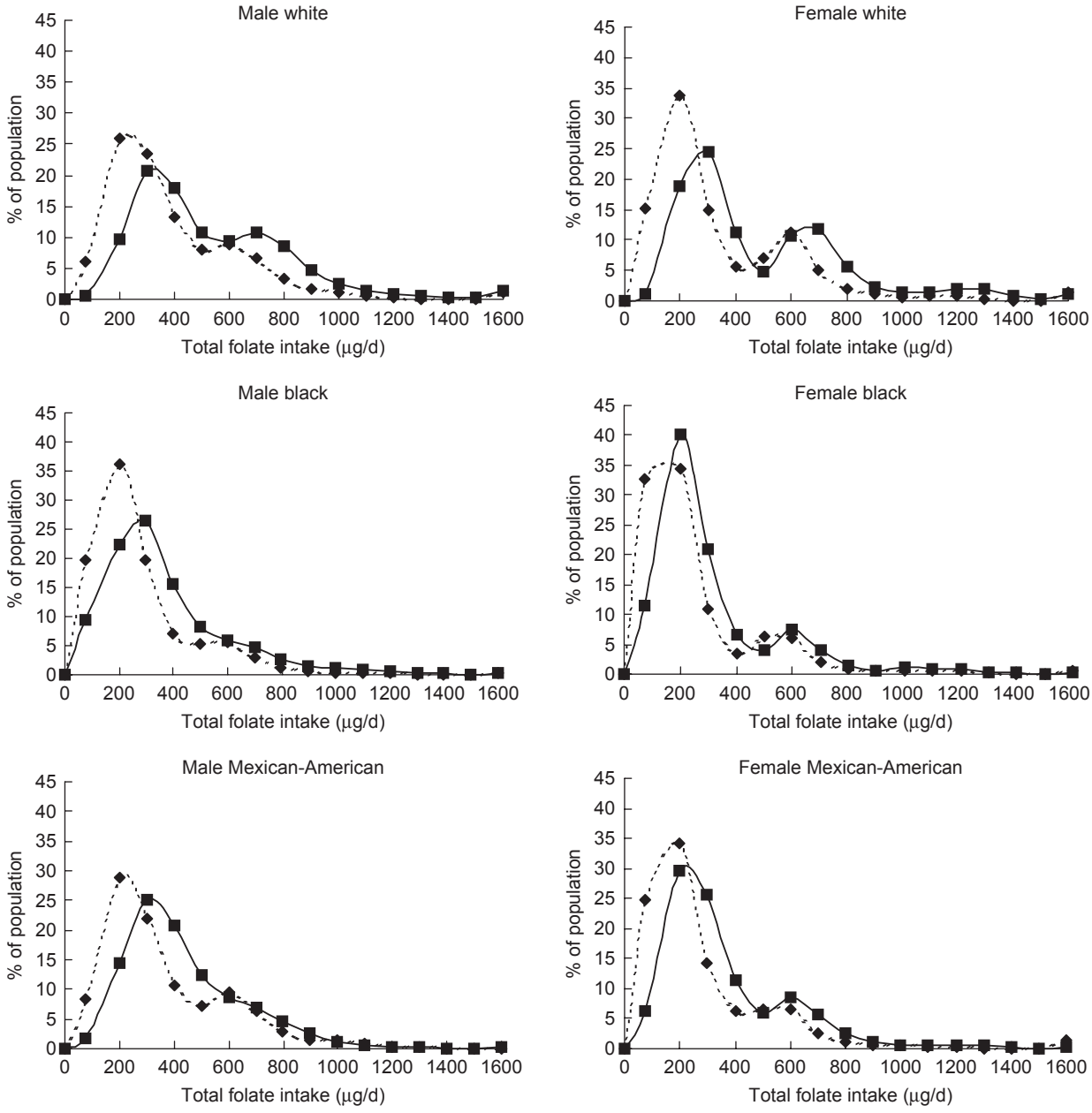

Fig. 1 Daily total folate intake distributions pre- *v.* -post fortification by gender and race/ethnicity, corrected for measurement error (···◆···, pre; —■—, post). Reprinted with permission from the American Public Health Association from Bentley TGK, Willett WC, Weinstein WC and Kuntz KM. Population-level changes in folate intake by age, gender, and race/ethnicity after folic acid fortification[22]

diagnosis was weighted by stage-specific mortality and we assumed a stage-weighted utility of 0·76[46].

