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# The effect of the National Birth Defects Intervention Project on the prevention of congenital disabilities among children in China: a natural experiment

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## Abstract

Most childhood disabilities are caused by congenital factors such as birth defects. The present study aims to evaluate the effect of periconceptional nutrition intervention on the prevention of congenital disability among Chinese children using the National Birth Defects Intervention Project as a natural experiment. We obtained individual-level data from the Second National Sample Survey on Disability, a nationally representative survey, and 110 365 children born between September 1999 and August 2003 were included for analysis. Difference-in-differences estimates of the project effects on congenital disability were captured by exploiting temporal variation in the timing of project exposure across four birth cohorts along with geographical variation in project category at the province level. The findings contribute to an emerging body of evidence showing that prenatal micronutrient intervention before and during early pregnancy could substantially reduce the risk of congenital disability in childhood (OR 0·73; 95 % CI 0·57, 0·94). The National Birth Defects Intervention Project improved the awareness of reproductive health and disability prevention in the population. It highlights the need for a potential policy change focusing on early-life health investment in China.

**Key words: Birth defects: Intervention programmes: Congenital disability: Children**

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Child health is one of the most important public health issues worldwide. Many crucial efforts have been recorded in low- and middle-income nations in the context of a shared commitment to the substantial reduction in mortality rates among children during the recent decades[1]. In China, the mortality rate among children aged 5 years and below decreased from 61·0 per 1000 live births in 1991 to 9·1 per 1000 live births in 2017[2]. Nevertheless, the improvement of child survival has raised global public awareness of another significant health outcome, that is, disability[3].

Most childhood disabilities are caused by congenital factors such as birth defects[4], and most birth defects result in physical or mental disabilities or are fatal[5], placing a heavy burden on children with disabilities, their families, and the social medical system[6]. At the beginning of the 21st century, birth defects and congenital disabilities were recognised as public health issues, coinciding with a growing global strategic planning process, with input from government, non-government and academic partners[5].

In 2000, the Chinese government conducted the National Birth Defects Intervention Project (NBDIP) to improve the quality of the birth population. In the first stage, a Periconceptional Multivitamin Supplements Introduction Program (PMSIP) was conducted in seven provinces to introduce the function and method of periconceptional multivitamin supplements and to investigate the knowledge, attitude and practice of eugenics and prevention of birth defects. Then, starting in September 2000, a Community-based Birth Defects Intervention Trial (CBDIT) was conducted in four provinces. In this trial, intervention was employed among current resident women planning a pregnancy by providing a multivitamin capsule containing twenty-three microelements, including vitamins and folic acid (namely, Forceval), from a time point of 2 months before conception and continuing until completion of the second month after conception. A follow-up study after 2 years indicated that the intervention could significantly reduce the risks of neural tube defects, with a protective rate of 80·4 %[7].

The present study, using the NBDIP as a natural experiment, was designed to robustly capture the potential long-term effect of periconceptional intervention on the risk of congenital disability in childhood based on difference-in-differences methods, established by examining the regional variations of project

**Abbreviations:** CBDIT, Community-based Birth Defects Intervention Trial; NBDIP, National Birth Defects Intervention Project; PMSIP, Periconceptional Multivitamin Supplements Introduction Program.

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exposure across birth cohorts. The findings contribute to the literature in terms of disability beyond morbidity and mortality focused on previous studies, especially the effects of early-life-specific micronutrient insufficiencies on child health from a nationwide perspective.

## Materials and methods

### The China National Sample Survey on Disability

The data used for this analysis were drawn from the China National Sample Survey on Disability, the most recent nationwide individual-level survey on disability, conducted from 1 April 2006 to 31 May 2006. This survey was designed to obtain basic information on the prevalence, types, severity and causes of disabilities, as well as the living conditions and health service demands and use among populations with disability in China[8].

The survey was subject to approval by the State Council of China (no. 20051104) and was conducted within the legal framework governed by the Statistical Law of the People's Republic of China (1996 Amendment). All survey respondents provided their informed written consent to participate in this survey.

