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## Cohort profile: the Taicang and Wuqiang mother-child cohort study (TAWS) in China

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Cohort profile: the Taicang and Wuqiang mother-child cohort study (TAWS) in China

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ABSTRACT

Purpose The Taicang and Wuqiang cohort study (TAWS) was established to examine the influences of early-life nutrition on children’s growth and health, and explore the potential roles of maternal health, metabolites and microbiota in two different regions of China.

Participants A total of 7041 mother-child pairs were recruited during early pregnancy (n=4035, 57.3%) and during the delivery phase (n=3006, 42.5%) from health services centers or hospitals in Taicang and Wuqiang of China since 2013. Mother-child pairs were followed for 3 times during pregnancy, 1 time during delivery, and 7-10 times during 3 years after delivery. Questionnaires were used to collect data on diets, supplements, lifestyles, medicines, and children’s intelligence quotient. Physical examination was performed at each follow-up to record anthropometric change. Pregnancy outcomes and diseases were extracted from clinical records. In addition, biological samples in the TAWS included venous blood, cord blood, urine, stool, breast milk, cord, and placenta.

Findings to date Data from the cohort showed different baseline characteristics of participants in the two sites of TAWS. Maternal abnormal blood glucose affected the metabolism of themselves and their newborns. Serum folate concentration above 14.5 ng/mL for mothers at early pregnancy could reduce the risk of delivering newborns with small for gestational age.

Future plans The abundant data and biological samples can be utilized to exploration of the mechanism of early-life nutrition on children’s growth and health. This prospective cohort study will be followed for a longer time.

KEYWORDS cohort study, early life, nutrition, mother, child

WORDS COUNT 2552

Strengths and limitations of this study

- The Taicang and Wuqiang mother-child cohort in China include two study sites, one is rich in southern China, and the other is poor in northern China, results from the study could partially reflect the diverse dietary and lifestyle patterns of China.
- Mother-baby pairs were enrolled during early pregnancy (n=4035, 57.3%) and delivery phase (n=3006, 42.7%) to avoid participants selection bias because nearly half of the women in Wuqiang did not get prenatal care during early pregnancy.
- Three follow-ups during pregnancy, 1 follow-up during the delivery phase, and 7-10 follow-ups after birth contributed to a large number of data and specimens for exploring the mechanisms of early nutrition on children’s growth and health.
Some participants lost to follow-up and biological samples were obtained only from some participants, which may lead to bias.

INTRODUCTION

Since it was first proposed in the 1980s, the ‘developmental origins of health and disease’ (DOHaD) paradigm has been bolstered by a large body of human epidemiological studies and animal models over the past decades. It is now well established that the first 1000 days of a person’s life-course, from conception to age of two, is a critical time window for developmental trajectory programming. Thus, adverse disturbances that occurred during this period may result in increased risks for chronic diseases across the lifespan and/or an epigenetic transgenerational inheritance of such risks. Of particular importance, extensive evidence suggests that for the offspring, maternal dietary and nutritional status is associated with altered risks of both short-term and long-term diseases in later life, including metabolic, immunological, mental, and reproductive diseases. Consequently, achieving optimal maternal nutrition during pregnancy and in early-life can be one critical step to substantially lower the disease burdens in the future.

China has the largest population worldwide, with around 15 million babies born each year. Given the population size, addressing early-life nutrition in an effort to prevent future diseases has tremendous benefits in lowering the social and economic burdens associated with these negative long-term consequences. Since 1990s, China has made significant improvements in maternal and child health, meeting the Millennium Development Goals and Sustainable Development Goals. In parallel with rapid economic growth and improved healthcare coverage, it is on the way further closing the gaps in maternal and newborn care across regions. Particularly, studies have suggested heterogeneity in maternal and infant health profiles across different geographic regions in China: rates of obesity-related maternal or infant complications are higher in more developed settings, whereas rates of undernutrition-related complications are more common in less developed settings, mainly due to differences in socioeconomic status, access to food choices, and dietary patterns, or a combination of these factors.

To date, a few population-based studies have been conducted in China to examine the impacts of dietary and nutritional status during the most nutritionally vulnerable periods, namely prenatal and postnatal periods, on birth outcomes and offspring nutritional status. Of particular importance, however, studies of later cohorts representing different Chinese sub-groups are needed to account for the noted differences in maternal and infant health profiles when examining maternal and/or early-life nutrition. Therefore, we sought to establish a multi-center mother-child nutrition and health cohort in China, aiming to improve our understanding of the long-term impacts of dietary intake and
nutritional status during pregnancy and first three years of life on children’s growth and well-beings, and ultimately to promote evidence-based policy makings.

