Supplementary Discussion

The health benefits of folate biofortified rice in China

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Abstract:

Although genetic modification is still a subject of discussion, both in political and research forums, the widespread adoption of biofortified food crops in China is likely to happen. In the scope of biofortification for improving human nutrition, folate biofortified rice was recently developed as a remedy against folate deficiency and its adverse health outcomes, among which neural-tube defects (NTDs). The objective of this paper is to analyze the potential health benefits of folate enriched rice in China, a rice consuming country characterized by large folate deficiencies. The Disability-Adjusted Life Years (DALY) method is used to calculate the impact of biofortification as the number of DALYs saved due to the reduced number of NTDs. A low and high impact scenario are simulated according to the coverage rate of folate enriched rice consumption. Our findings support folate biofortification of rice as a valuable alternative to increase folate intake and reduce folate deficiency in China. Implementing rice with a folate content of 1,200 µg per 100 g rice in China would increase the total daily folate intake for Chinese women of childbearing age to 1,120 µg, which is almost three times the recommended folate intake. As a consequence, around 116,090 DALYs in the low impact scenario and 257,345 DALYs in the high impact scenario would be saved by implementing biofortified rice. Although rice consumption is lower in northern areas, these regions account for the biggest health impact of biofortification in China. As expected, regions with high NTD prevalence rates, such as Shanxi Province, will benefit most from folate biofortification of rice. Further research is needed to assess the cost-effectiveness of this intervention and to compare different interventions to increase folate intake, such as a campaign to promote folic acid pills intake. Especially in poor, rural regions where other folate interventions are often unsuccessful, folate enriched rice could be an effective, complementary approach to combat folate deficiency.

Key words: Folate biofortified rice; folate deficiency, neural-tube defects; health impact; DALYs; China.

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Abbreviations

CBA, woman of childbearing age
CDPF, Chinese Disabled Person Federation
CNGOIC, China National Grain and Oils Information Center
DALY, Disability-Adjusted Life Year
GAIN, Global Alliance for Improved Nutrition
IDA, iron deficiency anemia
GM, Genetic modification
MOA, Chinese Ministry of Agriculture
MOH, Chinese Ministry of Health
MTHF(R), 5-methyl-tetrahydrofolate (reductase)
NTD, neural-tube defect
PNDC, Chinese Public Nutrition and Development Center
RDI, the recommended daily intake
SGA, State Grain Authority
VAD, Vitamin A deficiency
WHO, World Health Organization
WTO, World Trade Organization
YLL, years of life lost
YLD, years lived in disability

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1. Introduction

Micronutrient malnutrition is a major health problem, affecting more than half of the world population, especially in developing countries. Biofortification, enhancing the micronutrient content of staple food crops, is considered as an excellent alternative to other micronutrient interventions, such as supplementation, industrial fortification and diet diversification. In 2007, Storozhenko *et* al[1] developed rice with a high folate content as an alternative means to tackle folate deficiency. Folate deficiency, characterized by a below normal folate intake (< 400 µg per day), is an important type of micronutrient deficiency that is associated with an increased risk of diseases, such as neural-tube defects (NTD), which is the most common congenital malformation in the world[2]. The relationship between folate deficiency and its main adverse health outcome, NTDs, is well established in scientific literature[3-5]. Periconceptional folate intake reduces the risk of delivering a baby with an NTD.

Although not yet available on the market, previous research on folate biofortified rice explored consumers' acceptance and purchase intention in Shanxi Province[6]. The selection of this poor region in Northern China was based on its relation with NTDs and folate deficiency. Shanxi has one of the highest reported prevalence rates of NTDs in the world, with more than 60 NTDs per 10,000 births[7-9]. Furthermore, strongly related to this high NTD risk, this region is characterized by a low intake of folic acid pills[10-12] and dietary folate[13]. Expanding this study location to China as a whole would improve the evaluation of folate biofortified rice for two reasons. First of all, China is not only the world leader in the production and consumption of this staple crop, it is also considered as one of the pioneers of R&D and commercialization of genetically modified (GM) foods and, in particular, rice[14, 15]. Recently, China's Ministry of Agriculture (MOA) granted two bio-safety certificates and approved biotech Bt rice and phytase maize[16]. The permission to cultivate these important transgenic crops will lead to its large-scale production in about two to three years. Second, China as a rice consuming country is characterized by large folate deficiencies and high NTD prevalence rates[17], which makes rice an appropriate food vehicle for folate biofortification. Although there are significant differences in rice consumption and folate status between the northern and southern regions, a regional comparison of the health impact would further underpin the ex-ante evaluation of the health impact of folate biofortification in China.

Biofortification of the world's major staple crop is expected to have a large impact on folate related health problems. This paper is the first attempt to quantify the potential health benefits of a folate biofortified crop. Based on the Disability-Adjusted Life Year (DALY) framework[18], the health impact is measured in terms of "healthy" life years saved due to biofortification. Although the DALY framework has been criticized in the past[19, 20], it is increasingly used as a method in health impact studies of biofortified staple crops[21-24]. Previous impact studies evaluated the health effect of biofortified crops, such as Golden Rice[25, 26] or other provitamin A enriched crops such as cassava roots[27] or sweet potatoes[24], or iron fortified beans[28], on main micronutrient deficiencies (i.e. iron, zinc or vitamin A) in developing countries like Bangladesh, Philippines, Nigeria or India. This study focuses on the introduction of folate biofortified rice in China, which is a relatively new area to evaluate biofortified staple crops[24, 29], and investigates the differences in the health impact between northern and southern regions.

Figure 1 gives a brief overview of the application of the DALY framework to determine the health impact of the potential introduction of folate biofortified rice in China. The main concepts in this figure are elaborated in the next sections.

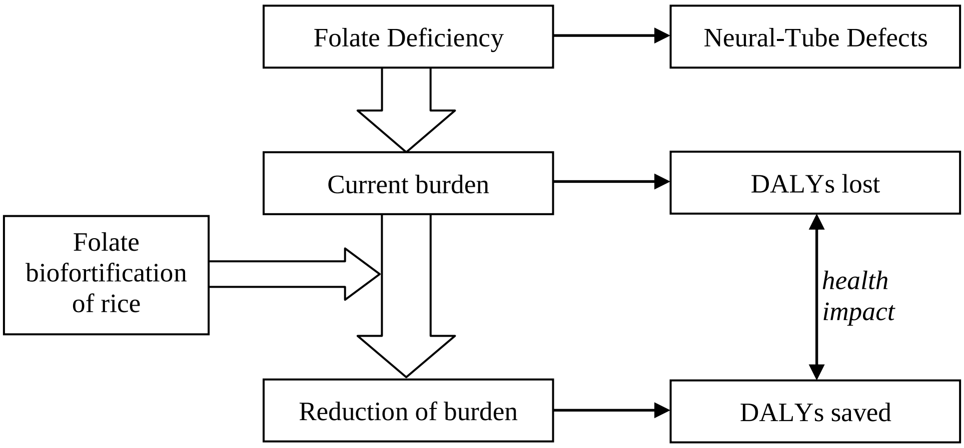

Figure 1 Application of the DALY approach to measure the health benefits of folate biofortified rice in disability-adjusted life years

Section 2 and 3 focus on folate deficiency and NTDs, respectively. Besides a general description, these sections present the status of folate deficiency and NTDs in the world and, in particular, in China. In section 4, the current burden of folate deficiency in China is estimated by means of the DALY formula. With respect to the theoretical background of this applied method, reference is made to the "Fourth HarvestPlus Technical Monograph"[23]. The fifth section gives an overview of the policy interventions to tackle folate deficiency, with specific attention to the Chinese (policy) context. The sixth section assesses the potential reduction of the current burden of folate deficiency due to the implementation of folate enriched rice, i.e. the health impact. Finally, some conclusions are drawn and recommendations for future research are presented.

2. Folate deficiency

Nutritional deficiency of folate or folate deficiency is characterized by an inadequate intake of folate, i.e. below 400 µg per person, per day. This is the daily recommended dose, as advised by the World Health Organization (WHO)[30] and the US Public Health Service[31]. Suboptimal folate intake may result in the onset of diseases and disorders, such as neural-tube defects (NTD), megaloblastic anemia and aggravation of iron deficiency anemia[32, 33]. In addition, albeit that a causal link still needs to be proven, folate deficiency has been correlated with certain types of cancer, such as leukemia, colorectal, breast, cervical, pancreatic and bronchial cancer, Alzheimer's, coronary and cardiovascular diseases[2]. These disorders can be broadly divided into three groups of causes, homocysteinemia, hypomethylation and an errant DNA biosynthesis[33], and can be prevented by an adequate folate intake[5, 34].

Folate is water-soluble vitamin, found in a wide variety of foods. The most important dietary folate sources are green and/or leafy vegetables (e.g. beans, peas and spinach), eggs, liver and certain fruits (e.g. citrus fruits and oranges)[35]. Potential side effects of (high) folate intake include cognitive impairment (only in combination with Vitamin B_{12} deficiency), facilitated progression and growth of preneoplastic lesions and subclinical cancers and impaired immune function of postmenopausal women[36]. On the contrary, folic acid is a synthetic form of folate, which does not occur naturally, but is commercially produced into pills (supplementation) or added to foods (fortification). However, humans may be much poorer at handling folic acid than what had been previously thought and there is now more concern that circulating unmetabolised folic acid may have some downsides[37]. Compared to folate, very high intakes of folic acid (>1,000 µg/day) can mask Vitamin B_{12} deficiency[38]. Besides masking micronutrient deficiencies, a high folate acid intake level may also lead to other adverse health effects, such as a cognitive decline in the elderly and a higher risk for colorectal cancer (for a review on potential side effects of folate, folic acid and other micronutrients, see Rogovik *et al*[39]). These potential negative health outcomes of raising the folic acid status partly explain the political reluctance to proceed to mandatory folic acid fortification in Europe[40, 41] (see section 5.1.2).

2.1. Folate deficiency in the world

As the most important staple foods, such as potatoes and cereals, are poor sources of folate[35], folate deficiency is a global problem for public health. Figure 2 and figure 3 summarize the scientific evidence of the magnitude of folate deficiencies, based on the plasma folate concentrations and the folate deficiency rate, respectively. These findings are based on a worldwide review on adult folate deficiency[42], which compared the results of the most representative survey of each reviewed country. The threshold of folate deficiency is defined by a plasma folate status below 10 Nmol/L[43], as suggested at the WHO Technical Consultation on folate and vitamin B12 deficiencies in 2005[44].

In line with other micronutrient deficiencies, folate deficiency is more prevalent in less developed, non-western countries. Most of the Western countries are well above this threshold, especially after the implementation of folic acid fortification programs (see section 5). However, a high average folate status does not imply that folate deficiency is absent, as figure 3 shows.

With respect to China, a regional comparison is made. If only the figures of China as a whole would be presented, the differences between Northern and Southern China would be masked. The average plasma folate concentration of Northern China is below the threshold of folate deficiency, by which the number of folate deficient adults is significantly higher than in Southern China (see section 2.2).

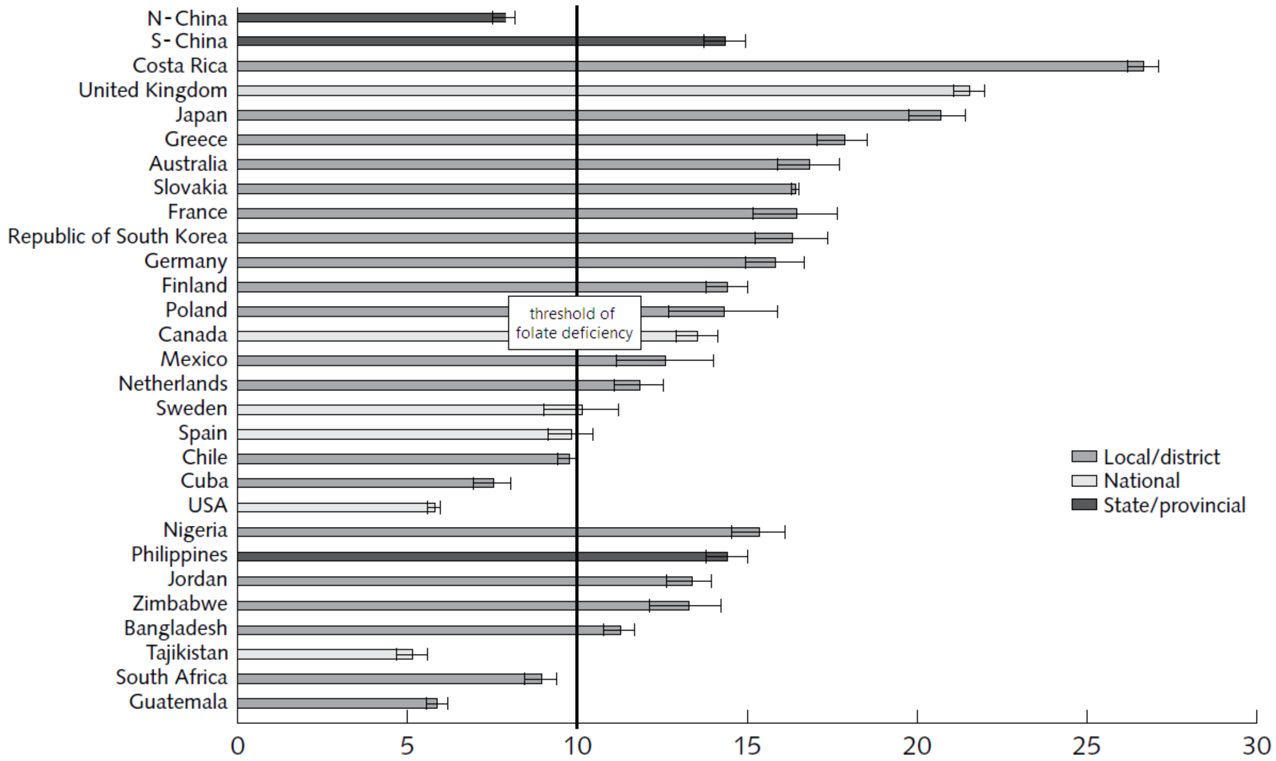

Figure 2 Folate deficiency in the world. Average plasma folate concentrations (in Nmol/L), per country
Source: Mclean *et al*[42], and Hao *et al*[45] for China
Remarks: Prefortification values are presented in countries with mandatory fortification programs (Canada, Chile, Costa Rica, and the United States). The threshold of folate deficiency is defined by a plasma folate concentration below 10 Nmol/L[43, 44].

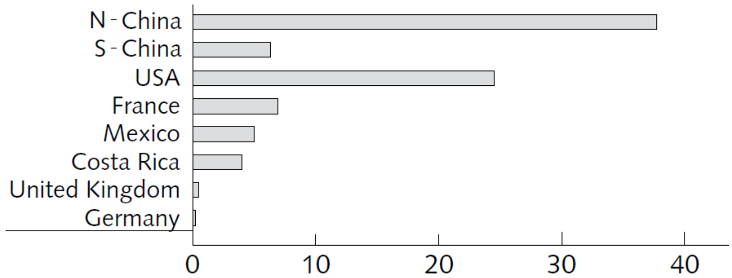

Figure 3 Folate deficiency in the world. Percentage of adults with folate deficiency, per country
Source: Mclean *et al*[42], and Hao *et al*[45] for China
Remarks: In countries with mandatory fortification programs, such as Costa Rica and the United States, prefortification values are presented.

2.2. Folate deficiency in China

Given the low folate content of China's main staple crop, rice, folate deficiency in China is expected to be high. However, scientific evidence on the number of folate deficient people in China is limited. Only two study reported the folate deficiency rate in Chinese regions spread across the country[17, 45]. Other folate status and intake assessment studies in China focused on specific regions, characterized by a low (Shanghai[46], Jiangsu[12, 47] and Anqing[48]) or high (Shanxi[12, 13, 47, 49] and Beijng[50]) NTD prevalence rate. The target group in most of these studies was limited to Chinese women of childbearing age (CBA), premarital women or pregnant women, due to their potential risk of having a baby with an NTD caused by folate deficiency.

The results of two Chinese studies, i.e. a study on folate deficiency of men and women versus the most recent study on folate status of women of childbearing age, are summarized in Table 1. The regional distribution of the number of folate deficient people, regardless of gender, indicates a significant difference between Northern and Southern China. In total, about 19.6 % or 258.8 million people in China are considered to be folate deficient, of which 81.7 % is living in

Northern China. The higher number of folate deficient people in Northern China is partly attributable to the lower availability and the limited variety of fresh vegetables, and the lower consumption of folate-rich food products[45]. The dietary folate intake of people from Northern China mainly depends on their consumption of grains, while folate-rich food products, such as (green) vegetables, are the main folate sources in Southern China[17]. With respect to Han populations, the most common ethnicity in China, regional differences could be also due to the higher frequency of mutation in the MTHFR (5-methyl-tetrahydrofolate reductase) gene of Han people from Northern China[12].