Costs

All costs were adjusted to 2005 dollars using the Consumer Price Index. For costs incurred with NTD, estimates from a published analysis[21] were used, weighted for relative proportions of spina bifida and anencephaly[9]. Costs incurred with MI events incorporated short-term care[43] as well as annual outpatient, medications and diagnostic costs for a typical CAD patient[45,47,48], which were assumed to be applicable to MI patients. Costs incurred with colon cancer incorporated stage-weighted estimates from the Institute of Medicine[49–56], and those associated with cases of masked B_{12} deficiency were based on calculations by the CDC[20]. Estimates of annual fortification costs for the 140 μg fortification strategy ($3·3 million) were based on those used by Grosse and colleagues[21], and those for the two hypothetical scenarios ($6·0 and $10·6 million for 350 μg and 700 μg fortification strategies, respectively) incorporated the fixed cost estimates from Grosse *et al.* and the CDC's estimates of bulk folic

Table 1 Estimates of annual disease risk per 100 000 persons*

	Men			Women		
	White†	Black†	Mexican-American	White†	Black†	Mexican-American
Neural tube defects						
15–44 years	–	–	–	6·10	4·58	13·31
Myocardial infarctions						
15–44 years	60·6	89·8	23·6	19·1	50·7	6·3
45–64 years	698·3	1100·0	449·7	349·0	918·1	253·3
65+ years	1627·7	2047·7	1306·8	886·3	1363·8	759·4
Colon cancer						
15–44 years	2·98	3·13	1·96	2·21	3·70	1·47
45–64 years	48·51	59·86	24·05	34·53	49·69	20·88
65+ years	247·59	222·24	147·80	199·03	230·91	96·50
Vitamin B_{12} masking‡						
15–44 years		0·012			0·029	
45–64 years		0·078			0·185	
65+ years		0·181			0·427	

*Some age categories have been combined for ease of presentation.
†Non-Hispanic white and non-Hispanic black.
‡Annual rate of vitamin B_{12} masking and pernicious anaemia and total folate intake $>1000\,\mu g/d$.

Table 2 Net costs incurred and QALY lost associated with NTD, MI, colon cancer and vitamin B_{12} masking events*

			Ranges for sensitivity analyses		
Disease outcome	Men	Women	Men	Women	Source
QALY					
NTD	–	18·91	–	13·0–28·0	Mersereau *et al.* (2004)[9]; Kelly *et al.* (1996)[20]; Kaplan *et al.* (1988)[39]
MI	2·12	2·03	1·17–3·07	1·12–2·94	Abby *et al.* (1998)[40]; Arias (2004)[41]; Thom *et al.* (2006)[42]; Cohen *et al.* (2001)[43]; Nease Jr *et al.* (1995)[44]; Kuntz *et al.* (1999)[45]
CC	2·54	2·96	1·40–3·68	1·63–4·29	Arias (2004)[41]; Ness *et al.* (1999)[46]
B_{12}	0·31		0·17–0·45		Kelly *et al.* (1996)[20]; Kaplan *et al.* (1988)[39]
Costs (thousands of dollars)					
NTD	–	$185·5	–	$5·0–$185·5	Mersereau *et al.* (2004)[9]; Grosse *et al.* (2005)[21]
MI	$32·6	$32·7	$5·0–$32·7		Thom *et al.* (2006)[42]; Cohen *et al.* (2001)[43]; Kuntz *et al.* (1999)[45]; Wong *et al.* (1990)[47]; Stinnett *et al.* (1996)[48]
CC	$31·8		$5·0–$31·8		Frazier *et al.* (2000)[49]; Khandker *et al.* (2000)[50]; Loeve *et al.* (2000)[51]; Ness *et al.* (2000)[52]; Pignone *et al.* (2005)[53]; Pignone *et al.* (2002)[54]; Vijan *et al.* (2001)[55]; Wagner *et al.* (1996)[56]
B_{12}	$5·3		$5·0–$50·0		Kelly *et al.* (1996)[20]

QALY, quality-adjusted life years; NTD, neural tube defects; MI, myocardial infarctions; CC, colon cancer; B_{12}, vitamin B_{12} masking.
*Assuming a 3% discount rate.

acid costs, adjusted for cost declines since 1996[20,21]. The fortification costs were doubled in sensitivity analysis.

Results

Incidence

Figure 2 shows the projected per cent decline in annual disease incidence for NTD, MI and colon cancer, comparing the post-fortification scenarios with pre-fortification.

For NTD-affected pregnancies, average annual incidence for all racial/ethnic groups was predicted to decrease by 5%, 24% and 39% for the 140, 350 and 700 μg/100 g fortification scenarios, respectively. Mexican-Americans were consistently projected to have the largest per cent declines and blacks the lowest. Average annual MI incidence was predicted to decrease by 2%, 8% and 14% for the lowest-to-highest post-fortification levels, while projected declines of colon cancer were 2%, 11% and 15%. The racial/ethnic subgroups with the greatest predicted benefit were those with the largest post-fortification increases in per cent reaching the risk-reduction folate intake thresholds for each disease outcome. Among older females, for example, whites were estimated to experience the largest increases in per cent consuming greater than 400 μg total folate/d, and were predicted to experience the greatest declines in disease incidence. On the other hand, older black females were predicted to experience a 0–1% increase in MI incidence, due to a decrease in the proportion consuming more than 400 μg/d.