Experts from the National Bureau of Statistics of China, the China Federation of Disabled Persons and the Division of Statistics of the UN reviewed the survey protocol and questions. The classification and grading standard, screening method, diagnostic method and relevant scales on disabilities were pretested in pilot studies with good reliability and validity[9]. More than 20 000 interviewers, 50 000 survey assistants and 6000 doctors of various specialties were involved in the survey. All were trained at national and provincial levels according to standards set by the expert committee of the survey[10].

A nationally representative sample was derived by multistage stratified random cluster sampling with probability proportional to size, following standard procedures for complex samples. A total of 2·6 million samples in 771 797 households were investigated from 5964 communities/areas, 2980 towns/townships and 734 counties of thirty-one provinces in mainland China, representing 1·9 per 1000 inhabitants of China.

### Measures

*Birth cohorts.* We restricted our analysis to four birth cohorts according to the birth time of participants relative to the time of prenatal exposure to the NBDIP. The term 'prenatal exposure' refers to maternal exposure to the intervention during the approximately 300 d from periconception to delivery. Since the intervention trial was conducted from a time point of 2 months before conception, as mentioned above, those exposed to NBDIP should be conceived starting from November 2000 and born starting from September 2001. The analytical sample thus included participants from (i) the reference cohort (born between September 1999 and August 2000), (ii) the pre-intervention cohort (born between September 2000 and August 2001), (iii) the during-intervention cohort (born between September 2001 and August 2002) and (iv) the post-intervention cohort (born between September 2002 and August 2003). As a result, 110 365 children born between September 1999 and August 2003 were used for analysis, at the ages of 2–6 years during the survey window.

*National Birth Defects Intervention Project category.* We implemented an ordinal category of the NBDIP at the provincial level by dividing the provinces into three groups. Category 'III' comprised provinces (Henan, Guizhou, Hunan and Jilin) where both the CBDIT and the PMSIP were conducted. Category 'II' included provinces (Yunnan, Shaanxi and Heilongjiang) where only the PMSIP was performed. Category 'I' encompassed all other provinces not developing PMSIP nor CBDIT in mainland China as the reference.

*Congenital disability.* In China National Sample Survey on Disability, children aged 0–6 years were all scheduled to undergo a health examination by paediatricians in various specialties and received a final, confirmed diagnosis of disability[11]. Congenital disability referred to one or more abnormalities in anatomical structure or the loss of a particular organ or function that occur during intra-uterine life and can be identified prenatally, at birth or very early life, affecting a person's ability to carry out a normal activity and to participate fully in study, work and community and social interaction in the later life[12]. Congenital disabilities can be caused by genetic factors, infections, environmental teratogens and maternal micronutrient deficiencies[12]. In the present study, root causes of congenital disabilities were diagnosed by paediatricians. These causes included hereditary factors, congenital abnormality, intra-uterine developmental malformation or retardation, premature birth, low birth weight, late birth, asphyxia neonatorium, pathological jaundice of newborn, Down's syndrome, cleft palate, achondroplasia, brain paralysis, brain diseases, mental retardation, pregnancy viral infection and pregnancy trauma.

*Control variables.* According to previous studies, demographic and socio-economic factors such as age, sex, residences and low-income are associated with congenital disabilities as well[12-15]. Thus, demographic and socio-economic variables were controlled in the present study, including age (1 year per group), sex (male or female), ethnicity (Han or minority), birth residence (rural or urban according to the Hukou status) and annual household income per capita (top, middle and bottom by tertiles). Province dummies were used to capture the provincial fixed effects.

### Statistical analyses

We employed a difference-in-differences method, a statistical method to estimate causal effects of events or interventions that affect entire aggregate units such as a nationwide programme or policy[16], to estimate the effects of the NBDIP. Traditionally, it calculates the effect of a treatment on an outcome by comparing both temporal and geographical variations, such as the difference of the average change over time between different groups (the treatment areas and the control areas of a policy).