Furthermore, Chinese men tend to be more folate deficient than women. Folate deficiency rates of males are approximately 2 to 5 times higher in Northern and Southern China, respectively.

As the total folate deficiency rates are derived from two Chinese studies, the estimation of the number of folate deficient people in China should be interpreted carefully. Nevertheless, the findings show that folate deficiency in Northern China is a major health problem.

Table 1 Folate deficiency in China. Percentage of folate deficient men and women (of childbearing age), and the estimated population affected by folate deficiency in China, per region

Region	**Folate deficiency rate (%)**				**Population[c] (million)**
	Men[a]	Women[a]	CBA[b]	Total[a]	Total
NORTH	51.5	24.1	20.0	38.0	211.4
Northeast	/	/	22.8	/	/
Northwest	/	/	14.5	/	/
SOUTH	11.0	1.9	1.5	6.2	47.4
Southeast	/	/	1.0	/	/
Southwest	/	/	2.0	/	/
CHINA[d]	**28.1**	**13.3**	**9.3**	**19.6**	**258.8**

CBA, women of childbearing age

[a] Own calculations, based on Hao *et al*[45]

[b] Based on Zhao *et al*[17]

[c] Own calculations, based on the total folate deficiency rate (column 5) and the total population size (see Table 3)

[d] Own calculations, means are weighted by population size (see Table 3)

Folate deficiency is of particular importance in one of the northern provinces in China, namely Shanxi Province. Together with the Balrampur District in India[51], this poor coal mining region has one of the highest NTD prevalence rates in the world (between 60 and 150 NTDs per 10,000 births[8, 9, 52, 53], up to an NTD rate of 199[7]). This high incidence is correlated with the high folate deficiency rates of pregnant women (43.8 %)[12] and the limited use of folic acid pills (see section 5.1.1.) in this region[10-13].

2.3. Folate deficiency compared with other micronutritional deficiencies in China

China, one of the largest countries in the world, is not only affected by folate deficiency. Table 2 summarizes the key indicators of folate deficiency and other micronutrient deficiencies (iron, vitamin A, iodine and zinc) in China. Although these indicators differ according to the type of micronutrient deficiency, this table provides an insight into the magnitude of micronutrient malnutrition in China.

Vitamin A deficiency, for instance, remains a serious health problem in Chinese preschool children (11.4 million) and mothers (396 million), especially those living in rural areas[54]. The average share of Vitamin A deficient preschool children varies between 12.2 %[55] and 16.0 %[56], of which 30,500 children die from increased susceptibility to infection[56].

With respect to zinc deficiency, a study of Ma *et al*[29] estimated the total number of Chinese zinc deficient people to be around 86 million.

Another important type of micronutrient deficiency is iron deficiency. The number of people affected by iron deficiency anemia (IDA), 208.6 million, is a reliable indicator of the importance of iron deficiency in China[29]. The high IDA prevalence rate of women of childbearing age (21 %) demonstrates that China's fight against iron deficiency is still going on[54, 56].

In comparison with important iodine deficient countries, the goitre (theroid swelling) rate in China - the main cause of iodine deficiency - is rather low. Nevertheless, more than 425 million people in China live in areas of endemic iodine deficiency[54].Iodine deficiency in pregnancy, for instance, is responsible for the annual birth of nearly 2 million Chinese babies with intellectual impairment[56].

Although there is a lack of folate deficiency indicators in China, besides the NTD prevalence rate (12.9 NTDs per 10,000 births[9]), the high prevalence rate of folate deficiency from the study of Hao *et al*[45] shows that folate deficiency is also an important micronutrient deficiency.

Table 2 Estimations of the main micronutritional deficiencies in China

	Vitamin A deficiency	**Zinc deficiency**	**Iron deficiency**	**Iodine deficiency**	**Folate deficiency**
Estimated affected population (million)	11.4[a] (< 6 years) 396.4[a] (maternal)	86.0[d]	208.6[d]	425[e] (living in ID areas) 1,9[c] (children born mentally impaired)	258.8[f]
Prevalence rate of micronutrient deficiency indicators	*VAD* 12.2 %[b] 16.0 %[c] (< 6 years)		*IDA* 8 % (< 5 years)[c] 21 % (CBA)[b]	*Goitre rate* 10[c]	*NTD* 12.9 NTDs per 10,000 births[g]

CBA, women of childbearing age; VAD, Vitamin A deficiency; IDA, iron deficiency anemia; ID, Iodine deficiency; NTD, neural-tube defects

[a] Based on the 5th UN Report on the World Nutrition Situation[57]

[b] Based on a Chinese study of Jingxiong *et al*[55]

[c] Based on a report of UNICEF and The Micronutrient Initiative[56]

[d] Based on a Chinese study of Ma *et al*[29]

[e] Based on a Chinese review of Shi-an *et al*[54]

[f] Own calculations, see Table 1

[g] Based on Dai *et al*[9] see Table 3

3. Neural-tube defects

Neural-tube defects, the main adverse health outcome of folate deficiency, are characterized by malformations of the spine (such as spina bifida), skull or brain (eg. anencephaly; encephalocele), and are considered to be the most common congenital malformations in the world[58]. These malformations occur when the open neural tube, formed in the early stages in the development of the human embryo, fails to close around the 28th day after fertilization. As a consequence, the development of skull and/or spine is hampered.

The relationship between maternal folate deficiency and the risk of having a baby with an NTD is widely established in scientific literature (for a review, see Lumley *et al*[5]). Worldwide, studies explored the impact of periconceptional folate intake on the prevalence of NTDs[3, 59-61]. Given that folate deficiency refers to a daily folate intake below 400 µg, between 50 % and 70 % of all NTDs in the world are considered to be attributable to folate deficiency. These global protective rates are understood as the percentage of NTDs that can be prevented by consuming the daily recommended folate level of 400 µg.

3.1. Neural-tube defects in the world

Folate deficiency leads to an annual number between 200,000 and 300,000 neural-tube defects[62-64] and is responsible for 1 out of 10 adult deaths from heart diseases[63]. Like all birth defects, NTDs are considered a global health problem, but almost all severe or fatal defects occur in developing, low-income countries[62]. Nevertheless, neural-tube defects are still present in the Western world[40]. Every year more than 4,500 births in the European Union are affected by neural tube defects[65]. In the United States the prevalence rates for the two most common NTDs, spina bifida and anencephaly, were 1.8 per 10,000 live births and 1.1 per 10,000 live births, respectively[66]. The lower prevalence of NTDs in the United States, about 3,000 per year, is partly based on the successful implementation of policy interventions to increase folate intake (see section 5.1.2.).

Figure 4 gives an overview of the top 20 countries according to the estimated annual number of neural-tube defects. The number of NTDs is considered as an important indicator of the magnitude of folate deficiency. There is a significant difference in the estimated number of NTDs between the two highest ranked countries, India and China, and the other countries. Inadequate folate intake levels in China are causing approximately 18,000 NTDs each year. These NTDs account for one-third of stillbirths and a quarter to a third of neonatal deaths, mainly due to the high prevalence of NTDs in Northern China[8, 9](see section 3.2.). When controlled for population size, African and Middle-Eastern countries are the most problematic (For a global report on birth defects and NTDs, see Christianson *et al*[62] and the UNICEF Global Damage Assessment Report[63], respectively).

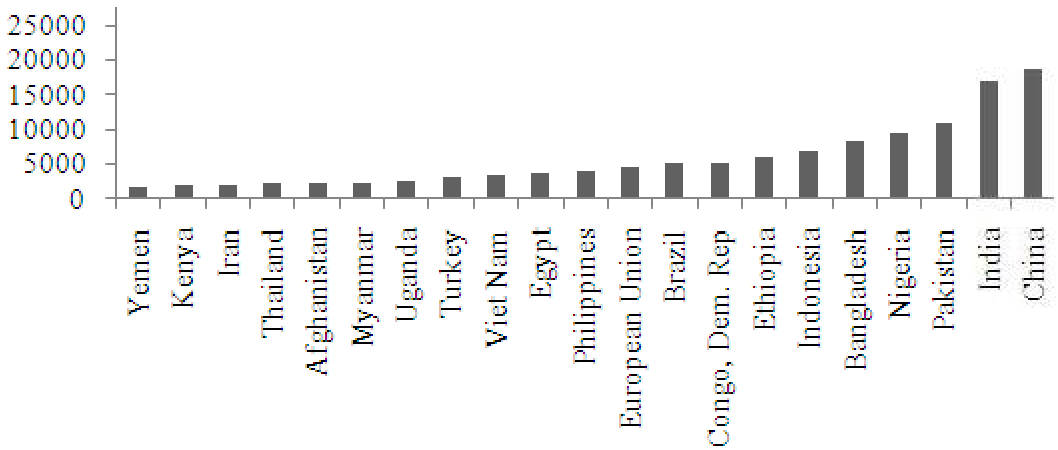

Figure 4 The estimated annual number of neural-tube defects, Top 20 countries.
Source: Own calculations based on UNICEF[63], Busby *et al*[65] (EU), Cherian *et al*[51] (India) and Table 4 (China)

3.2. Neural-tube defects in China

Given China's position in the world ranking of neural-tube defects (see Figure 4), this section further explores the number of neural-tube defects in China and its regions (For a map of the administrative areas/regions, see Annex 1, Figure 6). Table 3 presents the most relevant demographic statistics to calculate the total number of NTDs according to its main type (spina bifida, anencephaly or encephalocele). In 2007, China is characterized by a total population of 1.3 billion people and, based on a birth rate of 11.2 births per 1,000 population, approximately 14 million births. As no recent regional life expectancy rates are available, the life expectancy of these births, 71.24 years for China, refers to the year 2000[67]. The NTD prevalence rates per administrative area and region are expressed per 10,000 births and refer to NTD affected pregnancies within the period 1996 to 2000[9]. Therefore, these rates are used as approximate incidence rates. In Figure 7 of Annex 1, a graphical presentation of the NTD prevalence rates per administrative region is shown.

Table 3 Demographic profile of China, total population, birth rate, total births and life expectancy at birth, and NTD prevalence rates per functional outcome, per administrative area and region

Region/ Administrative area	**Population**[a] Total (x 1,000 persons)	**Births** Rate[b]	Total	Life expectancy[c]	**NTD rate**[d] (per 10,000 births) Anenc.	Spina	Enceph.	Total
NORTH	556,299	10.8	6,028,946	73.19	7.3	10.2	2.4	**19.9**
Northeast	458,688	10.4	4,761,446	73.59	6.6	10.3	2.3	**19.2**
Beijing	16,171	8.3	134,544	76.10	2.3	5.8	1.4	**9.6**
Tianjin	10,996	7.9	86,975	74.91	3.7	10.3	2.2	**16.2**
Hebei	70,557	13.3	940,520	72.54	5.1	9.2	2.6	**16.9**
Shanxi	34,521	11.3	390,089	71.65	27.2	27.2	6.6	**60.9**
Inner Mongolia	24,518	10.2	250,327	69.87	17.0	11.8	3.2	**32.0**
Liaoning	43,686	6.9	300,993	73.34	4.3	11.0	1.6	**16.9**
Jilin	27,852	7.6	210,284	73.10	5.0	8.2	0.9	**14.0**
Heilongjiang	39,103	7.9	308,134	72.37	4.6	5.2	1.3	**11.1**
Shandong	95,218	11.1	1,057,870	78.14	1.6	6.8	1.3	**9.7**
Henan	96,067	11.3	1,081,711	73.91	5.1	12.4	3.3	**20.8**
Northwest	97,611	13.0	1,267,500	72.39	9.4	9.9	2.9	**22.2**
Shaanxi	38,203	10.2	390,056	74.70	12.3	14.5	5.8	**32.6**
Gansu	26,656	13.1	350,254	71.85	11.7	12.2	2.6	**26.5**
Qinghai	5,606	14.9	83,691	72.55	6.6	6.6	2.0	**15.3**
Ningxia	6,178	14.8	91,431	68.95	9.2	10.1	1.8	**21.1**
Xinjiang	20,969	16.8	352,068	73.92	5.9	4.8	2.5	**13.3**
SOUTH	764,524	11.4	8,741,811	69.42	2.7	2.2	0.8	**5.8**
Southeast	565,087	11.5	6,524,892	69.96	2.7	2.1	0.8	**5.6**
Shanghai	18,564	9.1	168,380	71.54	0.7	0.8	0.4	**1.8**
Jiangsu	77,226	9.4	723,603	71.08	1.5	2.0	0.4	**3.9**
Zhejiang	50,938	10.4	528,734	70.66	2.6	2.8	0.3	**5.7**
Anhui	62,497	12.8	796,833	73.27	5.3	4.0	1.6	**10.8**
Fujian	36,393	11.9	433,081	71.29	4.3	1.5	1.2	**6.9**
Jiangxi	44,383	13.9	615,153	72.92	2.2	2.5	1.1	**5.8**
Hubei	58,231	9.2	535,144	71.73	2.9	2.0	1.3	**6.2**
Hunan	64,869	12.0	775,832	71.20	2.6	3.8	1.1	**7.4**
Guangdong	95,166	12.0	1,138,180	65.96	2.5	2.1	1.0	**5.6**
Guangxi	48,269	14.2	684,936	65.49	5.1	0.7	0.5	**6.2**
Hainan	8,551	14.6	125,017	64.37	2.7	1.0	0.2	**3.9**
Southwest	199,437	11.1	2,216,919	68.23	2.8	2.7	1.0	**6.6**
Sichuan	83,557	9.2	769,557	70.07	1.8	1.5	1.1	**4.4**
Guizhou	38,430	13.3	510,350	67.47	4.3	6.9	0.7	**11.9**
Yunnan	45,854	13.1	599,776	66.03	1.8	1.0	1.0	**3.8**
Tibet	2,874	16.4	47,141	70.17	3.6	3.6	0.0	**7.3**
Chongqing	28,722	10.1	290,094	67.41	4.0	2.0	1.6	**7.6**
CHINA	**1,320,823**	**11.2**	**14,770,757**	**71.24**	**5.0**	**6.3**	**1.6**	**12.9**

[a] Population figures of 2007 are based on the China Statistical Yearbook 2008[67]
[b] Birth rates are expressed per 1,000 population in 2007, based on the China Statistical Yearbook 2008[67]
[c] Regional life expectancy at birth in 2000 is expressed in years, based on the China Statistical Yearbook 2008[67]
[d] NTD prevalence rates between 1996 – 2000 are expressed per 10,000 births, based on a study of Dai *et al*[9].

Based on the population, the birth rate and the NTD prevalence rate (Table 3), the total number of NTDs can be calculated for each administrative area (Table 4). To define the number of NTDs per functional outcome, reference is made to the composition of NTDs in the study of Li *et al*[8], where NTDs were ascertained from live births, still births and induced abortions in Shanxi Province. While abortions are considered as a voluntary or spontaneous termination of a pregnancy, stillbirths are defined as births of a baby with no signs of life[68]. According to this Chinese study, 31 % of all NTDs are considered to be abortions, and live births and stillbirths account for 40.09 % and 28.91 % of all NTDs, respectively. These figures are in line with other studies in China[52, 69].

Within the group of NTD live births, the number of cases of spina bifida and encephalocele is determined by the proportion of their prevalence rate and the total NTD prevalence rate.