Table 3 shows the projected total annual number of events averted, QALY gained and costs incurred for the

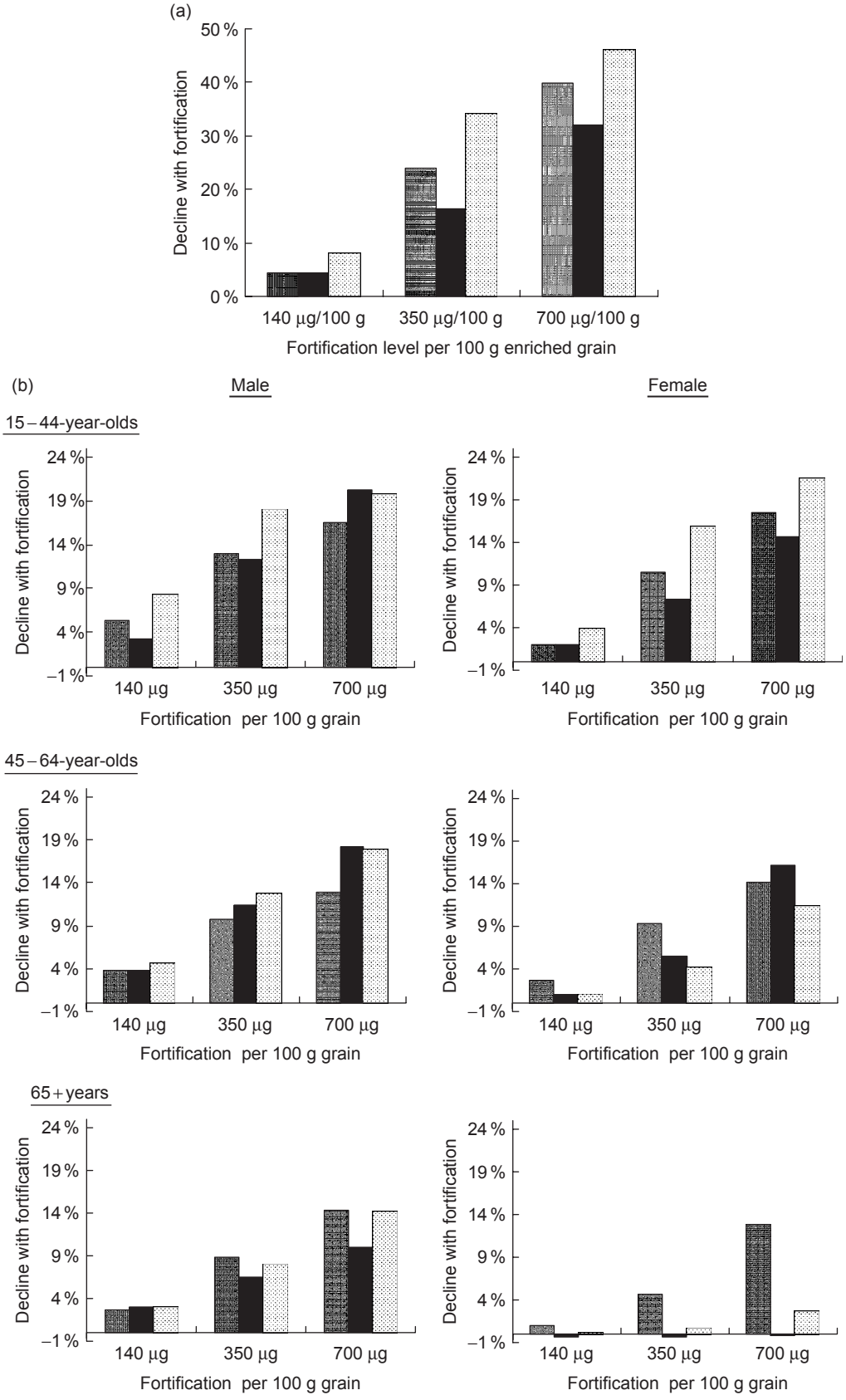

Fig. 2 (a) Per cent decline in annual incidence of neural tube defects, (b) myocardial infarctions and (c) colon cancers, after folic acid fortification, by age, gender, race/ethnicity and fortification strategy (▒, white; ■, black; □, Mexican-American)

