

[The China-US Study on the Prevention of Neural Tube Defects using Folic Acid \(1999\)](#) ^[1]

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From 1993 to 1995 researchers led by Robert J. Berry from the US Centers for Disease Control headquartered in Atlanta, Georgia, and Zhu Li from Beijing Medical University in Beijing, China, conducted a collaborative study in China on the prevention of [neural tube](#) ^[2] defects or NTDs using [folic acid](#) ^[3] supplements. NTDs are [birth defects](#) ^[4] in which openings in the spinal cord or the brain that occur during early development remain after birth. Neural-tube formation occurs in early [pregnancy](#) ^[5], often before a woman knows she is pregnant and therefore before she has begun taking prenatal vitamins. The researchers presented their findings in the article "Prevention of the Neural Tube Defects with Folic Acid in China" published in 1999 in *The New England Journal of Medicine*. The researchers from The China-US study found that women who took folic acid in the periconceptional period, or the time before [conception](#) ^[6] through the first twenty-eight days after [conception](#) ^[6], reduced the occurrence of NTDs.

The China-US Study was a collaborative study between Peking University Health Science Center, formally Beijing Medical University, and the US Centers for Disease Control and Prevention. In China, women who are considering marriage and [pregnancy](#) ^[5] need to register with a [pregnancy](#) ^[5] monitoring system and submit to a premarital examination. That examination allowed the China-US Study researchers to screen for women that fit the constraints of their study. Researchers conducted clinical trials in two regions of China, between 1993 and 1995. In the clinical trials, researchers instructed women to take 400 micrograms (µg) of folic acid daily from the time of their premarital examination until the end of the first [trimester](#) ^[7] of [pregnancy](#) ^[5]. Folic acid is a B vitamin, normally found in leafy green vegetables, which assists in many processes of development such as DNA synthesis, RNA synthesis, and protein synthesis. Previous double blind trials indicated that taking [folic acid](#) ^[3] supplements in the periconceptual period and the first [trimester](#) ^[7] of [pregnancy](#) ^[5] reduced the number of NTDs in fetuses and newborn infants.

In the 1960s, Bryan M. Hibbard, Elizabeth D. Hibbard, and Richard W. Smithells observed a correlation between nutritional deficiency and [birth defects](#) ^[4], especially [folic acid](#) ^[3], or folate, metabolism and the incidence of NTDs. In 1980, Smithells's group in the United Kingdom reported in a nonrandomized trial that [folic acid](#) ^[3] or other vitamin supplements could reduce the risk of recurrence of NTDs in women who had a previous affected [pregnancy](#) ^[5]. Two other trials, one in England reported in 1991 and one in Hungary reported in 1992, also tested the correlation between [folic acid](#) ^[3] intake in the periconceptual period and the decreased incident of NTDs.

Researchers in the United Kingdom conducted double blind clinical trials, in which neither the researcher or the patient knew what treatment the patient received. Researchers instructed the women to take the 4000 micrograms (µg) of [folic acid](#) ^[3] vitamin daily during the periconceptional period, and researchers examined infants for NTDs. The amount of NTDs decreased by seventy-two percent. The Hungarian study used 400µg, a significantly lower amount of [folic acid](#) ^[3], to determine the suggested amount to administer for effect. The researchers in Hungary reported a large decrease in NTDs as well regardless of the decrease in the amount of [folic acid](#) ^[3] administered to the women. The Public Health Service in the UK concluded that women should take a regulated amount of 400µg daily, and the amount became accepted worldwide when further studies showed 400µg to be an effective amount on women's reproductive health.

In the China-US Study, the researchers conducted clinical trials in three provinces in China, Hebei in the Northern Province with high rates of NTDs, five to six per 1000 births, and Zhejiang and Jiangsu in Southern Provinces both with lower rates of NTDs, approximately one per 1000 births. The researchers studied groups of both high NTD and low NTD populations to determine if the consumption of [folic acid](#) ^[3] supplements benefited populations that may be more predisposed to the defects like Hebei, and low NTD affected areas. Women were identified and enrolled in the study through the [pregnancy](#) ^[5]-monitoring system, in which pregnant women and women who prepare for marriage register and serves as a record for prenatal and delivery care. In China, all couples planning to marry must submit to a premarital examination. During this examination, researchers provided women with [folic acid](#) ^[3] supplements.