Table 4 Neural-tube defects in China, per functional outcome, per administrative area and region

Region/ Administrative area	Non-Fatal			Fatal			Total
	Spina	Enceph.	Total	Abort.	Stillb.	Total	
NORTH	3,957	1,031	4,988	3,857	3,597	7,454	**12,443**
Northeast	3,057	734	3,791	2,932	2,734	5,666	**9,457**
Beijing	41	10	52	40	37	77	**129**
Tianjin	47	10	56	44	41	84	**141**
Hebei	499	140	639	494	461	955	**1,594**
Shanxi	767	185	952	736	687	1 423	**2,375**
Inner Mongolia	253	68	321	248	231	479	**800**
Liaoning	178	26	204	158	147	305	**509**
Jilin	107	11	118	92	85	177	**295**
Heilongjiang	110	27	137	106	99	205	**343**
Shandong	345	65	410	317	295	612	**1,022**
Henan	711	191	902	697	650	1,347	**2,249**
Northwest	900	298	1,197	926	863	1,789	**2,986**
Shaanxi	365	145	509	394	367	761	**1,270**
Gansu	307	65	372	287	268	556	**927**
Qinghai	39	12	51	40	37	77	**128**
Ningxia	66	12	77	60	56	115	**193**
Xinjiang	123	64	187	145	135	280	**467**
SOUTH	1,584	651	2,236	1,729	1,612	3,341	**5,577**
Southeast	1,176	488	1,664	1,287	1,200	2,486	**4,150**
Shanghai	8	4	12	10	9	18	**31**
Jiangsu	96	17	113	87	82	169	**282**
Zhejiang	108	13	121	94	87	181	**302**
Anhui	248	97	345	267	249	516	**861**
Fujian	67	53	120	93	87	180	**300**
Jiangxi	99	44	143	111	103	214	**357**
Hubei	81	51	132	102	95	198	**330**
Hunan	180	50	231	178	166	345	**575**
Guangdong	170	85	255	197	184	381	**636**
Guangxi	103	68	171	132	123	256	**427**
Hainan	16	3	19	15	14	29	**49**
Southwest	409	163	572	442	413	855	**1,427**
Sichuan	80	56	136	105	98	203	**338**
Guizhou	220	24	244	189	176	365	**609**
Yunnan	45	45	90	70	65	135	**225**
Tibet	14	0	14	11	10	21	**34**
Chongqing	50	39	88	68	64	132	**220**
CHINA	**5,541**	**1,683**	**7,224**	**5,586**	**5,210**	**10,796**	**18,020**

Each year, a total of 18,020 pregnancies are affected with an NTD in China, most of them with a fatal result. It is important to notice that the total NTD figures in Table 2 refer to all NTDs, i.e. NTDs caused by folate deficiency or other factors, such as genetic or environmental[70], except for spontaneous NTD related abortions. Although there is evidence on the positive relationship between a history of spontaneous abortions and an increased prevalence of NTDs[71], the number of spontaneous NTD related abortions are not investigated in this study. If information on the number of NTDs that result in a spontaneous termination would be available, the number of NTDs in China would be higher.

When comparing Chinese regions, the NTD prevalence rate is more appropriate as an indicator of NTD-risk regions than the total number of NTDs. Although Shanxi Province, situated in the Northeast, obtains the highest NTD prevalence rate (60.9), Northwest China is considered as the most problematic Chinese region, with 22.2 NTDs per 10,000 births. The significant difference between Northern and Southern China is shown in both the NTD rate and the total number of NTD (see also Annex 1, Figure 7). While 31 % of all NTD affected pregnancies occur in Southern China, in its northern counterpart accounts for more than two thirds of all Chinese NTDs.

3.3. Neural-tube defects caused by folate deficiency in China

Although the total number of NTDs has been used as an indicator of the importance of folate deficiency (see section 3.1.), only a part of these NTDs are attributable to folate deficiency. This section estimates the number of neural-tube defects caused by folate deficiency in China. As there is a lack of data on the contribution of folate deficiency to other functional outcomes, NTDs caused by folate deficiency are the only functional outcomes of folate deficiency that will be included in the DALY framework to measure the current burden of folate deficiency (see section 4) and the health impact of folate biofortification (see section 6). This implies an underestimation of the global health benefits of folate biofortified rice. Its health impact would be significantly higher when other outcomes of folate deficiency could be included, such as megaloblastic anemia, heart diseases and cancer. Nevertheless, as NTDs are not only considered as the main adverse health outcome of folate deficiency, but also as the world's major congenital malformation, the number of NTDs is a valuable indicator to measure the current burden of folate deficiency.

As there is currently no data on the contribution of folate deficiency to NTDs in each administrative area, two regional contribution levels are used to determine the number of NTDs caused by folate deficiency. Based on a folic acid supplementation study among pregnant women (see section 5.1.1.), Berry *et al*[72] estimated that women in Northern and Southern China are able to reduce the risk of having a baby with an NTD by 85 % and 40 %, respectively, if they achieve the daily folate recommendation of 400 µg. In other words, respectively 85 % and 40 % of all NTDs are attributable to folate deficiency in northern and southern regions. Although this study only investigated some of the provinces in Northern and Southern China, similar protective rates are found in a Chinese study of Chen *et al*[73].

Based on these regional contribution levels and the total number of NTDs in Table 4, the number of NTDs caused by folate deficiency are calculated in Table 5. The use of different contribution levels in Northern and Southern China explains the increased regional difference in the number of NTDs caused by folate deficiency. No less than 83 % of all these NTD affected pregnancies in China occur in the north, and in particular, in the northwest. Even more striking is the number of the NTDs in Shanxi Province, which is almost as high as the whole southern part.

With respect to the different functional outcomes, almost 60 % of the NTDs has a fatal outcome. If the NTD results in a live birth, malformations in the back (i.e. spina bifida) are the most frequent outcome. When linking Table 5 to the input parameters of the DALY framework (see section 4.2.), the total number of non-fatal and fatal NTDs caused by folate deficiency are considered as the combined input parameters T_jI_{ij} and T_jM_j, respectively.

Table 5 Neural-tube defects caused by folate deficiency in China, per functional outcome, per administrative area and region

Region/ Administrative area	Non-Fatal			Fatal			Total
	Spina	Enceph.	Total	Abort.	Stillb.	Total	
NORTH	3,363	877	4,240	3,279	3,058	6,336	**10,576**
Northeast	2,599	624	3,223	2,492	2,324	4,816	**8,038**
Beijing	35	9	44	34	32	66	**110**
Tianjin	40	8	48	37	35	72	**120**
Hebei	424	119	543	420	392	812	**1,355**
Shanxi	652	158	809	626	584	1,209	**2,019**
Inner Mongolia	215	58	273	211	197	407	**680**
Liaoning	151	22	173	134	125	259	**433**
Jilin	91	9	101	78	73	150	**251**
Heilongjiang	93	23	117	90	84	175	**291**
Shandong	293	55	348	269	251	520	**868**
Henan	604	162	766	593	553	1,145	**1,912**
Northwest	765	253	1,018	787	734	1,521	**2,538**
Shaanxi	310	123	433	335	312	647	**1,080**
Gansu	261	55	316	244	228	472	**788**
Qinghai	33	10	44	34	32	65	**109**
Ningxia	56	10	66	51	47	98	**164**
Xinjiang	105	55	159	123	115	238	**397**
SOUTH	634	261	894	692	645	1,337	**2,231**
Southeast	470	195	666	515	480	995	**1,660**
Shanghai	3	2	5	4	4	7	**12**
Jiangsu	38	7	45	35	33	68	**113**
Zhejiang	43	5	48	37	35	72	**121**
Anhui	99	39	138	107	100	206	**345**
Fujian	27	21	48	37	35	72	**120**
Jiangxi	40	18	57	44	41	85	**143**
Hubei	32	21	53	41	38	79	**132**
Hunan	72	20	92	71	67	138	**230**
Guangdong	68	34	102	79	74	152	**255**
Guangxi	41	27	68	53	49	102	**171**
Hainan	6	1	8	6	6	12	**19**
Southwest	163	65	229	177	165	342	**571**
Sichuan	32	22	54	42	39	81	**135**
Guizhou	88	10	98	75	70	146	**243**
Yunnan	18	18	36	28	26	54	**90**
Tibet	6	0	6	4	4	8	**14**
Chongqing	20	15	35	27	25	53	**88**
CHINA	**3,997**	**1,137**	**5,134**	**3,970**	**3,703**	**7,673**	**12,807**

Note: These figures are determined by the total number of NTDs (Table 2) and the contribution level of folate deficiency to NTDs in Northern (85 %) and Southern China (40 %).

4. Current burden of folate deficiency in China

4.1. The DALY formula

The Disability-Adjusted Life Year method is used to quantify the burden of folate deficiency as a single index, i.e. the number of DALYs lost. This number equals the sum of the "Years Lived with Disability" (YLD) and "Years of Life Lost" (YLL), which represent, respectively, disability-weighted morbidity and cause-specific mortality due to folate deficiency. The DALY formula[23, 26] to estimate both the death and disease condition resulting from folate deficiency is expressed as:

$$\mathrm{DALYs_{lost}} = \mathrm{Y_{ears}L_{ived}D_{isability}} + \mathrm{Y_{ears}L_{ife}L_{ost}} = \sum_j T_j I_{ij} D_{ij}\left(\frac{1-e^{-rd_{ij}}}{r}\right) + \sum_j T_j M_j \left(\frac{1-e^{-rL_j}}{r}\right)$$

The input parameters of the formula are the total number of people in target group j (T_j); the mortality rate associated with the deficiency in target group j (M_j); incidence rate of functional outcome i in target group j (I_{ij}); the disability weight for functional outcome i in target group j, (D_{ij}); the duration of functional outcome i in target group j (d_{ij}); the average remaining life expectancy for target group j (L_j) and the discount rate for future life years (r).

When applying this formula to calculate the burden of folate deficiency, only NTDs caused by folate deficiency are included as functional outcomes. Therefore, the three main NTD types, i.e. spina bifida, encephalocele (also known as cranium bifidum) and anencephaly, in particular those NTDs that are attributable to folate deficiency, are considered as functional outcomes in this study. The target groups referring to these NTDs are births, both fatal and non-fatal, as these are the ones that will be directly influenced by their mother's biofortified diet. The functional outcomes related to these target groups are split up into a non-fatal (morbidity) and fatal (mortality) component. While the latter is determined by abortions and stillbirths, the former consists of live births suffering from spina bifida or encephalocele. The third NTD type, anencephaly, results in death before or shortly after birth and is considered as a part of the mortality component[74, 75]. The values of the input parameters of the DALY framework are further described in section 4.2.

4.2. Input parameters of the DALY formula

Table 6 summarizes all input parameters that are included in the DALY formula. The input parameters T_jI_{ij} and T_jM_j are presented in Table 5 and refer to non-fatal and fatal functional outcomes, respectively. Disability weights of the functional outcomes (D_{ij}) differ according to the level of severity or disability, and range from 0 ('healthy') to 1 ('death')[18]. The average remaining life expectancy (L_j) of stillbirths and abortions refers to the average life expectancy at birth (see Table 3). Also the duration of a non-fatal NTD (d_{ij}) is assumed to be permanent, by which d_{ij} equals L_j. Based on the global burden of disease study of Mathers *et al*[75], a disability weight of 0.593 and 0.52 is attributed to spina bifida and encephalocele, respectively. The discount rate for future life years (r) amounts to 3 percent, in accordance with previous health impact studies[23, 26].

Table 6 Overview of the input parameters of the DALY formula, applied to China

Functional outcome	$\mathbf{T_jI_{ij}}$	$\mathbf{T_jM_j}$	$\mathbf{D_{ij}}$	$\mathbf{L_j=d_{ij}}$	**r**
Morbidity					
Spina bifida	Table 5, column 2	NA	0.593	Table 3, column 5	3 %
Encephalocele	Table 5, column 3	NA	0.520		
Mortality					
Stillbirths	NA	Table 5, column 5	NA	Table 3, column 5	3 %
Abortions	NA	Table 5, column 6	NA		

T_j, total number of people in target group j; I_{ij}, incidence rate of functional outcome i in target group j; M_j, the mortality rate associated with the deficiency in target group j; D_{ij}, the disability weight for functional outcome i in target group j; L_j, the average remaining life expectancy for target group j; d_{ij}, the duration of functional outcome i in target group j; r, discount rate for future life years; NA, not applicable

4.3. The current burden of folate deficiency in China (DALYs lost)

The present burden of folate deficiency in China, i.e. the situation ‘without’ biofortification, can be calculated by entering the input parameters of Table 6 into the DALY formula. This burden is expressed in the number of DALYs lost per administrative area (Table 7). Based on the present consumption pattern, folate deficiency in China is responsible for an annual loss of 314,180 DALYs. With respect to the regional differences, the number of DALYs lost is significantly higher in Northern China, especially in the northeast. However, when these numbers are weighted according to the total population, the current situation is worst in Northwest China, with 6.39 DALYs lost per 10,000 persons, per year (see also Table 11, column 3). By way of comparison, the annual number of DALYs lost in the northeast is 4.31 per 10,000 persons. The relative burden in Southern China is significantly lower with 0.71 DALYs lost per 10,000 persons. These findings are mainly a consequence of differences in NTD prevalence rates and the regional contribution level of folate deficiency to NTDs. Regarding the functional outcomes, the burden of morbidity and mortality caused by folate deficiency amounts to 27.85 % and 72.15 %, respectively. Within these categories, spina bifida obtains the highest number of years lived with disability, while the lost life years are more or less equally divided between the two fatal outcomes.

Table 7 Burden of folate deficiency in China, per functional outcome, expressed in the number of DALYs lost, per year, per region and administrative area

Region/ Administrative area	Non-Fatal			Fatal			Total
	Spina	Enceph.	Total (YLD)	Abortions	Stillbirths	Total (YLL)	
NORTH	59,067	13,502	72,569	97,100	90,554	187,654	**260,223**
Northeast	45,642	9,600	55,242	73,791	68,816	142,608	**197,849**
Beijing	623	137	760	1,016	948	1,964	**2,724**
Tianjin	702	129	831	1,107	1,032	2,139	**2,970**
Hebei	7,429	1,832	9,261	12,411	11,574	23,986	**33,246**
Shanxi	11,381	2,414	13,794	18,429	17,187	35,616	**49,411**
Inner Mongolia	3,725	879	4,604	6,165	5,749	11,913	**16,517**
Liaoning	2,660	341	3,001	3,976	3,708	7,684	**10,685**
Jilin	1,601	146	1,747	2,305	2,150	4,455	**6,202**
Heilongjiang	1,637	359	1,995	2,668	2,488	5,155	**7,151**
Shandong	5,239	861	6,100	8,112	7,565	15,677	**21,777**
Henan	10,645	2,502	13,148	17,602	16,415	34,018	**47,165**
Northwest	13,425	3,902	17,327	23,309	21,737	45,046	**62,374**
Shaanxi	5,473	1,907	7,380	9,972	9,300	19,272	**26,652**
Gansu	4,560	845	5,404	7,202	6,716	13,918	**19,323**
Qinghai	586	158	744	999	931	1,930	**2,674**
Ningxia	963	150	1,113	1,479	1,379	2,858	**3,971**
Xinjiang	1,843	843	2,686	3,657	3,411	7,068	**9,754**
SOUTH	10,978	3,954	14,931	20,194	18,832	39,026	**53,957**
Southeast	8,169	2,968	11,137	15,066	14,050	29,115	**40,252**
Shanghai	57	25	82	112	104	216	**299**
Jiangsu	667	106	773	1,028	958	1,986	**2,759**
Zhejiang	753	79	832	1,099	1,025	2,125	**2,957**
Anhui	1,742	600	2,343	3,165	2,951	6,116	**8,459**
Fujian	466	327	793	1,094	1,021	2,115	**2,908**
Jiangxi	695	271	966	1,309	1,221	2,529	**3,495**
Hubei	565	315	880	1,205	1,124	2,329	**3,209**
Hunan	1,257	309	1,565	2,098	1,956	4,054	**5,619**
Guangdong	1,159	508	1,667	2,266	2,114	4,380	**6,047**
Guangxi	698	408	1,107	1,518	1,415	2,933	**4,040**
Hainan	110	19	129	172	160	332	**461**
Southwest	2,809	985	3,794	5,128	4,783	9,911	**13,705**
Sichuan	554	340	894	1,228	1,145	2,373	**3,267**
Guizhou	1,511	143	1,654	2,184	2,036	4,220	**5,874**
Yunnan	308	270	578	803	749	1,553	**2,131**
Tibet	96	0	96	125	116	241	**337**
Chongqing	340	232	572	789	736	1,524	**2,097**
CHINA	**70,044**	**17,456**	**87,500**	**117,294**	**109,386**	**226,680**	**314,180**

DALYs, Disability-Adjusted Life Years; YLD, years lived in disability; YLL, years of life lost

5. Policy interventions to tackle folate deficiency

Like other micronutrient deficiencies, folate deficiency can be addressed by four strategies: distributing folic acid supplements (pharmaceutical supplementation), fortifying foods with folic acid (industrial fortification), diversifying people's diets to increase the consumption of folate-rich foods (dietary diversification) or enhancing the folate content of staple crops (biofortification). While the former two interventions aim to limit folate deficiency through the increased intake of synthetic folic acid, the objective of the latter two strategies is to enhance the natural folate intake level. Folic acid based interventions are often criticized because of the relationship between excessive folic acid intake and masking anemia caused by vitamin B_{12} deficiency[76]. Although the folic acid fortification policy in the United States did not cause a major increase in the number of vitamin B_{12} deficient people[38], and a multi-micronutrient fortification policy to increase both folic acid and vitamin B_{12} could be a partial solution for the future[41, 76], the debate about the adverse health effects of high folic acid intake hampers the introduction of mandatory folic acid fortification in many (European) countries[77].