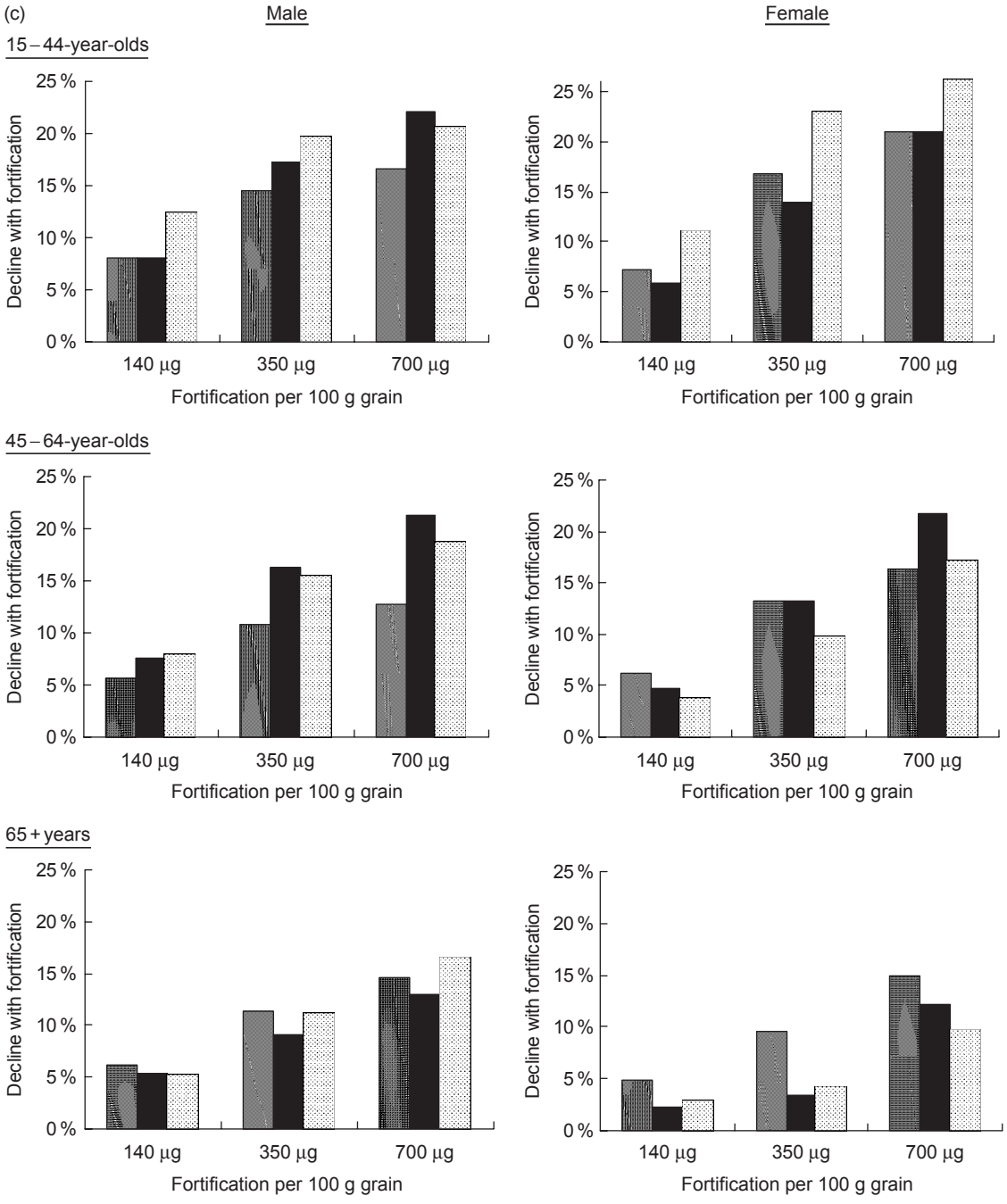

Fig. 2 *Continued*

US population. The model predicted that the greatest benefits would be in MI prevention, with 16 862 cases averted per year at the 140 µg fortification level and 88 172 at the highest fortification level. Between 6261 and 38 805 annual cases of colon cancer and 182 and 1423 annual NTD would be prevented, while 15–820 new annual cases of B_{12} masking would be caused.