According to previous studies used the same method in a cross-sectional study[17-19], in the present study, we identified whether an individual was prenatally exposed to the NBDIP with the variable of *birth cohort* as the temporal variation, and classified the variation of NBDIP treatment status in the same cohort

**Table 1.** Characteristics of study participants, by birth cohort
(Mean values and standard deviations; numbers and percentages)

| | | | Birth cohorts | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total (*n* 110 365) | | Reference cohort (*n* 27 534) | | Pre-intervention cohort (*n* 28 997) | | During-intervention cohort (*n* 26 985) | | Post-intervention cohort (*n* 26 849) | | |
| Characteristics | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % | *P* |
| Age (years) | | | | | | | | | | | <0·001 |
| Mean | 4·14 | | 5·60 | | 4·61 | | 3·62 | | 2·64 | | |
| SD | 1·20 | | 0·49 | | 0·49 | | 0·49 | | 0·48 | | |
| Sex | | | | | | | | | | | |
| Female | 50 128 | 45·42 | 12 628 | 45·86 | 13 215 | 45·57 | 12 140 | 44·99 | 12 145 | 45·23 | 0·182 |
| Male | 60 237 | 54·58 | 14 906 | 54·14 | 15 782 | 54·43 | 14 845 | 55·01 | 14 704 | 54·77 | |
| Birth residence | | | | | | | | | | | |
| Urban | 26 198 | 23·74 | 6499 | 23·60 | 6785 | 23·40 | 6405 | 23·74 | 6509 | 24·24 | 0·117 |
| Rural | 84 167 | 76·26 | 21 035 | 76·40 | 22 212 | 76·60 | 20 580 | 76·26 | 20 340 | 75·76 | |
| Ethnicity | | | | | | | | | | | |
| Han | 92 263 | 83·6 | 23 032 | 83·65 | 24 245 | 83·61 | 22 552 | 83·57 | 22 434 | 83·56 | 0·991 |
| Minority | 18 102 | 16·4 | 4502 | 16·35 | 4752 | 16·39 | 4433 | 16·43 | 4415 | 16·44 | |
| Annual household income per capita | | | | | | | | | | | |
| Top | 38 623 | 35·00 | 9603 | 34·88 | 10 152 | 35·01 | 9524 | 35·29 | 9344 | 34·80 | 0·077 |
| Middle | 35 139 | 31·84 | 8612 | 31·28 | 9249 | 31·90 | 8662 | 32·10 | 8616 | 32·09 | |
| Bottom | 36 603 | 33·17 | 9319 | 33·85 | 9596 | 33·09 | 8799 | 32·61 | 8889 | 33·11 | |

with the variable of *NBDIP category* as the geographical variation.

A logit regression model with difference-in-differences estimator can be obtained from

$$Y_{ipt} = \alpha_0 + \sum_{p=1}^{3} \theta_p \text{Category}_p + \sum_{t=1}^{4} \gamma_t \text{Cohort}_t + \sum_{p=1}^{3} \sum_{t=1}^{4} \beta_{pt} \left(\text{Category}_p \times \text{Cohort}_t\right) + \delta X_{ipt} + \varepsilon_{ipt},$$

where $Y_{ipt}$ denotes a congenital disability outcome for participant $i$ born in NBDIP category$_P$ and cohort$_t$; $X_{ipt}$ denotes the control variables and $\varepsilon_{ipt}$ denotes the random error; and $\beta_{pt}$, the coefficient of the interaction between birth cohorts and NBDIP category, that is, difference of the temporal variation in difference of the geographical variation, is the estimated effect of NBDIP on later-life congenital disability.

We estimated two models for each outcome variable. The first model did not include control variables, and the second model controlled for age, sex, residence, ethnicity, household income per capita and province fixed effects. The OR, adjusted OR and 95 % CI were calculated. In addition, we used standard weighting procedures to construct sample weights, allowing for the complex survey sample design, and to calculate the population-weighted numbers and prevalence of congenital disability among children where appropriate. All data were entered into a customised database and were analysed using STATA 13 (STATA Corp.). Statistical significance was set at a two-sided *P* value less than 0·05.

## Results

### *Characteristics of the study participants by birth cohort*

The study consisted of 110 365 children, with an average age of 4·14 (SD 1·20) years during the survey window. Among the analytical samples, all four cohorts were similar in terms of sex composition (54·14–55·01 % men), birth residence (75·76–76·60 % rural), ethnicity (83·56–83·65 % Han) and annual household income per capita tertile. The mean ages of the four cohorts were different, which was consistent with the date of birth set in the study design. Table 1 reports the cohort-specific descriptive statistics of characteristics of study participants by birth cohort.