The following sections briefly discuss the different policy interventions to tackle folate deficiency in relation to the (Chinese) policy context (For a general overview and comparison of the different interventions to tackle nutritional deficiencies, we refer to the Stein *et al*[25]). As not all interventions have been implemented in China, the experience of folate or other nutritional programs in other countries is also drawn.

5.1. Folic acid based interventions

5.1.1. Folic acid supplementation

Folic acid supplementation is an external nutritional intervention to tackle folate deficiency in specific target groups by promoting the use of folic acid or multivitamin supplements. Supplementation programs mainly target women of childbearing age. By encouraging them to consume daily folic acid pills from the periconceptional period until approximately three months of gestation, the number of NTDs can be reduced. The ability to focus on specific population groups is considered as both an advantage and disadvantage of this intervention. On the one hand, targeting women of childbearing age tackles folate deficiency where it is most needed. On the other hand, a population-based approach is needed, as folate deficiency is present in all sections of the population[42].

Folic acid pills generally contain 400 µg of folic acid, which is in line with the folate recommendations. Therefore, a daily consumption of such pills is currently considered as the most effective strategy for women of childbearing age in order to prevent them against a pregnancy affected by an NTD caused by folate deficiency (for a review of the relationship between folic acid supplementation and NTDs, see Lumley *et al*[5]). Besides these daily supplements, folic acid can also be given less frequently, e.g. 5 mg on a weekly basis. Although weekly supplementation could be a practical answer to the low compliance to consume folic acid supplements, evidence is needed to demonstrate that it is as effective as daily folic acid supplements[78].

Folic acid supplements can also be delivered with other micronutrients. By implementing such a multivitamin program, by which folic acid is incorporated in another vitamin supplement, such as vitamin A capsules, duplication of costs and efforts can be avoided.

Supplementation programs

Effective supplementation programs were introduced in Philippines, Cambodia, and Vietnam, where pregnant women received free daily iron and folic acid supplements and non-pregnant women were encouraged to take weekly supplements[79]. In Western and Northern Europe, folic acid supplementation policies are well established, but their effectiveness to reduce NTDs is rather limited[40, 65, 76]. The success of supplementation programs depends on the duration and the intensity of supplementation efforts, the accessibility of supplements, the effectiveness of the health system and the inclusion of a targeted educational component in the program[78, 80]. However, pharmaceutical supplementation is not considered as a long-term solution to tackle folate deficiency. Previous campaigns to promote folic acid supplementation in the United States[81] and The Netherlands[82], for instance, increased knowledge about folic acid, but were less effective in stimulating the use of folic acid supplements. And if a program is effective, the increased folic acid intake is often not sustainable and decreases again once the program ceased[83] (For a review of the success of folic acid supplementation programs, see Cordero *et al*[78]).

China and supplementation

Because of the one child per family policy, the prevention and control of birth defects is a high priority for the Chinese government. In their "2002-2010 National Action Plan for Reducing Birth Defects and Disabilities in China", the Ministry of Health (MOH) and the Chinese Disabled Person Federation (CDPF) recommend that all women of child-bearing age should obtain folic acid and health information on folic acid supplementation, in order to bring birth defects under effective control by 2010[84]. By the end of 2010, at least 60% of all married women who plan to be pregnant have to achieve the daily recommendation for folate. Therefore, a national public health education campaign and a national preconception care program is released. In 2009, for instance, about 12 million rural Chinese women of child-bearing age received free folic acid supplements[85].

Although such supplementation programs are expected to reduce the number of NTDs, the reduction is likely to be a short term effect. Between 1993 and 1995 for instance, a successful folic acid supplementation intervention was conducted as a part of the public health campaign[72]. This intervention reduced the number of NTDs by delivering folic acid supplements to women during their mandatory premarital health examination. However, once the program ceased, the NTD prevalence rate increased to its pre-supplementation value[86].

Despite previous supplementation efforts, the current intake of folic acid supplements is very low in rural areas and high risk regions. In Shanxi Province, for example, only 10 % of women of childbearing age once used folic acid pills, regardless of their knowledge about the correct time of use[10, 11]. The low compliance of taking folic acid supplements in such poor, rural areas might be determined by the price of folic acid (30 pills of 400 µg folic acid is about 10 yuan or 1.5 dollar) and the limited access[86]. Low compliance of taking folic acid supplements is also a consequence of the large number of unintended pregnancies in China. Most Chinese women are not aware of the need to take folic acid supplements during the periconceptual period. Therefore, implementing a targeted folic acid supplementation program will be more difficult when all women of childbearing age need to be reached and continuation of the program is crucial to keep them motivated[78].

5.1.2. Folic acid fortification

While folic acid supplementation targets a specific population group, (industrial) folic acid fortification, i.e. adding folic acid directly to staple crops during the first stage of milling, is currently considered as the most effective population-based strategy to fight folate deficiency without altering dietary habits[41]. As successful folic acid fortification requires specialized infrastructure, strict quality control and strong partnerships between public and private sectors, folic acid fortification is less feasible in developing countries and regions that are characterized by large micronutrient deficiencies[78, 80, 87]. In line with the multivitamin strategy, folic acid can be added to existing fortified foods, which is successfully demonstrated in Costa Rica[88].

Fortification programs

In 2005, about 38 countries had opted for a mandatory folic acid fortification policy[76]. In the United States[34, 89] and Canada[60], for example, cereal grain products were fortified with folic acid to a level of 140 and 150 µg per 100 g, respectively. Other countries focused their mandatory folic acid fortification policy on one (e.g. wheat flour in Chile[90]) or more food vehicles (e.g. wheat flour, corn flour, milk and rice in Costa Rica[88]). In general, these mandatory fortification programs led to increased folic acid consumption levels[78]. As a consequence, the folate intake requirements for most adults were met or exceeded, and the number of NTDs decreased, e.g. from 4,000 to 3,000 NTD affected pregnancies in the United States[91]. In Europe, most countries have voluntarily folic acid fortified foods and in some cases, such as in Ireland and in the UK, the introduction of mandatory folic acid fortification has been advocated[40, 76, 92]. Only Eastern Europe and Eurasia currently embrace mandatory folic acid fortification. Kazakhstan, for example, is in the process of implementing the laws to require a certain level of folic acid in flour (Flour Fortification Initiative; http://www.sph.emory.edu/wheatflour/).

China and fortification

In 2003, the flour fortification pilot program "Flour Fortification in the Western Region of China" was initiated by the State Grain Bureau and the Ministry of Health in China[93, 94]. With the support of the Global Alliance for Improved Nutrition (GAIN), a market-based, voluntary fortification program was introduced, with a folic acid fortification level of 200 µg per 100 g. This resulted in the production of fortified flour, often known as "7+1 flour", in a few companies. However, due to delays in implementation, this project came to an end in 2008.

Between 2006 and 2007, folic acid fortified flour was introduced to more than 60,000 consumers in the high NTD risk region of Shanxi Province, as a part of the "Strong Newborn" project[93]. The objective of this program was to evaluate the effect of flour fortification in the prevention of NTDs. Although the findings indicate a positive effect, there were significant problems to guarantee the quality of fortified flour and to obtain funding in order to start a province-wide implementation.

In 2008, the Chinese Public Nutrition and Development Center (PNDC) developed a voluntary flour fortification standard, which was released by the State Grain Authority (SGA)[93, 95]. However, at present, very little flour is voluntary fortified in China (about 1 %)[93]. Given the limited access to voluntary folic acid fortified foods in China, the main challenge will be to guarantee that the fortified food vehicle will actually (continue to) reach the Chinese consumer, especially in the rural regions of China. As policy makers have still concerns on the feasibility of folic acid fortification in China, the Chinese Ministry of Health intend to undertake additional flour and rice fortification trials in the future[86, 93]. Nevertheless, the actual implementation of provincial flour fortification in the market will depend largely on provincial authorities' interest and commitment.

5.2. Folate based interventions

5.2.1. Dietary diversification

Dietary diversification aims to modify the dietary patterns of consumers through interventions that promote the consumption of micronutrient-rich foods, e.g. home gardening, as well as nutrition education, e.g. learning consumers to retain micronutrients during processing. Previous food-based strategies focused mainly on the reduction of Vitamin A or iron deficiencies (for a review, see Ruel[96]). Although this strategy is considered to be the most sustainable solution, there are currently no scientific reports of population-based interventions which promoted a folate-rich diet (e.g. green leafy vegetables and orange-fleshed fruits)[78]. While a vegetarian eating pattern, characterized by long-term high consumption of vegetables, positively affects the folate intake[97], dietary folate interventions are not necessarily effective to address folate deficiency[98].

Furthermore, such food-based strategies rely on food varieties that are already available in the market. Due to the limited availability and consumption of folate-rich products in Northern China, it will be difficult to modify the eating behaviors in this high NTD risk region[17, 45]. Especially in the poor rural areas, where consumers mainly consume folate-poor staple crops, such as rice, increasing the consumption of folate-rich food products is less feasible than pro-poor interventions, such as folate biofortification (see section 5.2.2.).

5.2.2. Folate biofortification

Biofortification is a pro-poor and pro-rural strategy that uses plant breeding techniques, such as conventional breeding or transgenic techniques, to develop staple food crops for higher micronutrient content[99]. The first example of a genetically engineered biofortified staple crop is rice enriched with beta-carotene to tackle Vitamin A deficiency, also known as Golden Rice[100].

Folate biofortification, the enhancement of folate in staple food crops, can improve the folate intake of malnourished rural populations that are unlikely to benefit from folic acid fortification or supplementation. Currently, rice with a high folate content, developed by metabolic engineering, is the most advanced folate biofortified staple crop[33, 101, 102]. Storozhenko *et al*[1] obtained different transgenic lines with a folate content ranging from 350 to 1,700 µg per 100 g of raw polished grains. These figures are 20 to 100 times higher than normal folate levels in rice[103]. Even though there is a clear potential to use conventional plant breeding techniques to increase the folate content of rice (e.g. conventional biofortification of other vitamins in maize, wheat, beans, cassava, and rice[104]), it may be hard to reach the same level of enhancement as in transgenic techniques, because of the low intrinsic folate concentrations in natural rice varieties[102, 105] (For a detailed discussion on the technological issues regarding folate biofortification of food plants and rice, see Storozhenko *et al*[1] and Bekaert *et al* [102], respectively).

As such, folate biofortification of rice, the world's main staple crop, can be considered as an alternative and complementary approach to the above mentioned strategies, especially in regions where other interventions are less successful or feasible. First of all, unlike folic acid fortification or supplementation, folate biofortification does not rely on industrial food processing, specialized distribution channels or accessible health systems. Second, it is considered to be a more sustainable approach due to the possibility of re-sowing the biofortified seeds from the previous harvest. Third, possible negative side effects of folic acid fortification, such as masking Vitamin B_{12} deficiency and the increased risk of colorectal cancer, are less likely to occur with folate biofortification (see section 2).

However, in comparison with the targeted approach of folic acid supplementation, there is no assurance that the population will achieve to consume the recommended amount of folate. Furthermore, folate in food is subject to additional losses due to the processing methods, such as cooking[106], and its bioavailability degree (50 %) is significantly lower than in folic acid fortified foods or supplements, respectively 85 % and 100 %[107, 108]. Moreover, biofortification, initially applied to improve the micronutritional content of staple crops, may alter other attributes, such as appearance and taste. Such negative attributes may limit consumer acceptance and, in turn, reduce the potential impact of this intervention. Consumers in Kenya[109] and Mozambique[110], for instance, preferred traditional white maize over yellow-orange biofortified maize, which is enriched with provitamin A. In the latter study, the authors even found a negative consumer perception of the flavor of biofortified maize. Although folate biofortification is not expected to change sensory and visual product attributes[102], similar to folic acid fortification[111], further research is needed to determine the influence of folate biofortification on product attributes and its consumer acceptance.

China and biofortification

China is considered as one of the world leaders in the field of R&D and commercialization of genetically modified foods. Research on biofortification of staple crops became increasingly important for China's food security policy, especially after China's entry into the World Trade Organization (WTO) in 2001[80, 112]. The HarvestPlus China Program, for example, initiated in 2004 eight research projects related to the development of biofortified maize, wheat, sweet potato and rice in China, in order to address specific micronutrient deficiencies, such as Fe or Vitamin A[113] (http://www.harvestplus-china.org/). Nevertheless, no transgenic crop was approved for animal or human consumption until recently, when China's Ministry of Agriculture (MOA) granted two bio-safety certificates and approved phytase maize (feed crop) and biotech Bt rice (food crop)[16]. The permission to cultivate these major transgenic crops is expected to lead to full commercialization in about two to three years. As a consequence, China will be the first to introduce a troika of key transgenic crops into the market place, i.e. Bt cotton (fiber), phytase maize (feed) and Bt rice (food)[114]. The approval and deployment of the latter will probably lead to the approval of other transgenic food crops, including biofortified staple crops.

Even though this might be promising for biofortified staple crops, including folate enriched rice, the process and outcome of the standard food safety and environmental field trials makes it impossible to predict if and when these biotech crops will be approved in China. Furthermore, if (transgenic) biofortified crops will be introduced, labeling of transgenic food crops will probably be required, as outlined by the Chinese State Council[80]. With respect to the Chinese Intellectual Property Rights (IPR), patent registration and enforcement probably need to be reformed and centralized in order to improve IPR-protection for biofortified crops (for more information on biofortification policy issues in China, we refer to Campos-Bower *et al*[80] and Pray *et al* [112]).

Although the approval of BT rice might be a catalyst of approving biofortified staple crops, there is a clear difference between these two types of transgenic crops. While the former encompasses improvements of agronomic traits, i.e. insect resistance, the latter improves quality traits, such as a higher folate content[115]. From a policy point of view it can be argued that GM crops that are attractive to both farmers (e.g. by increasing yields due to the improved crop quality; 1st generation crops) and consumers (e.g. by improving health due to the enhanced nutritional quality; 2nd generation crops), will increase public acceptance, and thus, gain political acceptance. The combination of a nutritional and an agronomic trait in staple food crops is considered to be more than the sum of parts. Besides its potential for cost-reduction through the combined implementation efforts, these crops improve farmer's health directly, through consumption, and indirectly, through promoting sustainable agriculture (increased yields, productivity and income)[116]. Together with multi-biofortification, where one staple crop is enriched with a full range of nutrients, among which folate, this strategy should be put as a priority on the research agenda. Targeting different micronutrient deficiencies at once is a strategy which is also found in other policy interventions, such as pharmaceutical supplementation (e.g. multivitamin supplements), food fortification (e.g. multi-micronutrient fortification, including folic acid and Vitamin B_{12}) and dietary diversification, if it aims to tackle malnutrition as a whole by improve dietary habits. Golden Rice, for example, is assumed to be cost-effective, as shown in scientific literature (see for instance, Stein, *et al*[25]). Crossing our folate trait into this biofortified crop would be an interesting approach to tackle folate and Vitamin A deficiencies and to improve the health impact by introducing one multi-biofortified crop. However, combining first and second generation GM crops, such as Bt rice with a high folate content, would definitely go further by providing an economic incentive to farmers.

This paper focuses on the world's most consumed staple crop, rice, as the food vehicle for folate biofortification. China is one of the key players in terms of producing and consuming rice, as well as GM rice[14, 15]. While Japonica rice is the dominant rice variety in Northern China, Indica rice is mainly planted in Southern China. With respect to folate biofortified rice in China, it will be important to cross folate biofortified rice into local varieties to reach the poorest consumers in the rural regions. In addition, to ensure that Chinese farmers will produce this variety, the trait needs to be crossed into a variety that has a high yielding potential, such as Bt rice, and the product should be incorporated into existing marketing chains[102]. The success of introducing folate biofortified rice further depends on the efficacy of systems to disseminate such improved rice varieties.

6. The health impact of folate biofortified rice in China

The health impact of the introduction of folate enriched rice depends on different factors, as Figure 5 depicts. Two important determinants are directly related to folate enriched rice, namely its efficacy (section 6.1.) and coverage rate (section 6.2.). While the former determines the folate dose, the latter defines the market potential of this crop and, thus, the response to this dose. Information about the current folate intake levels and the current rice consumption patterns is used to calculate the total folate intake after biofortification, which reduces the number of maternal folate deficiencies and, thus, reduces the number of neural-tube defects, i.e. the response or the health benefits.

This framework to assess the health benefits of folate biofortified rice is based upon previous health impact studies[26, 99]. Because the health impact is related to the number of NTDs in China, two target groups are considered. On the one hand, newborns are considered as the target group of the health benefits, as they carry the risk of having a neural-tube defect. On the other hand, due to the relationship between maternal folate deficiency and the risk of delivering a baby with an NTD, women of childbearing age are the target group for folate biofortified rice consumption. The calculation method and the assumptions for each determinant are described in the next two sections. The health impact of introducing folate biofortified rice in China is presented in section 6.3 and compared with other health impact studies in section 6.4.