Quality-of-life and cost measures

Fortification was predicted to be cost-saving and to provide positive net QALY gains at all fortification levels, and the 700 µg/100 g strategy was projected to have the largest health gain and cost savings, with over 320 000 QALY gained and over $4 billion saved per year (Table 3). The predicted annual gains of over 26 000 QALY and savings of over $263 million from NTD prevention alone far outweighed the QALY lost and costs incurred from B_{12} masking and fortification itself, which combined were predicted to result in annual losses of fewer than 260 QALY and $15 million even at the highest fortification level. QALY gains and cost savings due to MI and colon cancers averted each year would be even greater, with MI

Table 3 Annual QALY and costs associated with US folic acid fortification, by fortification strategy and outcome

Strategy*	NTD	MI	CC	B_{12}	Net	
Events averted						
140 μg/100 g	182	16 862	6261	−15	23 289	
350 μg/100 g	883	53 011	20 110	−184	73 821	
700 μg/100 g	1423	88 172	38 805	−820	127 579	
QALY gained						
140 μg/100 g	3436	35 458	17 402	−5	56 291	
350 μg/100 g	16 697	111 121	57 403	−57	185 165	
700 μg/100 g	26 899	184 149	112 146	−254	322 940	
					Fortification costs	Net costs
Costs incurred (millions of dollars)†						
140 μg/100 g	−$33·7	−$550·8	−$199·4	$0·1	$3·3	−$780·5
350 μg/100 g	−$163·8	−$1731·5	−$640·4	$1·0	$6·0	−$2528·8
700 μg/100 g	−$263·9	−$2880·0	−$1235·7	$4·3	$10·5	−$4364·8

QALY, quality-adjusted life years; NTD, neural tube defects; MI, myocardial infarctions; CC, colon cancer; B_{12}, vitamin B_{12} masking.
*Strategies labelled by amount of fortification in μg of folic acid added per 100 g of enriched grain product.
†Disease-specific costs do not include fortification costs.

Table 4 Annual QALY and costs (millions of dollars) associated with US folic acid fortification, by gender, age and race/ethnicity

	Non-Hispanic white		Non-Hispanic black		Mexican-American	
Strategy*	QALY	Costs	QALY	Costs	QALY	Costs
Men aged 15–44 years						
140 μg/100 g	3041	−$45·23	506	−$7·50	265	−$3·86
350 μg/100 g	7241	−$108·51	1849	−$27·84	551	−$8·11
700 μg/100 g	9078	−$135·52	2996	−$45·19	600	−$8·72
Men aged 45–64 years						
140 μg/100 g	12 939	−$194·42	2336	−$35·05	642	−$9·65
350 μg/100 g	31 967	−$482·75	6846	−$103·34	1700	−$25·68
700 μg/100 g	41 703	−$630·77	10 745	−$162·67	2358	−$35·68
Men aged 65+ years						
140 μg/100 g	13 204	−$190·82	1663	−$24·61	334	−$4·94
350 μg/100 g	38 477	−$569·02	3394	−$50·56	860	−$12·79
700 μg/100 g	59 677	−$888·08	5129	−$76·52	1483	−$22·15
Women aged 15–44 years						
140 μg/100 g	2627	−$27·21	532	−$6·18	1068	−$10·17
350 μg/100 g	13 404	−$141·13	1923	−$22·68	4426	−$43·23
700 μg/100 g	22 210	−$233·64	3722	−$43·99	5964	−$57·89
Women aged 45–64 years						
140 μg/100 g	5335	−$78·24	802	−$11·60	113	−$1·61
350 μg/100 g	16 605	−$251·04	3998	−$60·75	412	−$6·10
700 μg/100 g	24 415	−$372·64	10 916	−$169·90	1017	−$15·45
Women aged 65+ years						
140 μg/100 g	6295	−$79·78	87	−$0·38	48	−$0·58
350 μg/100 g	18 833	−$262·02	192	−$1·52	95	−$1·26
700 μg/100 g	42 384	−$618·09	924	−$9·45	279	−$3·86

QALY, quality-adjusted life years.
*Strategies labelled by amount of fortification in μg of folic acid added per 100 g of enriched grain product.

prevention alone predicted to save 184 000 QALY and $3 billion annually at the 700 μg level.

The model predicted the 700 μg fortification level to yield the greatest net QALY gains and cost savings for all age, gender and racial/ethnic subgroups (Table 4). Benefits were projected to increase with age, with males predicted to benefit more than females in most populations. At all fortification levels, the highest gains were expected in white males aged 65 years and older, with predicted annual gains of over 13 000 QALY and $190 million at the currently enacted level and over 59 000 QALY and $888 million at the 700 μg level. Among racial/ethnic categories, whites were projected to experience the greatest gains and Mexican-Americans the fewest.

Sensitivity analyses

This analysis projected substantial fortification benefits despite predicting at the currently enacted fortification level a 5% reduction in NTD rates, which is far less than the 20–30% declines estimated from observed data[6,8,9,17]. Due to lack of adequate dose–response data, the model allows only for reduced NTD risk at folate consumption of >400 μg/d, yet there may be benefits in NTD risk-reduction at lower levels.