The researchers divided the women into three distinct groups, the periconceptional group, late group, and early discontinuation group. The periconceptional group consisted of women who took the folic acid before their last menstrual cycle and stopped taking the supplement after the first [trimester](#) ^[7] of [pregnancy](#) ^[5]. The late group consisted of women who started taking the supplement during first [trimester](#) ^[7] but after their last menstrual cycle. The early discontinuation group included women who started and stopped taking the supplement before confirmation of [conception](#) ^[6], or last menstrual cycle. The researchers considered women who took more than eighty percent of the thirty-one pills given each month as optimal usage. They claimed

the optimal usage to be important in validating the importance of taking the supplement pills.

Once a woman became pregnant, the researchers used a surveillance system, which was established in China in January 1993, to document cases of fetuses with external structural [birth defects](#)^[4]. The system collects detailed data about live and stillborn infants and spontaneous aborted fetuses with detailed photographs of the fetuses and infants to determine developmental abnormalities. The researchers included results of fetuses with defects at twenty weeks or more of [gestation](#)^[8] and live birth infants up to six weeks of age in the defect study. The researchers collected information on all pregnancies even if less than twenty weeks of [gestation](#)^[8] if electively terminated because of a [prenatal diagnosis](#)^[9] of any birth defect. They included all stillborn infants and questioned the women about symptoms leading to the stillbirth.

Three pediatricians analyzed the reports of each [fetus](#)^[10] and infant, without knowing the treatment group of each woman to avoid a bias outlook on the symptoms. A clinical geneticist also evaluated each [fetus](#)^[10] and infant to validate the diagnoses of the physician. NTDs included in the study were anencephaly, where a major portion of brain and spinal cord is missing, [spina bifida](#)^[11], where the spinal column is not fully closed, iniencephaly, where the head bends backward on the cervical spine, craniorachischisis, where the brain and spinal cord remain open, and encephalocele, where a sac protrudes from an opening in the skull.

Ultimately, 247,831 pregnant women were included in the results of the study, with 31,960 women from the northern region and 215,871 from the southern region. There were 275 women who had a [fetus](#)^[10] or infant with a NTD, with 112 in the north and 163 in the south. The fetuses and infants with NTDs were more likely to be female. In the northern region, forty-seven percent of the defects had a diagnosis of spina bifida, twenty percent anencephaly, and twenty-one percent craniorachischisis. In the southern region, forty-one percent of infants' diagnosis show [spina bifida](#)^[11], thirty-three percent of defects consists of anencephaly, and thirteen percent craniorachischisis. The researchers included the women who took the [folic acid](#)^[3] pills most frequently in the periconceptional group.

Although the rate of NTDs increased more in the north than in the south, the lowest affected infants and fetuses consisted of the women who took the pills in the periconceptional group. The research showed women who took the majority of the pills in the northern region, showed an eighty percent improvement over women who registered before their last menstrual period and took no folic acid. The [reduction](#)^[12] in risk in the southern region of forty-one per cent was also significant. The researchers concluded that the intake of 400ug of [folic acid](#)^[3] daily during the periconceptional period could reduce the incidence of NTDs in both areas of high and low rates of these defects.

Possible differences in the research results between the northern and southern regions include that the southern area is wealthier, which gives the people more access to better nutrition than the northern area. The southern regions in the study are statistically the wealthiest in China. The production of crops in the southern region has a much longer season than the northern region. The researchers concluded that daily ingestion of [folic acid](#)^[3] may help decrease the frequency of NTDs throughout the world. Following the study in 1999, the researchers published their results in the *The New England Journal of Medicine* in the article "Prevention of the Neural Tube Defects with Folic Acid in China." The standards determined in the article impacted the Center for Disease Control standards in a United States Public Health Service recommendation for the dose of 400µg [folic acid](#)^[3], that women should consider taking to avoid complications in development of fetuses and infants such as NTDs. The CDC states that [folic acid](#)^[3] assists in the prevention of two specific NTDs, [spina bifida](#)^[11] and anencephaly. That helped pave the way for more studies to assist in the possible avoidance of NTDs.

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