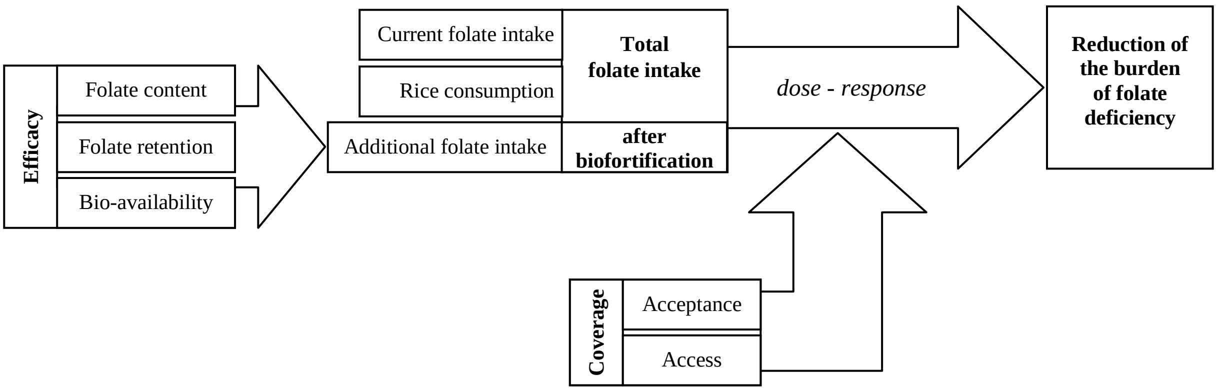

Figure 5 The health impact of folate biofortified rice

Remarks: Efficacy = (folate content in rice, µg per 100 g)*(% folate retention, %)*(degree of bio-availability, %)
Additional folate intake = (efficacy, µg per 100 g) - (initial folate content of 100 g rice)
Coverage rate = (maternal acceptance rate, %)*('access' = farmers' acceptance rate, %)
Total folate intake after biofortification = (current folate intake, µg) + (additional folate intake, µg per g)*(rice consumption, g)

6.1. Total folate intake after folate biofortification of rice in China

The efficacy of folate biofortified rice is calculated by multiplying the amount of additional folate in rice with the retention of folate after processing the rice and its bioavailability. For the calculations in this paper we have used 1,200 µg per 100 g raw polished grains. This folate content will be reduced by 50 % during rice processing, i.e. cooking[1]. To take into account the bioavailability upon ingestion, this folate retention will be reduced by 50 %[107, 108]. Combining these three efficacy parameters results in a total folate intake of biofortified rice of 300 µg per 100 g rice. Given the initial folate content of rice, 8 µg per 100 g[35], the total added folate intake amounts 292 µg per 100 g.

Given that the current rice patterns do not differ after introducing folate biofortified rice, the total folate intake of Chinese women of childbearing age after biofortification can be estimated by adding the additional folate intake to the current folate intake (Table 8). The average daily rice consumption can be calculated for each administrative area, based on data from the China's National Grain and Oils Information Center[117]. The lack of regional rice consumption data for women of childbearing age is an important limitation of this study. The maternal intake of rice could be lower than the average, which could influence the total folate intake after biofortification and, thus, the success of the intervention. Although most of the administrative areas have high folate intake levels after biofortification, this could be a problem in, for instance, Shandong and Xinjiang. However, this can be tackled by implementing a transgenic line with a higher folate content, such as 1,700 µg per 100 g of raw polished grains (see section 5.2.1.).

Rice consumption in Southern China is twice as large as in Northern China. On average, a Chinese person consumes 315.29 g of rice per day. Also the current daily folate intake is higher in Southern China (212.9 µg per woman of childbearing age) than in Northern China (188.0 µg per woman of childbearing age). This is in accordance with a study of Dexter[118] which found a higher prevalence of micronutrient deficiencies in rice consuming regions. A geographical presentation of this relationship is included in Annex 1, where rice consumption (Figure 8), rice production (Figure 9) and folate intake after biofortification (Figure 10) in China are juxtaposed.

Given the current rice consumption, the current folate intake and the additional folate intake of biofortified rice, a scenario where Chinese women completely switch to folate biofortified rice and do not alter their rice consumption pattern results in an average folate intake of 1,120.41 µg per day, per woman of childbearing age. This is almost three times the required intake or 280 % of the recommended daily intake (RDI). Regional folate intake levels after biofortification vary from 552.18 µg, per day, per person in Shandong (northeast) to 1,941.66 µg, per day, per person in Hunan (southeast). The contribution of the total folate intake after biofortification to the recommended dose varies between 136.29 % in Xinjiang (northwest) and 485.41 % in Hunan (southeast). Although rice consumption and folate intake in the northern regions are significantly lower, the required daily folate intake can still be achieved if folate biofortified rice is consumed.

When reporting folate levels above 1,000 µg, doubts about the risk of masking Vitamin B_{12} deficiency can be raised[102, 106, 107] (see also section 2). Vitamin B_{12} deficiency is characterized by macrocytic anemia and neurological impairment. The diagnosis of Vitamin B_{12} may be delayed by folic acid (reduction to H4folate), as the latter can correct the macrocytosis. However, as our folate biofortified rice mainly contains 5-methyl-tetrahydrofolate (MTHF), the effect of masking this micronutrient deficiency is absent[1]. This is because the synthesis of H4folate from 5-MTHF is catalyzed by a Vitamin B_{12} dependent enzyme (methionine synthase). Therefore, a functional folate deficiency occurs when Vitamin B_{12} is lacking, which makes an early diagnosis of Vitamin B_{12} deficiency possible[36]. Furthermore, in regions with folate intake levels higher than 1,000 µg after folate biofortification, such as in Southern China (except Tibet), a transgenic line with a lower folate content can be deployed to avoid negative side effects associated with high folate intake levels.

Table 8 Folate biofortification of rice in China in an optimal scenario (100 % consumption of biofortified rice). Current rice and folate consumption, added and total folate intake after biofortification, and % of RDI, per administrative area and region

Region/ Administrative area	**Current** rice cons.[a]	**Current** folate intake[b]	**Added** folate intake[c]	**Total** folate intake[d]	**Total** % of RDI[e]
	g /day/person	µg /day/CBA	µg /day/CBA	µg /day/CBA	
NORTH	181.14	188.0	528.92	**716.92**	179.23
Northeast	186.48	190.9	544.51	**735.41**	183.85
Beijing	379.50	190.9	1,108.15	**1,299.05**	324.76
Tianjin	286.54	190.9	836.70	**1,027.60**	256.90
Hebei	134.35	190.9	392.31	**583.21**	145.80
Shanxi	157.14	190.9	458.85	**649.75**	162.44
Inner Mongolia	166.50	190.9	486.18	**677.08**	169.27
Liaoning	279.71	190.9	816.75	**1,007.65**	251.91
Jilin	321.66	190.9	939.24	**1,130.14**	282.54
Heilongjiang	294.27	190.9	859.26	**1,050.16**	262.54
Shandong	123.73	190.9	361.28	**552.18**	138.04
Henan	133.18	190.9	388.90	**579.80**	144.95
Northwest	156.06	182.7	455.69	**638.39**	159.60
Shaanxi	159.21	182.7	464.88	**647.58**	161.90
Gansu	153.15	182.7	447.19	**629.89**	157.47
Qinghai	161.29	182.7	470.96	**653.66**	163.42
Ningxia	252.78	182.7	738.13	**920.83**	230.21
Xinjiang	124.12	182.7	362.44	**545.14**	136.29
SOUTH	412.90	212.9	1,205.66	**1,418.56**	354.64
Southeast	435.53	215.1	1,271.73	**1,486.83**	371.71
Shanghai	360.09	215.1	1,051.47	**1,266.57**	316.64
Jiangsu	390.25	215.1	1,139.52	**1,354.62**	338.65
Zhejiang	493.75	215.1	1,441.76	**1,656.86**	414.21
Anhui	284.95	215.1	832.04	**1,047.14**	261.79
Fujian	484.06	215.1	1,413.45	**1,628.55**	407.14
Jiangxi	520.37	215.1	1,519.49	**1,734.59**	433.65
Hubei	394.74	215.1	1,152.65	**1,367.75**	341.94
Hunan	591.29	215.1	1,726.56	**1,941.66**	485.41
Guangdong	358.42	215.1	1,046.60	**1,261.70**	315.42
Guangxi	575.54	215.1	1,680.59	**1,895.69**	473.92
Hainan	278.74	215.1	813.93	**1,029.03**	257.26
Southwest	348.79	210.4	1,018.46	**1,228.86**	307.22
Sichuan	357.40	210.4	1,043.60	**1,254.00**	313.50
Guizhou	300.85	210.4	878.48	**1,088.88**	272.22
Yunnan	307.11	210.4	896.75	**1,107.15**	276.79
Tibet	142.97	210.4	417.47	**627.87**	156.97
Chongqing	475.03	210.4	1,387.08	**1,597.48**	399.37
CHINA	**315.29**	**199.8**	920.64	**1,120.41**	280.10

CBA, woman of childbearing age; RDI, the recommended daily intake (i.e. folate)
[a] The daily rice consumption per person is expressed per person, in 2007[119].
[b] The current, regional folate intake before biofortification refers to findings from Zhao *et al*[17].
[c] The total added folate intake due to biofortification is based on the total current rice intake (column 1), folate intake (column 2) and additional folate content of biofortified rice, 2.92 µg per g.
[d] Sum of the current and additional folate intake.
[e] Calculated by comparing the total folate intake after biofortification with the recommended daily intake (RDI) of folate, i.e. a daily average folate intake of 400 µg folate per person.

6.2. Assumptions to measure the health impact of folate biofortified rice in China

In order to assess the health impact of folate biofortification, assumptions have to be made with respect to the effect of additionally absorbed folate on folate deficiency, the so-called "dose-response". The "dose" is understood as the average daily folate intake after biofortification in China and its regions (see Table 8, column 5). Although a few studies investigated the effect of different folate doses on the reduction of NTD incidence[59, 61], there is still a lack of scientific evidence to measure the health impact of each of the regional total folate intake levels in China. To overcome this problem, the "response" is evaluated by comparing the total folate intake level of women of childbearing age in each of the Chinese administrative areas with the recommended folate intake (see Table 8, column 6). In accordance to previous literature, the "response" to a daily folate intake of 400 µg or higher is understood as the prevention of folate deficiency and its adverse health outcomes, e.g. NTDs[2, 5]. Given that each administrative area in China exceeds the recommended daily folate intake of 400 µg per childbearing woman, consumption of folate biofortified rice with an initial folate content of approximately 1,200 µg per 100 g rice is assumed to prevent maternal folate deficiency and the risk of having a baby affected with an NTD caused by folate deficiency. The use of average, regional folate intake levels in the dose-response relationship is an important limitation, which may bias the results. Therefore, it is important to notice that it is the average women of childbearing age that can recover from folate deficiency through a biofortified diet. Nevertheless, a regional comparison of average folate intake levels with the recommended folate dose is also a valuable approach, as the effectiveness of biofortification as a strategy to combat folate deficiency in all Chinese administrative areas can be evaluated.

Because only women who agree to consume the folate biofortified rice will recover from folate deficiency and its health risks, the dose after biofortification only refers to a part of the market. This part is determined by the coverage rate, which combines women's acceptance of and their access to farmers willing to produce folate enriched rice. According to a recent Chinese study[6], 55.4 % of female rice consumers are willing to accept rice with a high folate content, while 32.3 % react indifferent and 12.3 % are reluctant. The findings for farmers are even more positive, with 66.7 % accepting and only 6.6 % of the farmers rejecting the rice. Although this study was conducted in Shanxi Province, the results are in line with other Chinese consumer studies on other GM food products[120-123]. Therefore, by combining acceptance and access to farmers, a low and high coverage rate are defined. While the former (36.95 %) contains only accepting female consumers which have access to approving farmers, the high coverage rate (81.91 %) also takes into account females and farmers that are indifferent to folate biofortified rice. These coverage rates are defined as the percentage of women that switch completely to folate biofortified rice, compared to women that hold on to traditional rice. In that way, they determine the percentage of women that can recover from folate deficiency by a biofortified diet. It is important to notice that it will depend on policy decisions regarding labeling and the availability of, and access to folate biofortified rice, and its product characteristics, such as visual and sensory attributes, whether women will actually be able and willing to switch completely to folate biofortified rice, instead of consuming a mix of rice varieties. Assuming such a mix may lead to a lower health impact of folate biofortification compared to the health benefits of a complete switch to folate biofortified rice.

6.3. The health impact of folate biofortification of rice in China (DALYs saved)

Based on the product and market characteristics of folate biofortified rice, described in the previous sections, the benefits to public health can be assessed by comparing the number of DALYs lost under the current situation ("without") with two biofortification scenario's ("with"). A low and high impact scenario are defined by the coverage rate of folate biofortified rice, i.e. 36.95 % (low) and 81.91 % (high) of Chinese women who are willing to accept and have access to this crop. These scenarios start from the assumption that the total folate intake under biofortification in each administrative area in China is significantly higher than the threshold to prevent folate deficiency and the risk of delivering a baby affected with an NTD (see Table 8). Table 9 and Table 10 summarize the health benefits of folate biofortification of rice in China under a low and high impact scenario, respectively. The results are expressed as the number of DALYs saved through the implementation of folate enriched rice. It is the difference between the number of DALYs lost under the current situation, shown in Table 7, and the DALYs lost under a folate biofortification scenario. This health impact, expressed in DALYs saved, refers to the number of children with an NTD that are "saved", which is based on the number of their mothers that recover from folate deficiency through a biofortified diet, i.e. the coverage rate. Since some of the parameters of the DALY framework are based on different years (i.e. NTD prevalence rate in 2004, rice consumption in 2007, coverage rate in 2008), this annual number of DALYs gained through biofortification has to be perceived as a theoretical number, rather than a real figure.

The potential introduction of folate biofortified rice in China increases the folate intake for women of childbearing age to 1,120 µg per day, and saves annually 116,090 DALYs in the low and 257,345 DALYs in the high biofortification scenario. Regarding the functional outcomes, fatal outcomes gain the largest number of DALYs, followed by spina bifida and encephalocele. While the burden in the low biofortification scenario is still around 200,000 DALYs per year, the high impact scenario reduces the annual number of DALYs lost to approximately 57,000. In other words, 63.05 % and 18.09 % of all NTDs caused by folate deficiency are still present after folate biofortification in the low and high impact scenario, respectively. This is equal to the percentage of women who did not switch to folate biofortified rice and, therefore, did not recovered from folate deficiency. When focusing on the four Chinese regions, the highest number of DALYs saved is obtained in Northeast China. Shanxi Province, characterized by one of the highest NTD prevalence rates in the world, benefits the most from the introduction of folate biofortified rice. The health impact in the northwest, southwest and southeast of China is significantly lower.

According to the target group, newborns or their mothers, the health impact can be interpreted in two ways. First, the health benefits can be expressed in terms of DALYs saved, based on the reduced number of births affected with an NTD, due to their mothers biofortified diet. Second, based on the coverage rate of folate biofortified rice, the health impact can also be understood as the number of women of childbearing age, including mothers, recovering from folate deficiency. This "double" health impact is an important argument to underpin future communication strategies in order to tackle folate deficiency and its adverse health outcomes.