To evaluate the effect of this possibility, three additional NTD dose–response assumptions were tested (Fig. 3a), allowing women to benefit from folate intake over 200 μg/d[57–60]. Curve A assumes a dose–response gradient similar to that of colon cancer – albeit through different

mechanisms – while B and C were calculated by decreasing the risk ratios of function A by 25% and 50%, respectively. All three functions maintained the base-case assumption of a 50% reduced risk for intake >400 μg/d compared with ≤400 μg/d. Given the use of a similar 400 μg/d threshold for reducing the risk of MI by folate intake and evidence of potential benefit at lower levels without a threshold effect[61], an analogous sensitivity analysis on this dose–response function was performed (Fig. 3b).

When risk reduction benefits for NTD and MI were allowed at lower folate intakes, the model predicted that more events would be prevented and there would be greater reductions in disease incidence. The use of NTD function B predicted at the 140 μg level a 23% risk reduction, the closest approximation to observed data. When applying these functions for both NTD and MI dose–response, the 700 μg strategy was predicted to save 370 000 QALY and $5 billion, compared with 320 000 QALY and $4 billion in the base case (Table 5).

To evaluate the effect of the model's other assumptions, a range of estimates were applied for QALY and costs (Table 2), relative risk of NTD-affected pregnancy (10% and 90%), masking risk (30–200% of base case), female PA risk (150% of base case)[34,35,62], and discount rate (0% and 5%). Even with extreme estimates that would bias results away from fortification, none of these variations – applied individually or concurrently – changed the rankings between strategies or the conclusion that QALY gains and cost savings would result from fortification up to the highest level considered. When biasing against fortification overall, the conclusions remained the same, even though the predicted QALY gained and costs saved were smaller: for all subgroups, fortification would remain cost saving, and the 700 μg strategy would provide the greatest total QALY gains, with $486 million saved and over 196 000 QALY gained.

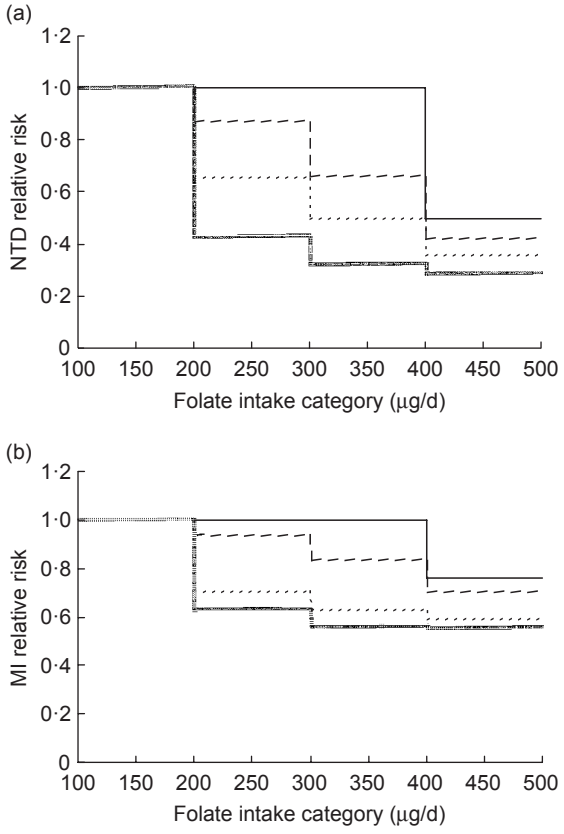

Fig. 3 Dose–response assumptions used in sensitivity analyses for (a) neural tube defects (NTD) and (b) myocardial infarctions (MI). Risk is relative to an average folate intake of <200 μg per day (—, base case; ----, A; ·····, B; ▒, C)

Discussion

It was predicted for three post-fortification strategies that the projected health and economic benefits gained from preventing NTD, MI and colon cancers in the US population far exceeded those lost due to fortification itself and increased B_{12} masking risk, with significant variations by age, gender and race/ethnicity. For all health outcomes, the QALY and cost benefits to whites were projected to be significantly greater than those to blacks and Mexican-Americans. With predicted population benefits of 322 940 QALY gained and $4·4 billion saved, fortifying at 700 μg/100 g enriched grain product – the highest level considered in this analysis – strongly dominated all other scenarios. The benefits of higher fortification levels were predicted to far outweigh the associated risks for all populations, and in all sensitivity analyses.