### *Congenital disability among children*

Among the study children, 2265 (2·05 %) were living with a disability at the time of the survey. Among them 1066 had congenital disability, accounting for 47·06 % of the children with disability. After weighting, the study participants were equivalent to a weighted total of 58 111 828 children of China. Among them, it is estimated that a weighted number of 570 511 children were living with congenital disability in China. The weighted prevalence of congenital disability was 0·98 % (95 % CI 0·92, 1·04) among children participants. The prevalence of congenital disability among each cohort is presented in Table 2.

### *The effect of National Birth Defects Intervention Project on prevention of congenital disability among children*

Table 3 and Fig. 1 show the difference-in-differences estimates of the NBDIP effect on the prevention of child congenital disability. We found that the post-intervention cohort prenatal exposure to NBDIP category ‘III’ had significantly lower odds (OR 0·73; 95 % CI 0·57, 0·94) of congenital disability compared with the reference category after controlling for multiple covariates. The post-intervention cohort exposure to NBDIP category ‘II’ also had lower odds (OR 0·91; 95 % CI 0·66, 1·25), but the effect was not statistically significant. The protective effect of category ‘III’ was significantly higher than category ‘II’ (adjusted $P_{\text{trend}} = 0·009$).

**Table 2.** Prevalence of congenital disability, by cohort
(Numbers, percentage values and 95 % confidence intervals)

| | Total children | | Children with congenital disability | | Weighted prevalence of congenital disability (%) | |
|---|---|---|---|---|---|---|
| Cohort | SN (persons) | WN (persons) | SN (persons) | WN (persons) | % | 95 % CI |
| Reference cohort | 27 534 | 14 472 112 | 300 | 162 895 | 1·13 | 0·99, 1·26 |
| Pre-intervention cohort | 28 997 | 15 254 745 | 267 | 140 736 | 0·92 | 0·81, 1·04 |
| During-intervention cohort | 26 985 | 14 175 251 | 242 | 130 083 | 0·92 | 0·80, 1·04 |
| Post-intervention cohort | 26 849 | 14 209 719 | 257 | 136 798 | 0·96 | 0·84, 1·09 |
| All cohorts | 110 365 | 58 111 828 | 1066 | 570 511 | 0·98 | 0·92, 1·04 |

SN, sample number; WN, weighted number.

**Table 3.** Effect of the National Birth Defects Intervention Project (NBDIP) on congenital disability among children
(Adjusted odds ratios and odds ratios and 95 % confidence intervals)

| | Univariate analysis | | | Multivariable analysis* | | |
|---|---|---|---|---|---|---|
| Birth cohort × NBDIP category | OR | 95 % CI | *P* | Adjusted OR | 95 % CI | *P* |
| Pre-intervention × *I* | 1·00 | | | 1·00 | | |
| Pre-intervention × *II* | 0·94 | 0·71, 1·26 | 0·692 | 0·95 | 0·72, 1·26 | 0·735 |
| Pre-intervention × *III* | 1·09 | 0·75, 1·59 | 0·642 | 1·12 | 0·76, 1·63 | 0·575 |
| $P_{trend}$ | | 0·668 | | | 0·860 | |
| During intervention × *I* | 1·00 | | | 1·00 | | |
| During intervention × *II* | 1·10 | 0·65, 1·87 | 0·724 | 1·11 | 0·66, 1·88 | 0·693 |
| During intervention × *III* | 1·11 | 0·60, 2·03 | 0·746 | 1·10 | 0·60, 2·05 | 0·752 |
| $P_{trend}$ | | 0·675 | | | 0·944 | |
| Post-intervention × *I* | 1·00 | | | 1·00 | | |
| Post-intervention × *II* | 0·90 | 0·64, 1·26 | 0·536 | 0·91 | 0·66, 1·25 | 0·552 |
| Post-intervention × *III* | 0·72 | 0·55, 0·94 | 0·015 | 0·73 | 0·57, 0·94 | 0·015 |
| $P_{trend}$ | | 0·042 | | | 0·009 | |

* Adjusting for age, sex, residence, ethnicity, annual household income per capita and province fixed effects.