Table 9 The health impact of folate biofortification of rice in China, low impact scenario, per functional outcome, expressed in the number of DALYs saved, per year, per region and administrative area

Region/ Administrative area	Non-Fatal			Fatal			Total
	Spina	Enceph.	Total (YLD)	Abortions	Stillbirths	Total (YLL)	
NORTH	21,825	4,989	26,814	35,879	33,460	69,338	**96,152**
Northeast	16,865	3,547	20,412	27,266	25,428	52,694	**73,105**
Beijing	230	51	281	375	350	726	**1,007**
Tianjin	259	48	307	409	381	791	**1,098**
Hebei	2,745	677	3,422	4,586	4,277	8,863	**12,285**
Shanxi	4,205	892	5,097	6,810	6,351	13,160	**18,257**
Inner Mongolia	1,376	325	1,701	2,278	2,124	4,402	**6,103**
Liaoning	983	126	1,109	1,469	1,370	2,839	**3,948**
Jilin	592	54	646	852	794	1,646	**2,292**
Heilongjiang	605	133	737	986	919	1,905	**2,642**
Shandong	1,936	318	2,254	2,997	2,795	5,793	**8,047**
Henan	3,933	925	4,858	6,504	6,066	12,570	**17,428**
Northwest	4,960	1,442	6,402	8,613	8,032	16,645	**23,047**
Shaanxi	2,022	705	2,727	3,685	3,436	7,121	**9,848**
Gansu	1,685	312	1,997	2,661	2,482	5,143	**7,140**
Qinghai	216	58	275	369	344	713	**988**
Ningxia	356	55	411	546	510	1,056	**1,467**
Xinjiang	681	312	993	1,351	1,260	2,612	**3,604**
SOUTH	4,056	1,461	5,517	7,462	6,959	14,420	**19,937**
Southeast	3,018	1,097	4,115	5,567	5,191	10,758	**14,873**
Shanghai	21	9	30	41	39	80	**110**
Jiangsu	246	39	286	380	354	734	**1,020**
Zhejiang	278	29	307	406	379	785	**1,093**
Anhui	644	222	866	1,169	1,091	2,260	**3,126**
Fujian	172	121	293	404	377	781	**1,075**
Jiangxi	257	100	357	484	451	935	**1,291**
Hubei	209	116	325	445	415	861	**1,186**
Hunan	464	114	578	775	723	1,498	**2,076**
Guangdong	428	188	616	837	781	1,618	**2,234**
Guangxi	258	151	409	561	523	1,084	**1,493**
Hainan	41	7	48	63	59	123	**170**
Southwest	1,038	364	1,402	1,895	1,767	3,662	**5,064**
Sichuan	205	126	330	454	423	877	**1,207**
Guizhou	558	53	611	807	752	1,559	**2,171**
Yunnan	114	100	214	297	277	574	**787**
Tibet	35	0	35	46	43	89	**124**
Chongqing	126	86	211	291	272	563	**775**
CHINA	**25,881**	**6,450**	**32,331**	**43,340**	**40,418**	**83,758**	**116,090**

DALYs, Disability-Adjusted Life Years; YLD, years lived in disability; YLL, years of life lost

Note: These figures are determined by a low coverage rate of folate biofortified rice, i.e. 36.95 %. The coverage rate is the percentage of women who consume folate biofortified rice and recover from folate deficiency. It is also the percentage of NTDs caused by folate deficiency that can be prevented by a mother's biofortified diet.

Table 10 The health impact of folate biofortification of rice in China, high impact scenario, per functional outcome, expressed in the number of DALYs saved, per year, per region and administrative area

Region/ Administrative area	Non-Fatal			Fatal			Total
	Spina	Enceph.	Total (YLD)	Abortions	Stillbirths	Total (YLL)	
NORTH	48,382	11,060	59,441	79,535	74,173	153,707	**213,149**
Northeast	37,385	7,863	45,248	60,442	56,367	116,810	**162,058**
Beijing	511	112	623	832	776	1,609	**2,231**
Tianjin	575	105	681	907	846	1,752	**2,433**
Hebei	6,085	1,501	7,585	10,166	9,481	19,647	**27,232**
Shanxi	9,322	1,977	11,299	15,096	14,078	29,173	**40,472**
Inner Mongolia	3,051	720	3,771	5,049	4,709	9,758	**13,529**
Liaoning	2,179	279	2,458	3,257	3,037	6,294	**8,752**
Jilin	1,311	120	1,431	1,888	1,761	3,649	**5,080**
Heilongjiang	1,341	294	1,634	2,185	2,038	4,223	**5,857**
Shandong	4,291	706	4,997	6,645	6,197	12,841	**17,838**
Henan	8,720	2,050	10,769	14,418	13,446	27,864	**38,633**
Northwest	10,996	3,197	14,193	19,092	17,805	36,897	**51,090**
Shaanxi	4,483	1,562	6,045	8,168	7,618	15,786	**21,831**
Gansu	3,735	692	4,427	5,899	5,501	11,401	**15,827**
Qinghai	480	129	609	818	763	1,581	**2,190**
Ningxia	789	123	912	1,211	1,130	2,341	**3,252**
Xinjiang	1,510	691	2,200	2,996	2,794	5,789	**7,989**
SOUTH	8,992	3,238	12,230	16,541	15,426	31,966	**44,197**
Southeast	6,691	2,431	9,122	12,340	11,508	23,848	**32,971**
Shanghai	47	21	67	92	86	177	**245**
Jiangsu	546	87	633	842	785	1,627	**2,260**
Zhejiang	617	65	681	901	840	1,740	**2,422**
Anhui	1,427	492	1,919	2,592	2,417	5,010	**6,929**
Fujian	382	268	650	896	836	1,732	**2,382**
Jiangxi	569	222	791	1,072	1,000	2,072	**2,863**
Hubei	463	258	721	987	921	1,908	**2,628**
Hunan	1,029	253	1,282	1,718	1,602	3,321	**4,603**
Guangdong	949	416	1,365	1,856	1,731	3,588	**4,953**
Guangxi	572	334	906	1,243	1,159	2,402	**3,309**
Hainan	90	16	106	141	131	272	**377**
Southwest	2,301	807	3,108	4,201	3,917	8,118	**11,226**
Sichuan	454	279	732	1,006	938	1,944	**2,676**
Guizhou	1,238	117	1,355	1,789	1,668	3,456	**4,812**
Yunnan	252	221	474	658	614	1,272	**1,745**
Tibet	78	0	78	102	95	197	**276**
Chongqing	279	190	469	646	603	1,249	**1,717**
CHINA	**57,373**	**14,298**	**71,671**	**96,076**	**89,598**	**185,674**	**257,345**

DALYs, Disability-Adjusted Life Years; YLD, years lived in disability;YLL, years of life lost

Note: These figures are determined by a high coverage rate of folate biofortified rice, i.e. 81.91 %. The coverage rate is the percentage of women who consume folate biofortified rice and recover from folate deficiency. It is also the percentage of NTDs caused by folate deficiency that can be prevented by a mother's biofortified diet.

As the health benefits of folate biofortified rice depend on demographic characteristics, such as population number and birth rate, a comparison of the regional results should be carefully analyzed. One way to overcome this, is to standardize the regional saved DALYs (Table 11). When the number of DALYs are expressed per 10,000 persons, the burden and health impact is relatively the highest in the Northwest China, while the absolute numbers are the highest in the Northeast. The current situation is most problematic in Shanxi (northeast), Gansu (northwest), Anhui (southeast) and Guizhou (southwest).

Table 11 Burden of folate deficiency (DALYs lost) and the health impact of folate biofortification (DALYs saved) in China, expressed in the total number of DALYs and per 10,000 persons, per year, per region and administrative area

Region/ Administrative area	**Current burden (DALYs lost)**		**Folate biofortication (DALYs saved)**			
			Low impact		High impact	
	Total	Per 10,000 persons	Total	Per 10,000 persons	Total	Per 10,000 persons
NORTH	260,223	4.68	96,152	1.73	213,149	3.83
Northeast	197,849	4.31	73,105	1.59	162,058	3.53
Beijing	2,724	1.68	1,007	0.62	2,231	1.38
Tianjin	2,970	2.70	1,098	1.00	2,433	2.21
Hebei	33,246	4.71	12,285	1.74	27,232	3.86
Shanxi	49,411	**14.31**	18,257	**5.29**	40,472	**11.72**
Inner Mongolia	16,517	6.74	6,103	2.49	13,529	5.52
Liaoning	10,685	2.45	3,948	0.90	8,752	2.00
Jilin	6,202	2.23	2,292	0.82	5,080	1.82
Heilongjiang	7,151	1.83	2,642	0.68	5,857	1.50
Shandong	21,777	2.29	8,047	0.85	17,838	1.87
Henan	47,165	4.91	17,428	1.81	38,633	4.02
Northwest	62,374	6.39	23,047	2.36	51,090	5.23
Shaanxi	26,652	6.98	9,848	2.58	21,831	5.71
Gansu	19,323	**7.25**	7,140	**2.68**	15,827	**5.94**
Qinghai	2,674	4.77	988	1.76	2,190	3.91
Ningxia	3,971	6.43	1,467	2.37	3,252	5.26
Xinjiang	9,754	4.65	3,604	1.72	7,989	3.81
SOUTH	53,957	0.71	19,937	0.26	44,197	0.58
Southeast	40,252	0.71	14,873	0.26	32,971	0.58
Shanghai	299	0.16	110	0.06	245	0.13
Jiangsu	2,759	0.36	1,020	0.13	2,260	0.29
Zhejiang	2,957	0.58	1,093	0.21	2,422	0.48
Anhui	8,459	**1.35**	3,126	**0.50**	6,929	**1.11**
Fujian	2,908	0.80	1,075	0.30	2,382	0.65
Jiangxi	3,495	0.79	1,291	0.29	2,863	0.65
Hubei	3,209	0.55	1,186	0.20	2,628	0.45
Hunan	5,619	0.87	2,076	0.32	4,603	0.71
Guangdong	6,047	0.64	2,234	0.23	4,953	0.52
Guangxi	4,040	0.84	1,493	0.31	3,309	0.69
Hainan	461	0.54	170	0.20	377	0.44
Southwest	13,705	0.69	5,064	0.25	11,226	0.56
Sichuan	3,267	0.39	1,207	0.14	2,676	0.32
Guizhou	5,874	**1.53**	2,171	**0.56**	4,812	**1.25**
Yunnan	2,131	0.46	787	0.17	1,745	0.38
Tibet	337	1.17	124	0.43	276	0.96
Chongqing	2,097	0.73	775	0.27	1,717	0.60
CHINA	**314,180**	**2.38**	**116,090**	**0.88**	**257,345**	**1.95**

DALYs, Disability-Adjusted Life Years

6.4. Comparison of health impact studies with respect to biofortified staple crops

By expressing the number of DALYs gained per 10 000 persons, the potential health impact of folate biofortified rice in China can be compared with results from other health impact studies that applied the DALY approach. Table 12 presents the estimated potential health impact of introducing different transgenic and non-transgenic biofortified staple crops in several developing countries.

In comparison with the burden of micronutrient deficiencies in other health impact studies, the burden of folate deficiency in this study is relatively the lowest. However, as only NTDs caused by folate deficiency are included as functional outcomes, only a part of this burden is calculated in this study. If other functional outcomes would be included, such as heart diseases, the target group would be extended to the total population. Given the estimated total number of folate deficient people in China, 258 million, the actual burden of folate deficiency would be much higher.

With respect to the health impact, most of the DALYs are saved through the introduction of Vitamin A biofortification in Uganda (sweet potato) and Congo (cassava roots). The relative impact of iron or zinc biofortification on public health is the highest in India and Pakistan, and North-East Brazil (iron) and Bangladesh (zinc). While the burden of our folate biofortified rice in China is relatively low, this intervention obtains relatively one of the highest number of DALYs. This is mainly due to the high folate intake levels after biofortification (see section 6.1.) and the assumption that these intake levels prevent maternal folate deficiency and the risk of having a baby with an NTD (see section 6.2).

Although this comparison is useful to place folate biofortification in the context of other biofortified interventions to tackle micronutrient deficiencies in developing countries, these findings should be interpreted with caution. First, the parameters of the DALY framework and the characteristics of the impact scenarios differ from one study to another. Second, as there is currently no biofortified staple crop commercialized, regardless of the technique that has been used, the expected micronutrient content after biofortification is mostly based on estimates from plant breeders. This is, for instance, the case in the HarvestPlus health impact analyses (http://www.harvestplus.org) of Meenakshi *et al*[22].

Table 12 Comparison of the burden of micronutrient deficiencies (DALYs lost) and the health impact of potential biofortified staple crops (DALYs saved), per crop, nutrient, and country, in DALYs lost/saved per 10,000 persons and in % reduction of the burden

					Health impact			
				Burden of	Pessimistic		Optimistic	
Crop	**Nutrient**	**Technique**	**Target country**	**deficiencies**	Relative	%	Relative	%
Rice	Vitamin A	T	India[b]	20.52	1.80	8.8	12.19	59.4
			Philippines[c]	32.06	1.82	5.7	10.11	31.5
	Iron	C	Bangladesh[a]	34.36	2.75	8.0	0.91	2.6
			India[a]	35.27	1.76	5.0	7.22	20.5
			India[e]	35.27	4.41	12.5	5.29	15.0
			Philippines[a]	8.31	0.33	4.0	12.19	146.7
	Zinc	C	Bangladesh[a]	30.86	5.25	17.0	10.18	33.0
			India[a]	24.96	4.99	20.0	13.98	56.0
			Philippines[a]	9.50	1.23	12.9	4.08	42.9
	Folate	T	China[f]	2.38	0.88	37.0	1.95	81.9
			Shanxi Province[f]	14.31	5.29	37.0	11.72	81.9
Wheat	Iron	C	India[e]	35.27	2.65	7.0	13.76	39.0
		C	India[a]	35.27	2.47	37.0	13.23	375.0
			Pakistan[a]	57.65	3.46	7.5	8.82	15.3
	Zinc	C	India[a]	24.96	2.25	6.0	11.98	48.0
			Pakistan[a]	40.11	2.01	9.0	13.24	33.0
Maize	Vitamin A	C	Ethiopia[a]	52.76	0.53	5.0	8.97	17.0
			Kenya[a]	32.27	2.58	1.0	10.33	32.0
Cassava roots	Vitamin A	C	Congo[a]	1206.93	36.21	8.0	386.22	32.0
			Nigeria[d]	100.26	7.05	3.0	21.11	21.1
			Nigeria[a]	57.14	1.71	7.0	16.00	28.0
			North-East Brazil[a]	10.00	0.40	3.0	1.90	19.0
Beans	Iron	C	Honduras[a]	57.65	1.06	4.0	16.14	28.0
			Nicaragua[a]	53.61	1.61	1.8	5.84	10.9
			North-East Brazil[a]	40.00	3.60	3.0	8.58	21.5
	Zinc	C	Honduras[a]	13.27	0.40	9.0	1.99	15.0
			Nicaragua[a]	17.87	0.36	3.0	1.97	11.0
			North-East Brazil[a]	20.00	1.00	2.0	4.00	20.0
Sweet potato	Vitamin A	C	Uganda[a]	56.64	21.52	5.0	36.25	64.0

DALYs, Disability-Adjusted Life Years; T, biofortification using transgenic methods; C, biofortification using conventional methods
[a] Own calculations, based on Meenakshi *et al*[22]
[b] Own calculations, based on Stein *et al*[25]
[c] Own calculations, based on Zimmermann & Qaim[26]
[d] Own calculations, based on Manyong[27]
[e] Own calculations, based on Stein *et al*[28]
[f] These figures are based on Table 11, column 5 (burden), 7 (pessimistic) and 9 (optimistic)

7. Conclusions

This paper evaluates the potential health benefits of a biofortified staple crop, namely rice with a high folate content, in China. By means of the Disability-Adjusted Life Years approach, the health impact on folate deficiency is measured in terms of the number of DALYs lost. As China is the world leader in rice consumption and production, and a key player in the research field of genetically modification of rice, China was selected as the study location. Due to the specific differences in terms of NTD prevalence, rice consumption and current folate intake, this health impact analysis is conducted at regional and administrative divisional level.

Application of the DALY method reveals that the current burden of folate deficiency amounts to an annual loss of 314,180 DALYs. The introduction of rice with a folate content of 1,200 µg per 100 g rice in China would save 116,090 DALYs in the low impact scenario and 257,345 DALYs in the high impact scenario. The burden and the health impact are the highest in

Northern China, in absolute (northeast) as well as relative numbers (northwest). The region with the highest NTD prevalence rate, Shanxi Province, will benefit the most from folate biofortification.

The regional health benefits in China are based on average daily folate intakes between 545 µg and 1,941 µg per woman of childbearing age, which are significantly higher than the recommended folate intake of 400 µg. Although these numbers refer to averages, the high folate intake level in China demonstrates that folate biofortification of rice can be a valuable means to reduce folate deficiency and neural-tube defects. Especially in poor, rural regions where other folate interventions are less feasible the introduction of folate enriched rice could be important. Even in the northern regions, where wheat is more popular than rice, folate biofortification of rice could contribute to achieve the recommended folate dose.

The DALY framework is a popular method to analyze the health impact of implementing biofortified staple crops. As this is the first attempt to measure the health benefits of folate biofortification, some recommendations can be made to further improve the research results. First, collecting primary or fine tune secondary data would significantly benefit this health impact study. While some parameters of the DALY framework have to be further explored (e.g. a stable folate content of folate enriched rice and the exact degree of bioavailability), others need to be adapted according to the study location (e.g. the current folate intake and the contribution level of folate deficiency to NTDs, per administrative area) or the target group (e.g. rice consumption of women of childbearing age). Second, to be able to calculate all health benefits of folate biofortified rice, additional research is required to define the contribution of folate deficiency to each of its functional outcomes.