Table 5 QALY and costs (millions of dollars) associated with folic acid fortification, using alternative NTD and MI dose-response functions*

	Annual QALY gains					
Strategy†	NTD	MI	CC	B_{12}	Net QALY gain	Annual net costs
No fortification	0	0	0	0	0	$0
140 μg/100 g	15 842	114 532	17 402	−5	147 770	−$2154
350 μg/100 g	28 445	193 475	57 403	−57	279 267	−$3958
700 μg/100 g	33 268	224 325	112 146	−254	369 485	−$5078

QALY, quality-adjusted life years; NTD, neural tube defects; MI, myocardial infarctions; CC, colon cancer; B_{12}, vitamin B_{12} masking.
*NTD dose-response function assumes the following relative risks of NTD-affected pregnancy: 0·36; 0·50 and 0·65 for maternal folate intake of >400, 301–400 and 201–300 μg/d, respectively, compared to ≤200 μg/d. MI dose-response function assumes the following relative risks of MI: 0·59; 0·63 and 0·70 for folate intake of >400, 301–400 and 201–300 μg/d, respectively, compared to ≤200 μg/d.
†Strategies labelled by amount of fortification in μg of folic acid added per 100 g of enriched grain product.

The substantial racial/ethnic differences predicted in disease outcomes were caused primarily by differences in total folate intake. Although disease incidence was not projected to decrease among all populations, this effect was caused by the unrealistic discontinuous risk functions used to avoid interpolating the epidemiological data analysed in risk strata. Targeted supplement-use interventions may be necessary to further mitigate disparities and reduce disease prevalence, and future research should aim to identify racial/ethnic differences in intake of fortified and non-fortified foods.

The results of the present analysis provide evidence for recommending that fortification be increased to at least 700 μg of folic acid per 100 g of enriched grain product, corroborating prior research that predicted greater economic gains at higher fortification levels[20]. The analysis demonstrates that the benefits of higher fortification would exceed the risks even in the most unfavourable subgroups. It also addresses other important considerations by using estimates of folate intake that are national, subgroup-specific, and corrected for the bias caused by the use of 1 d dietary intake data.

There are several limitations to consider when interpreting these results. The use of limited data on the dose–response relationships between folate intake and disease risk may have underestimated the post-fortification health benefits. However, even when using more realistically continuous – albeit uncertain – dose–response assumptions for both NTD and MI, the conclusions of positive benefit–risk trade-offs for all subgroups – and of greater benefit at higher fortification levels – did not change, and the model predicted that more NTD and MI would be prevented and that the NTD reduction would be consistent with that observed post-policy[6,8,9,17].

A related source of uncertainty is that synthetic folic acid is more bioavailable to absorption by the human body than is naturally occurring folate. While this factor can be incorporated using dietary folate equivalents (DFE) – a measure that adjusts intake estimates for these absorption differences – we were unable to include DFE in our analysis due to data limitations. With fortification resulting in greater proportions of intake from synthetic folic acid, the model's use of total folate may thus have caused the benefits of fortification to be underestimated, and the risks to be overestimated. Conversely, because this factor was not considered in estimating folate-specific risks of MI and colon cancer, the benefits for dietary sources of folate may be overstated. The model's projected cost savings associated with fortification may have been underestimated, as lifetime caregiving costs of NTD-affected individuals were not included, reduced costs associated with the proportion of NTD ending in a terminated pregnancy were excluded, and MI costs were used that may not consider the increased costs of today's standards of care. By the same token, we may have overestimated QALY losses due to MI because survival has been improved by today's standards of care. Taken as a whole, it is unlikely that any such positive or negative effects would substantially impact the results of the analysis, or alter the conclusions of overall benefit.

Given the suggestion of possible insignificant or even adverse effects of increased folate intake on MI risk and on colorectal cancer progression among individuals with pre-existing disease[3,63–67], the benefits to MI as well as to colon cancer could be less than predicted by our model. However, recent evidence also indicates a positive folate–stroke association[68–70] and an overall cardiovascular benefit[16], and our results may thus underestimate benefits. The potential risk to colorectal cancer progression may appear to be supported by recent published research indicating a possible temporary delay in the ongoing decline in colorectal cancer incidence[71], but this could be in part an artefact of increased use of colonoscopy. In addition, a recent report from the National Cancer Institute indicates that not only is incidence still decreasing at 2 % per year, but also mortality – which one would expect to increase if fortification were accelerating growth of existing tumours – is also declining at an annual rate of close to 4 %[72]. This analysis is thus important for motivating further trials among people without existing disease, while simultaneously suggesting caution among policymakers who may be considering potential fortification increases.

By not formally allowing competing risks between disease outcomes while allocating benefit for each disease event averted, the model may have double-counted some of the benefits gained because multiple events may be occurring per individual. The analysis did not incorporate potential associations of folic acid intake with increased twinning[73–76], with other cancers[77–79], or with cognitive decline[80]. Given the lack of consistent evidence for such outcomes, it is unclear in which direction their inclusion may impact results, yet the strength of the findings from our analysis suggests that the conclusion of overall benefit associated with increased folate intake would not be changed.