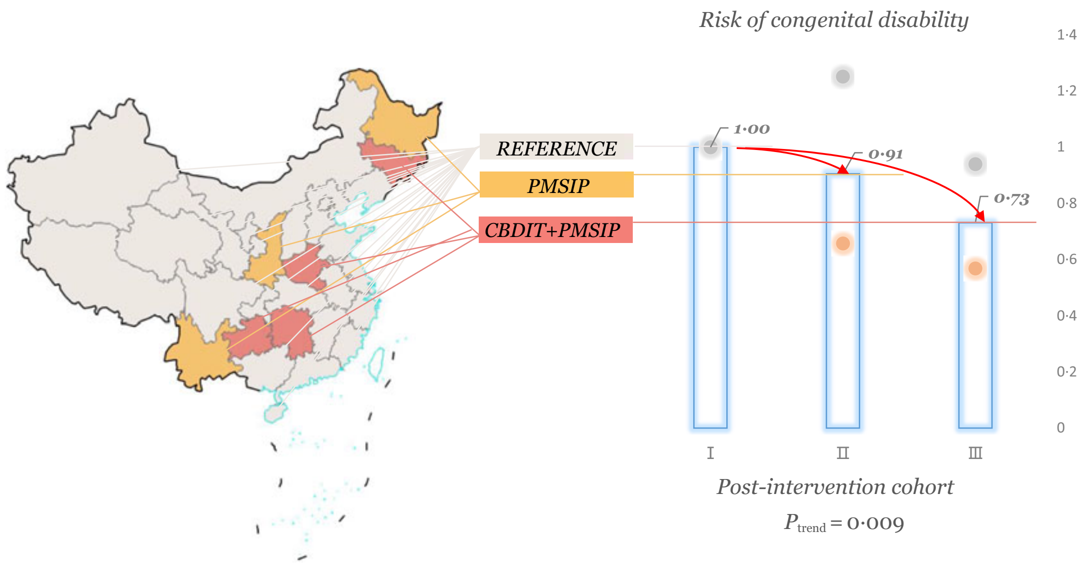


**Fig. 1.** Effect of the National Birth Defects Intervention Project on the prevention of congenital disabilities among children in China. PMSIP, Periconceptional Multivitamin Supplements Introduction Program; CBDIT, Community-Based Birth Defects Intervention Trial. No data for Chinese Taipei were used in the present study. (▢), Adjusted OR; (●), 95 % CI lower; (●), 95 % CI upper.

**Table 4.** Robustness analyses: the effect of the National Birth Defects Intervention Project (NBDIP) on congenital disability among children (Adjusted odds ratios and 95 % confidence intervals)

| | Multivariable analysis* | | |
|---|---|---|---|
| Birth cohort × NBDIP category | Adjusted OR | 95 % CI | *P* |
| During intervention × *I* | 1·00 | | |
| During intervention × *II* | 1·17 | 0·69, 1·99 | 0·558 |
| During intervention × *III* | 0·99 | 0·52, 1·91 | 0·986 |
| Post-intervention × *I* | 1·00 | | |
| Post-intervention × *II* | 0·95 | 0·71, 1·27 | 0·746 |
| Post-intervention × *III* | 0·66 | 0·44, 0·98 | 0·040 |

* The pre-intervention cohort was used as the reference for the robustness analyses. Adjustments were made for age, sex, residence, ethnicity, annual household income per capita and province fixed effects.

### *Sensitivity checks*

To check the sensitivity of our study, we further set up the pre-intervention cohort as the reference for the robustness analyses. As shown in Table 4, after controlling for covariates, we could still observe a significant effect of prenatal exposure to NBDIP category 'III' on reducing the risk of cognitive impairment among children of the post-intervention cohort (OR 0·66; 95 % CI 0·44, 0·98).