However, before folate biofortified rice can be approved, it still needs to be figured out how it will be introduced in China. The price, the availability, the accessibility and the dissemination of folate biofortified rice, labeling and other legislation requirements, the selection of the transgenic line and the rice variety (e.g. multi-biofortification) and product attributes will influence consumer and farmer acceptance. Thus, public acceptance will be a crucial determinant of the approval and the success of folate biofortified rice. Therefore, to further increase the health impact of folate biofortified rice in China, once commercialization is approved, communication strategies should focus on the coverage rate of folate biofortified rice. The higher the coverage rate, the more women recover from folate deficiency, by which more NTDs will be prevented.

Building upon the investigated (regional) health impact, future research should focus on analyzing the cost-effectiveness of folate biofortified rice in China. This can be done by juxtaposing the costs of biofortification and the calculated health benefits. Another research topic is to involve and compare different strategies to improve folate intake. As awareness and use of folic acid pills in China is often low, especially in rural regions, and altering dietary habits is less feasible in poor, rural regions, folate biofortified rice has to be considered as a complementary means to combat folate deficiency. Although folate biofortification has particular advantages due to its pro-poor and pro-rural approach, a combination of policy interventions will be probably the most feasible and effective method to tackle folate deficiency in all sections of the population.

References

1 Storozhenko S *et al.* Folate fortification of rice by metabolic engineering. *Nat Biotechnol*. 2007 **25**: 1277-9.

2 Molloy A, Scott J. Folates and prevention of disease. *Public Health Nutr*. 2001 **4**: 601-9.

3 MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *Lancet*. 1991 **338**: 131-7.

4 Stockley L, Lund V. Use of folic acid supplements, particularly by low-income and young women: a series of systematic reviews to inform public health policy in the UK. *Public Health Nutr*. 2008 **11**: 807-21.

5 Lumley J, Watson L, Watson M, Bower C. Periconceptional supplementation with folate and/or multivitamins for preventing neural tube defects. *Cochrane Database Syst Rev*. 2001: Issue 3, CD001056. .

6 De Steur H *et al.* Willingness to Accept and Purchase Genetically Modified Rice with High Folate Content in Shanxi Province, China. *Appetite*. 2010 **54**: 118-25.

7 Gu X *et al.* High Prevalence of NTDs in Shanxi Province: A Combined Epidemiological Approach. *Birth Defects Res A Clin Mol Teratol*. 2007 **79**: 702-7.

8 Li Z, Ren A, Zhang L, Guo Z, Li Z. A population-based case-control study of risk factors for neural tube defects in four high-prevalence areas of Shanxi province, China. *Paediatr Perinat Epidemiol*. 2006 **20**: 43-53.

9 Dai L *et al.* Dynamic monitoring of neural tube defects in China during 1996 to 2000 (Article in Chinese). *Zhonghua Yu Fang Yi Xue Za Zhi*. 2002 **36**: 402-5.

10 Li Z, Ren A, Zhang L, Liu J, Li Z. Periconceptional use of folic acid in Shanxi Province of northern China. *Public Health Nutr*. 2007 **10**: 471-6.

11 Ren A *et al.* Awareness and use of folic acid, and blood folate concentrations among pregnant women in northern China - An area with a high prevalence of neural tube defects. *Reprod Toxicol*. 2006 **22**: 431-6.

12 Ren A *et al.* Comparison of blood folate levels among pregnant Chinese women in areas with high and low prevalence of neural tube defects. *Public Health Nutr*. 2007 **10**: 762-8.

13 Zhang B *et al.* Correlation Between Birth Defects and Dietary Nutrition Status in a High Incidence Area of China. *Biomed Environ Sci*. 2008 **21**: 37-44.

14 Jia H, Jayaraman K, Louët S. China ramps up efforts to commercialize GM rice. *Nat Biotechnol*. 2004 **22**: 642.

15 Wang Y, Johnston S. The status of GM rice R&D in China. *Nat Biotechnol*. 2007 **25**: 717-8.

16 Shuping N, Miles T. *Top rice producer China approves GMO strain. Reuters. 2009-11-27*, 2009.

17 Zhao Y *et al.* Plasma folate status and dietary folate intake among Chinese women of childbearing age. *Matern Child Nutr*. 2009 **5**: 104-16.

18 Murray C, Lopez A. *The Global Burden of Disease*. Cambridge: Harvard University, 1996.

19 Anand S, Hanson K. DALYs: Efficiency versus equity. *World Dev*. 1998 **26**: 307-10.

20 Lyttkens C. Time to disable DALYs? On the use of disability-adjusted life years in health policy. *Eur J Health Econ*. 2003 **4**: 195-202.

21 Horton S. The Economics of Food Fortification. *J Nutr*. 2006 **136**: 1068-71.

22 Meenakshi J *et al. How cost-effective is biofortification in combating micronutrient malnutrition? An ex-ante assessment. HarvestPlus Working Paper No. 2*. Washington, D.C.: International Food Policy Research Institute, 2007.

23 Stein A *et al. Analyzing the Health Benefits of Biofortified Staple Crops by Means of the Disability-Adjusted Life Years Approach: a Handbook Focusing on Iron, Zinc and Vitamin A. HarvestPlus Technical Monograph 4*. Washington, D.C.: International Food Policy Research Institute, 2005.

24 Fan Y, Wan J, Lei X. Progress of HarvestPlus China Program. *J Agr Sci Technol*. 2009 **11**: 1-6.

25 Stein A, Sachdev H, Qaim M. Potential impact and cost-effectiveness of Golden Rice. *Nat Biotechnol*. 2006 **24**: 1200-1.

26 Zimmermann R, Qaim M. Potential Health Benefits of Golden Rice: a Philippine Case Study. *Food Policy*. 2004 **29**: 147-68.

27 Manyong V. Ex-Ante Evaluation of Nutrition and Health Benefits of Biofortified Cassava Roots in Nigeria: The Dalys Approach. *Proceedings of the Inaugural Symposium*. Nairobi, Kenya, 2004

28 Stein A *et al.* Potential impacts of iron biofortification in India. *Soc Sci Med*. 2008 **66**: 1797-808.

29 Ma G *et al.* Iron and zinc deficiencies in China: what is a feasible and cost-effective strategy? *Public Health Nutr*. 2007 **11**: 632-8.

30 WHO. *Standards for Maternal and Neonatal Care. Iron and folate supplementation.* Geneva: World Health Organization, 2006.

31 USFDA. Food labeling: Health Claims and Label Statements; Folate and Neural Tube Defects. Final Rule. *Fed Regist*. 1996 **61**: 8752-81.

32 Geisel J. Folic acid and neural tube defects in pregnancy - A review. *J Perinat Neonatal Nurs*. 2003 **17**: 268-79.

33 Blancquaert D *et al.* Folates and folic acid: from fundamental research towards sustainable health. *Crit Rev Plant Sci*. 2008 **29**: 14-35.

34 Rader J, Schneeman B. Prevalence of neural tube defects, folate status, and folate fortification of enriched cereal-grain products in the United States. *PEDIATRICS*. 2006 **117**: 1394-9.

35 US Department of Agriculture. Agricultural Research Service. USDA National Nutrient Database for Standard Reference, release 21. ed, 2008.

36 Tam C *et al.* Periconceptional Folic Acid Supplementation: A New Indication for Therapeutic Drug Monitoring. *Ther Drug Monit*. 2009 **31**: 319-26.

37 Wright A, Dainty J, Finglas P. Folic acid metabolism in human subjects revisited: potential implications for proposed mandatory folic acid fortification in the UK *Br J Nutr*. 2007 **98**: 667-75.

38 Mills J *et al.* Low vitamin B-12 concentrations in patients without anemia: the effect of folic acid of grain. *Am J Clin Nutr*. 2003 **77**: 1474-7.

39 Rogovik A, Vohra S, Goldman R. Safety Considerations and Potential Interactions of Vitamins: Should Vitamins Be Considered Drugs? *Ann Pharmacother*. 2010 **44**: 311-24.

40 EUROCAT. *EUROCAT Special Report: Prevention of Neural Tube Defects by Periconceptional Folic Acid Supplementation in Europe, 2nd Edition*: EUROCAT Central Registry, University of Ulster, 2005.

41 Finglas P *et al.* Research goals for folate and related B vitamin in Europe. *Eur J Clin Nutr*. 2006 **60**: 287-94.

42 Mclean E, Benoist B, Allen L. Review of the magnitude of folate and vitamin B12 deficiencies worldwide. *Food Nutr Bull*. 2008 **29**: S38-51.

43 Selhub J, Jacques P, Dallal G, Choumenkovitch S, Rogers G. The use of blood concentrations of vitamins and their respective functional indicators to define folate and vitamin B12 status. *Food Nutr Bull*. 2008 **29**: S67-73.

44 De Benoist B. Conclusions of a WHO Technical Consultation on folate and vitamin B12 deficiencies. *Food Nutr Bull*. 2008 **29**: S238-44.

45 Hao L *et al.* Geographical, Seasonal and Gender Differences in Folate Status among Chinese Adults. *J Nutr*. 2003 **133**: 3630-5.

46 Shrubsole M *et al.* Dietary folate intake and breast cancer risk: results from the Shanghai Breast Cancer Study. *Cancer Res*. 2001 **61**: 7136-41.

47 Li Z *et al.* Difference in prevalence and seasonal variations of folate deficiencies among pre-marital women from high and low risk areas of neural tube defects (in Chinese). *Zhongguo Yousheng Youyu Zazhi*. 1996 **1**: 1-4.

48 Ronnenberg A, Goldman M, Aitken I, Xu X. Anemia and Deficiencies of Folate and Vitamin B-6 Are Common and Vary with Season in Chinese Women of Childbearing Age. *J Nutr*. 2000 **130**: 2703-10.

49 Zhang L *et al.* Folate concentrations and folic acid supplementation among women in their first trimester of pregnancy in a rural area with a high prevalence of neural tube defects in Shanxi, China. *Birth Defects Res A Clin Mol Teratol*. 2006 **76**: 461-6.

50 Gao X *et al.* Dietary pattern is associated with homocysteine and B vitamin status in an urban Chinese population. *J Nutr*. 2003 **133**: 3636-42.

51 Cherian A, Seena S, Bullock R, Antony A. Incidence of neural tube defects in the least-developed area of India: a population-based study. *Lancet*. 2005 **366**: 930-1.

52 Moore C *et al.* Elevated rates of severe neural tube defects in a high-prevalence area in northern China. *Am J Med Genet*. 1997 **73**: 113-8.

53 Xiao K. The epidemiology of neural tube defects in China. *Zhonghua Yi Xue Za Zhi*. 1989 **69**: 189-91.

54 Shi-an Y, Mason J, Mathys E, Deitchler M. The status of micronutrients and the efficiency of intervention in China. *Food Nutr Bull*. 2004 **25**: 81-2.

55 Jingxiong J, Toschke A, Kries VR, Koletzko B, Liangming L. Vitamin A status among children in China. *Public Health Nutr*. 2006 **9**: 955-60.

56 UNICEF and The Micronutrient Initiative. *Vitamin and Mineral Deficiency: A Damage Assessment Report for China*. New York, NY, USA: UNICEF, 2004.

57 UN. *5th report on the world nutrition situation*. Geneva: UN SCN, 2004.

58 Pinar T, Tatevosyants N, Singer D. Central Nervous System Malformations in a Perinatal/Neonatal Autopsy Series. *Pediatr Dev Pathol*. 1998 **1**: 42-8.

59 Daly S *et al.* Minimum effective dose of folic acid for food fortification to prevent neural-tube defects. *Lancet*. 1997 **350**: 1666-9.

60 De Wals P *et al.* Reduction in Neural-Tube Defects after folic acid fortification in Canada. *N Engl J Med*. 2007 **357**: 135-42.

61 Moore L, Bradlee M, Singer M, Rothman K, Milunsky A. Folate intake and the risk of Neural Tube Defects: An estimation of Dose-Response. *Epidemiology*. 2003 **14**: 200-2005.

62 Christianson A, Howson C, Modell B. *March of Dimes. Global Report on Birth Defects* White Plains, New York: March of Dimes Birth Defects Foundation, 2006.

63 UNICEF and The Micronutrient Initiative. *Vitamin and Mineral Deficiency: A Global Damage Assessment Report*. New York, NY, USA: UNICEF, 2004.

64 Kondo A, Kamihira O, Ozawa H. Neural tube defects: Prevalence, etiology and prevention. *Int J Urol*. 2009 **16**: 49-57.

65 Busby A. Preventing neural tube defects in Europe: population based study. *Br Med J*. 2005 **330**: 574-5.

66 Mathews T. *Trends in Spina Bifida and Anencephalus in the United States, 1991-2005*. Hyattsville, MD: National Center for Health Statistics, 2007.

67 National Bureau of Statistics of China. *China Statistical Yearbook 2008*. Beijing: China Statistics Press, 2008.

68 WHO. *Definitions and Indicators in Family Planning, Maternal and Child Health and Reproductive Health*. Geneva: WHO, 2001.

69 U.S. Department of Health and Human Services PHS, Centers for Disease Control. *The Risk Approach in Perinatal Health. Shunyi County, People's Republic of China*. Washington, DC: Government Printing Office, 1989.

70 Sever L. Looking for causes of neural tube defects: where does the environment fit in? *Environ Health Perspect*. 1995 **103**: 165-71.

71 Todoroff K, Shaw G. Prior spontaneous abortion, prior elective termination, interpregnancy interval, and risk of neural tube defects. *Am J Epidemiol*. 2000 **151**: 505-11.

72 Berry R *et al.* Prevention of Neural-Tube Defects with folic acid in China. *N Engl J Med*. 1999 **341**: 1485-91.

73 Chen G *et al.* Prevention of NTDs with Periconceptional Multivitamin Supplementation Containing Folic Acid in China. *Birth Defects Res A Clin Mol Teratol*. 2008 **82**: 592-6.

74 Access Economics. *Cost benefit analysis of fortifying the food supply with folic acid. Report for Food Standards Australia New Zealand*. Melbourne: Access Economics, 2006.

75 Mathers C, Vos T, Stevenson C. *The burden of disease and injury in Australia. AIHW cat. no. PHE 17*. Canberra: AIHW, 1999.

76 Czernichow S *et al.* Case for folic acid and vitamin B12 fortification in Europe. *Semin Vasc Med*. 2005 **5**: 156-62.

77 Cornel M, De Smit D, De Jong-Van Den Berg L. Folic acid - the scientific debate as a base for public health policy. *Reprod Toxicol*. 2005 **20**: 411-5.

78 Cordero J, Do A, Berry R. Review of interventions for the prevention and control of folate and vitamin B12 deficiencies. *Food Nutr Bull*. 2008 **29**: S188-95.

79 Cavalli-Sforza T, Berger J, Smitasiri S, Viteri F. Weekly iron-folic acid supplementation of women of reproductive age: Impact overview, lessons learned, expansion plans, and contributions toward achievement of the millennium development goals. *Nutr Rev*. 2005 **63**: S152-8.

80 Campos-Bowers M, Wittenmyer B. Biofortification in China: policy and practice. *Health Res Policy Sys*. 2007 **5**: 1-7.

81 Centers for Disease Control and Prevention. Use of dietary supplements containing folic acid among women of childbearing age - United States, 2005. *MMWR Morb Mortal Wkly Rep*. 2005 **54**: 955-8.

82 Van Der Pal-De Bruin K *et al.* Influence of educational level on determinants of folic acid use. *Paediatr Perinat Epidemiol*. 2003 **17**: 256-63.

83 Lawrence M *et al.* Design and evaluation of interventions promoting periconceptional multivitamin use. *Am J Prev Med*. 2003 **25**: 17-24.

84 Chinese Ministry of Health. *National Action Plan for Reducing Birth Defects and Disabilities in China for 2002-2010*. Beijing: Ministry of Health of the People's Republic of China, 2001.

85 Juan S. *Program to help lower birth defects*, China Daily. 2009-06-18.

86 Li Z, Hao L. National Neural Tube Defects Prevention Program in China. *Food Nutr Bull*. 2008 **29**: S196-204.

87 Underwood B. Overcoming micronutrient deficiencies in developing countries: Is there a role for agriculture? *Food Nutr Bull*. 2000 **21**: 356-60.

88 Chen L, Rivera M. The Costa Rican experience: Reduction of neural tube defects following food fortification programs. *Nutr Rev*. 2004 **62**: S40-3.

89 Choumenkovitch S *et al*. Folic acid intake from fortification in United States exceeds predictions. *J Nutr*. 2002 **132**: 2792-8.

90 Hertrampf E *et al.* Consumption of folic acid-fortified bread improves folate status in women of reproductive age in Chile. *J Nutr*. 2003 **133**: 3166-9.