While these benefit–risk estimates assume a steady state, in reality fortification's effect on NTD and B_{12} maskings would be relatively immediate, while that for MI and colon cancer could take up to 5[36] and 15 years[37], respectively. However, not only were fortification's benefits for NTD alone predicted to outweigh the potential B_{12} masking risk, this risk may in fact have been overestimated given our use of a conservative risk threshold of 1000 μg/d despite no evidence of harm below 5000 μg/d[10]. It is also important to note that while there is conflicting evidence regarding whether masking has increased since fortification[81–83], current medical knowledge regarding appropriate screening measures for B_{12} deficiency suggests that the fear of delayed diagnosis by physicians may not in fact be realised. The risk, however, may be that symptom improvement due to

masking could reduce patients' likelihood of seeking medical advice until after neurological complications have occurred[84]. Nevertheless, with the low prevalence of potential masking – estimated at 0·09 % in older women before fortification and 0·61 % after[83] – even with conservative estimates our model predicted that this risk would be outweighed by the benefits.

Given the uncertainty involved, future research should clarify the dose–response relationships and benefit–risk associations between folate intake and disease risk. This is especially important for outcomes such as MI, colon cancer, stroke, cognitive decline and B_{12} masking, for which causality has not yet been established; there has been conflicting evidence on potential risks, in particular among individuals with pre-existing disease; or there remains debate over the validity of the evidence[3,16,67–70,81–88]. In addition, future policy decisions may consider B_{12} co-fortification or a more stringent screen for B_{12} deficiency to offset the potentially elevated B_{12} masking risks due to higher fortification, and may evaluate a broader range of fortification levels to better determine the optimal fortification strategy.

In summary, folic acid fortification was implemented in the USA in 1998 to reduce the chance of NTD in newborns. While there are potential risks of increased folate intake to populations with vitamin B_{12} deficiency, there may also be benefits in preventing MI and colon cancer. Overall, in considering the benefit–risk trade-offs of folic acid fortification, the present study suggests that the health and economic gains may outweigh the losses for the US population as a whole, and that additional studies on the potential benefits and hazards associated with folate intake – as well as an in-depth evaluation of the level of fortification – deserve further consideration in order to maximise net gains among all racial/ethnic, age and gender-specific subgroups.

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Appendix: Population total folate consumption by age, gender, race/ethnicity and folic acid fortification level

	Folate intake*															
	No fortification				140 μg/100 g†				350 μg/100 g				700 μg/100 g			
	≤200	201–300	301–400	>400	≤200	201–300	301–400	>400	≤200	201–300	301–400	>400	≤200	201–300	301–400	>400
Males																
Non-Hispanic white (%)																
15–44 years	19	28	17	36	0	17	23	57	0	3	11	86	0	0	1	99
45–64 years	13	21	14	52	3	13	18	66	0	3	9	88	0	0	1	99
65+ years	17	23	15	45	4	19	21	55	0	5	17	78	0	0	1	99
Non-Hispanic black (%)																
15–44 years	26	46	14	14	5	35	33	27	0	8	28	64	0	0	4	96
45–64 years	41	24	12	23	15	27	21	38	2	11	19	68	0	1	5	94
65+ years	49	23	10	19	35	20	12	32	26	16	12	46	19	12	10	59
Mexican-American (%)																
15–44 years	27	35	17	21	2	17	27	54	0	1	6	93	0	0	0	100
45–64 years	25	29	16	29	6	23	24	47	0	5	16	78	0	0	2	98
65+ years	26	28	16	30	13	25	21	41	3	16	20	60	0	4	11	84
Females																
Non-Hispanic white (%)																
15–44 years	41	23	5	31	9	32	20	39	0	7	22	71	0	0	1	99
45–64 years	28	19	8	46	7	21	16	56	0	5	14	80	0	0	1	98
65+ years	23	21	8	48	8	25	15	52	0	11	24	65	0	0	5	95
Non-Hispanic black (%)																
15–44 years	60	18	4	18	31	29	14	26	10	22	20	48	2	8	13	76
45–64 years	52	19	5	24	24	34	14	28	3	23	29	46	0	1	11	88
65+ years	53	23	7	17	41	35	7	16	11	65	7	16	0	23	61	16
Mexican-American (%)																
15–44 years	63	21	4	12	12	35	25	28	0	6	18	77	0	0	1	99
45–64 years	44	21	6	29	25	29	13	33	8	25	22	45	1	8	19	73
65+ years	30	25	12	33	22	29	15	34	11	31	22	36	2	19	36	43

*Folate intake categories defined by total average folate intake in μg/d.
†Strategies labelled by amount of fortification in μg of folic acid added per 100 g of enriched grain product.