## Discussion

Comprehensive literature has indicated that women's nutrition before and during early pregnancy could affect pregnancy and infant outcomes. Previous studies show that poor nutritional status or micronutrient deficiencies may increase the risk of adverse pregnancy outcomes and cause birth defects or congenital malformations[20]. Interventions such as periconceptional intake of folic acid and vitamin and mineral supplements are associated with a reduced risk of neural tube defects, neonatal death and low birth weight, small for gestational age neonates and preterm deliveries of offspring[21]. However, little is known about the effect of prenatal nutrition intervention on the long-term health outcomes of the live offspring.

In the present study, for the first time, we identified that prenatal microelement supplementation before and during early pregnancy has an enduring protective effect on congenital disability in childhood using the NBDIP as a natural experiment. The findings indicate that the intervention significantly reduced the risk of congenital disability in the cohort after the project, and the protective effect in areas where both the CBDIT and PMSIP were conducted was particularly significant and higher than where only PMSIP was conducted. As mentioned above, PMSIP was only an introduction programme to improve the knowledge, attitude and practice of individuals, while the multi-vitamin intervention and long-term follow-up and education were employed during CBDIT. This may partly account for this non-significant result in areas where only PMSIP was conducted. Nevertheless, this finding indicates that the National Birth Defects Intervention Project with two stages improved the awareness of reproductive health and disability prevention among the population and obtained an intended effect. The findings of the present study are consistent with previous studies that reported a significant effect of folic acid or vitamin and mineral supplementation on congenital anomaly prevention in China and other countries[7,22]; moreover, the findings present supplementary evidence from the perspective of disability. Data for the present study were gleaned from large representative samples of the most recent national population-based survey on disability in China. The findings of our study contributed to the literature as an epidemiological verification in a large population in China focusing on disability and using robust methodology.

Previous studies indicated that preventing diseases by maternal microelement supplementation is both low cost and highly effective[23,24]. Due to the introduction of mandatory fortification of grains with folate in the USA, 266 649 quality-adjusted life years are gained, and $3·6 billion is saved annually[23]. A previous study indicated that the disability-adjusted life years in the group intervened by folic acid-fortified flour were approximately 58·5 % lower than in the control group in a high neural tube defects risk region of China[24]. Our results further confirm the effectiveness of maternal nutritional intervention in preventing disability.

From a life-course perspective, many adults' physical and mental health outcomes can be traced back to early-life experiences. Child congenital disability is also associated with adult intellectual performance, disability and mortality[25]. Currently, the Chinese government is developing the Healthy China Plan as a national strategy to promote health through 2030, in which health promotion for the entire population and throughout the total life cycle is the main theme[26]. Our findings indicate that early-life health investment is not only an imperative pathway but also a sufficient condition for the realisation of the Healthy China Plan. China is currently implementing 100 pilots for comprehensive disability prevention, in which a disability reporting system has been established. The screening, assessment and services for child disability will be more systematic and improved.

The present study has several limitations. First, we assumed that all child participants were currently living where their mothers were living at the time of their births; thus, the estimates may be affected by the population migration. However, the population migration is greatly restricted by the Hukou system in China, especially the rural–urban migration; additionally, preschool children generally do not migrate with parents. Second, the validity of our findings may be threatened by the effect of selective mortality caused by birth defects intervention. Given that those who were not intervened by the NBDIP were more likely to have died and were less likely to have survived to the survey age, even though they survived birth, our results would probably underestimate rather than overestimate the protective effect of the NBDIP on the congenital disability of children. In view of the comprehensiveness of the effect of NBDIP, the complexity of the causes of congenital disabilities and the limitation of the data, we did not separate the specific causes of congenital disabilities in the present study. Despite these limitations, the present study, on the basis of its robust data and methods, is also a unique contribution to the knowledge pool regarding the effects of prenatal micronutrient supplementation on predicting reduced risk for childhood cognitive impairment.

## Conclusions

In sum, the present study supports the view that prenatal micronutrient intervention has a protective impact on the health outcome of the offspring from the perspectives of disability and disease and mortality indicators. The findings of the study indicate that the National Birth Defects Intervention Project improved the awareness of reproductive health and disability prevention among the population. Moreover, the findings highlight the need for a potential policy change focusing on early-life health investment in China. More effort should be done to enhance periconceptional nutrition and healthcare to improve maternal health and the health and development of children.

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