91 Centers for Disease Control and Prevention. Spina bifida and anencephaly before and after folic acid mandate. United States, 1995-1996 and 1999-2000. *MMWR Morb Mortal Wkly Rep*. 2004 **53**: 362-5.

92 SACN (Scientific Advisory Committee on Nutrition). *Folate and Disease Prevention*. London: TSO, 2005.

93 FFI (Flour Fortification Initiative). *Overview of Progress Toward Fortification. China. Executive Summary.* Atlanta, GA: FFI, 2009.

94 Lawrence M *et al.* Examination of selected national policies towards mandatory folic acid fortification. *Nutr Rev*. 2009 **67**: S73-S8.

95 WHO *et al. Recommendations on wheat and maize flour fortification. Meeting Report: Interim Consensus Statement.* Geneva: World Health Organization, 2009.

96 Ruel M. *Can food-based strategies help reduce vitamin A and iron deficiencies? A review of recent evidence. Food Policy Review No. 5*. Washington D.C.: International Food Policy Research Institute, 2001.

97 Koebnick C, Heins U, Hoffmann I, Dagnelie P, Leitzmann C. Folate status during pregnancy in women is improved by long-term high vegetable intake compared with the average western diet. *J Nutr*. 2001 **131**: 733-9.

98 Cuskelly G, McNulty H, Scott J. Effect of increasing dietary folate on red-cell folate: implications for prevention of neural tube defects. *Lancet*. 1996 **347**: 657-9.

99 Qaim M, Stein A, Meenakshi J. Economics of biofortification. *26th International Association of Agricultural Economists (IAAE) Conference*. Gold Coast, Australia, 2006

100 Beyer P *et al.* Golden Rice: introducing the β-carotene biosynthesis pathway into rice endosperm by genetic engineering. *J Nutr*. 2002 **132**: S506-10.

101 McIntosh S, Brushett D, Henry R. GTP cyclohydrolase 1 expression and folate accumulation in the developing wheat seed. *J Cereal Sci*. 2008 **48**: 503-12.

102 Bekaert S *et al.* Folate biofortification in food plants. *Trends Plant Sci*. 2008 **13**: 28-35.

103 US Department of Agriculture Agricultural Research Service. USDA National Nutrient Database for Standard Reference, release 21. ed, 2009.

104 Bouis H. Plant breeding: a new tool for fighting micronutrient malnutrition. *J Nutr*. 2002 **132**: S491-4.

105 Rébeillé F *et al.* Folates in plants: biosynthesis, distribution, and enhancement *Physiologia Plantarum*. 2006 **126**: 330-42.

106 Scott J, Rébeillé F, Fletcher J. Folic acid and folate: the feasibility for nutritional enhancement in plant foods. *J Sci Food Agric*. 2000 **80**: 795-824.

107 Bailey L. Folate and Vitamin B12 Recommended intakes and status in the United States. *Nutr Rev*. 2004 **62**: 14-20.

108 FSAI. *Report of the national committee on folic acid food fortification*. Dublin: FSAI, 2006.

109 De Groote H, Kimenju S. Comparing consumer preferences for color and nutritional quality in maize: Application of a semi-double-bound logistic model on urban consumers in Kenya. *Food Policy*. 2008 **33**: 362-70.

110 Stevens R, Winter-Nelson A. Consumer acceptance of provitamin A-biofortified maize in Maputo, Mozambique. *Food Policy*. 2008 **33**: 341-51.

111 Achanta K, Boeneke C, Aryana K. Characteristics of Reduced Fat Milks As Influenced By the Incorporation of Folic Acid. *J Dairy Sci*. 2007 **90**: 90-8.

112 Pray C, Huang J. Biofortification for China: Political Responses to Food Fortification and GM Technology, Interest Groups, and Possible Strategies. *AgBioForum*. 2007 **10**: 161-9.

113 Bouis H, McClafferty B. *The Biofortification Challenge Program. 2007 Annual Report for the Executive Council of the CGIAR*. Washington, D.C.: HarvestPlus, 2008.

114 James C. *China Approves Biotech Rice and Maize in Landmark Decision*, ISAAA Crop Biotech Update. 2009.

115 Engel K-H, Frenzel T, Miller A. Current and future benefits from the use of GM technology in food production. *Toxicol Lett*. 2002 **127**: 329-36.

116 Juma C, Paarlberg R, Pray C. Patterns of political support and pathways to final impact. *AgBioForum*. 2007 **10**: 201-7.

117 CNGOIC. *Food Grains Weekly Report. Newsletter, various issues*. Beijing: CNGOIC, 2009.

118 Dexter P. *Rice fortification for developing countries*. Fayetteville: University of Arkansas, 1998.

119 CNGOIC. *Monthly Report on Food Grains Supply and Demand Situation, no. 114*. Beijing: CNGOIC, 2009.

120 Ho P, Vermeer E, Zhao J. Biotechnology and food safety in China: consumer's acceptance or resistance? *Dev Change*. 2006 **37**: 227-54.

121 Huang J, Qiu H, Bai J, Pray C. Awareness, acceptance of and willingness to buy genetically modified foods in Urban China. *Appetite*. 2006 **46**: 144-51.

122 Li Q, Curtis K, McCluskey J, Wahl T. Consumer attitudes toward genetically modified foods in Beijing, China. *AgBioForum*. 2002 **5**: 145-52.

123 Lin W, Somwaru A, Tuan F, Huang J, Bai J. Consumer attitudes toward biotech foods in China. *J Int Food Agribus Mark.* 2006 **18**: 177-203.

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Annex 1 Geographical presentation of the main characteristics of the study location related to the DALY framework

Figure 6 Administrative areas and provinces in China, per region

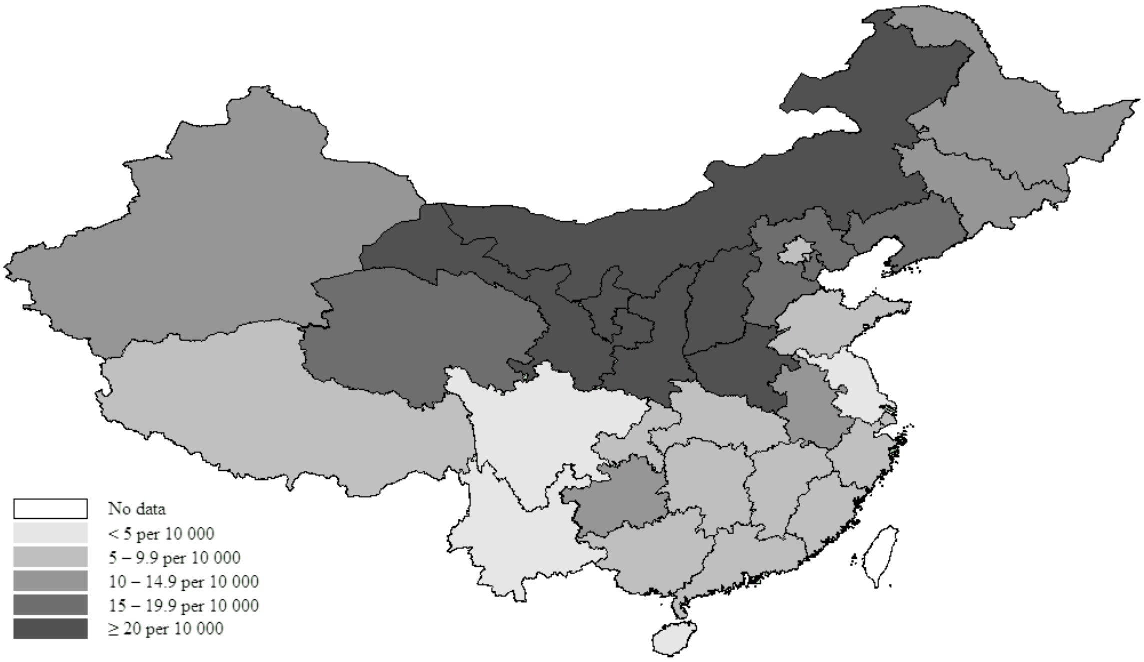

Figure 7 NTD prevalence rates in China, per administrative region (1996-2000), in number of NTDs per 10,000 births
Source: Table 1, based on Dai *et al*[9]

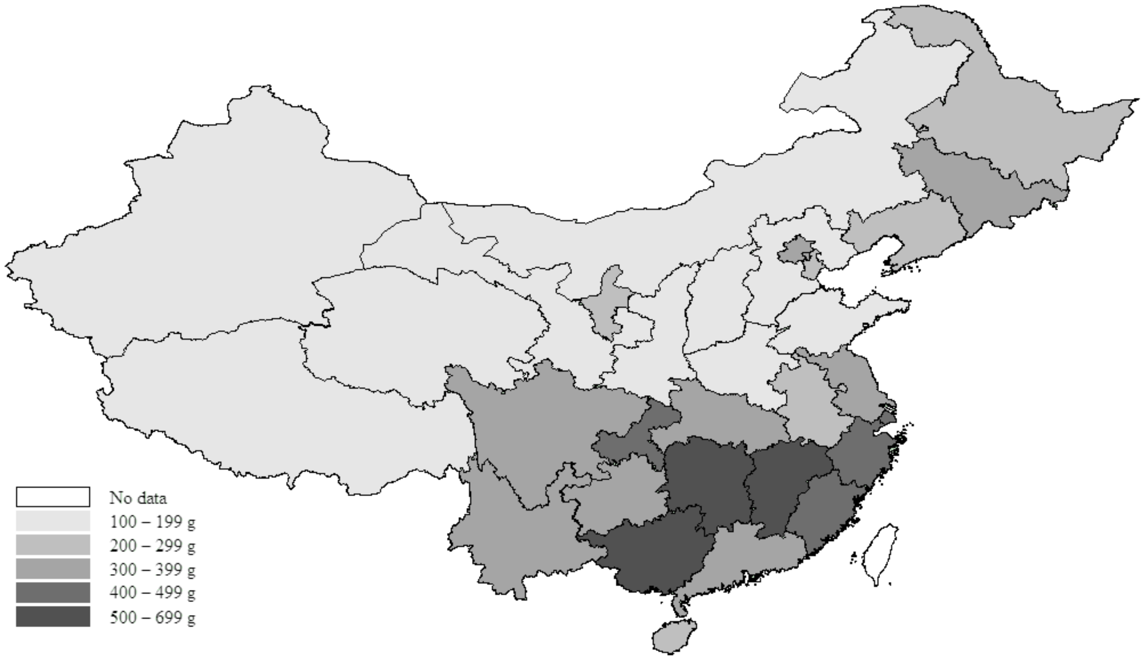

Figure 8 Current rice consumption patterns in China, per administrative region, in g per day per women of childbearing age
Source: Table 6, based on rice consumption data of the CNGOIC[119]

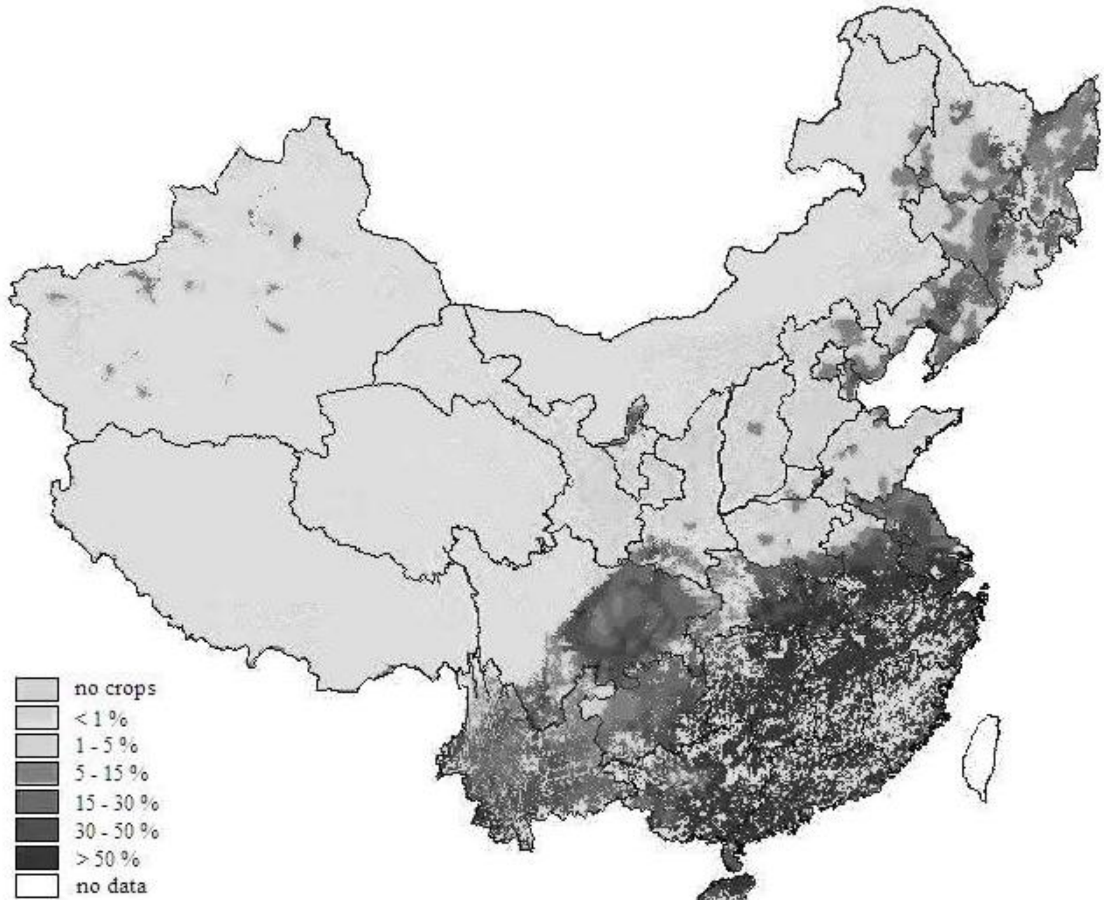

Figure 9 Share of rice production in cropland usage in China
Source: IIASA, International Institute for Applied Systems Analysis

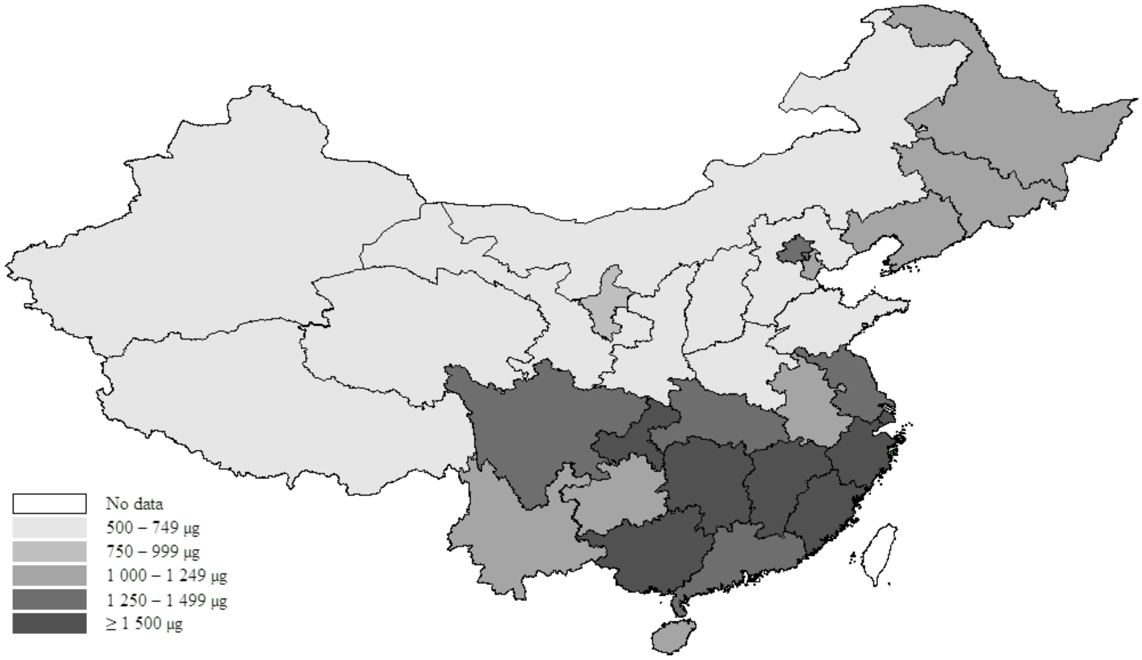

Figure 10 Total daily folate intake after biofortification in China, per women of childbearing age
Source : Table 6, based on Zhao *et al*[17], CNGOIC data[119] and Storozhenko *et al*[1]