COHORT DESCRIPTION

Cohort setup and quality control
The Taicang and Wuqiang Study (TAWS) consisted of two study sites including Taicang (Jiangsu Province of China) and Wuqiang (Hebei Province of China), under the main supervision of the National Institute for Nutrition and Health (formerly National Institute for Nutrition and Food Safety, NINH). The two study sites underwent participant screening, recruitment, and follow-up separately at local healthcare centers and obstetric hospitals.

The Taicang sub-cohort was hosted under the Taicang Service Center for Mother and Child Health and Family Planning (TC-MCH), doctors in the prenatal clinics and child care clinics of all 22 community health centers took charge of recruitment and follow-up during pregnancy and postpartum, and nurses in the obstetric clinics of all 5 hospitals were responsible for follow-up during delivery phase. The Wuqiang sub-cohort was hosted under the Wuqiang Center for Disease Control and Prevention (WQ-CDC), doctors in all 8 township health centers and the Maternal and Child Health Hospital were responsible for recruitment and follow-up during pregnancy and postpartum, and nurses in obstetric clinic of Wuqiang County Hospital took charge of recruitment and follow-up during delivery phase.

The principal investigators from NINH performed project design and validation, and they set up standardized procedures, questionnaires, and database platform for the study. All doctors and nurses involved in the study were well trained to administer questionnaires, assess anthropometry, and process biological samples.

The study recruitment period was from May 2013 to December 2017 in Taicang, and from June 2016 to December 2021 in Wuqiang. Figure 1 and Figure 2 illustrate the enrollment and follow-up schedule of the study in Taicang and Wuqiang.

Participants
The participants were recruited at two stages: (1) early pregnancy (n=4035, early-pregnancy cohort) and (2) during delivery (n=3006, delivery-cohort). Pregnant women coming for prenatal care at their first trimester were considered as potential participants and were approached by trained doctors or nurses for eligibility screening. They were eligible if: 1) aged 18-45 years, 2) less than 16 weeks of gestation, 3) no history of recurrent abortion, 4) self-reported to be overall healthy without significant past medical history (i.e., hypertension, diabetes, mental disorders, cancer and other malignant
diseases, 5) plan to receive prenatal care and deliver at local hospitals, 6) plan to stay in Wuqiang/Taicang in the next four years, 7) be willing to cooperate and have regular visits per the study request, 8) be able to write and communicate well. For the pregnant women not receiving prenatal care during early pregnancy in Wuqiang, they were approached and screened by nurses prior to or immediately after labor, with the identical eligibility criteria outlined above, except 2) and 5). Women who agreed to be enrolled in the study provided written informed consent.

Baseline data were collected at enrollment by questionnaires, including general characteristics of the pregnant women and their husbands, dietary habits before pregnancy (by a food frequency questionnaire, FFQ), supplementary intake before pregnancy, history of past pregnancies and diseases.

Cohort follow-up and data collection
During pregnancy, mothers were followed at early-, mid-, and late-pregnancy. Questionnaires were used to collect dietary intake (by 3-day food records), supplementary intake, physical activity (by mobile monitoring devices or self-reported), symptoms or medicines used. A physical examination and a standard obstetric examination were carried out to check the health of mothers and development of fetuses. Twenty milliliters of urine samples and 5 mL of venous blood were collected from mothers in Wuqiang at each follow-up (Table 1).

During the delivery phase, medical records on physical health and pregnancy outcomes (gestational week at delivery, delivery mode, gestational diseases, postpartum hemorrhage, birthweight and length of the newborn, Apgar score, etc.) were extracted from medical records. Biological samples of maternal venous blood (5 mL) and neonatal cord blood (5 mL) were collected, in addition, maternal urine (20 mL), placenta (4 sites), umbilical cord (3 cm), and meconium (2 g) were collected in a subset of participants in Wuqiang (Table 1).

| Table 1 Data collection from enrollment to delivery in the TAWS<sup>a</sup> |
|---|---|---|
| **Time** | **Items** | **Data collection during pregnancy and delivery** |
| Early pregnancy | Questionnaires | Demographics, pre-pregnancy diet (FFQ), early pregnancy diet (3-day food records), nutrient supplementation, health-related behaviors, physical activity, medical history, history of past pregnancies, symptoms or medicines used, husband-related information (body weight, height, smoking) |
| Mid-pregnancy | Questionnaires | Diet (3-day food records), nutrient supplementation, health-related behaviors, physical activity, symptoms or medicines, scale for depression |
|--------------|----------------|--------------------------------------------------------------------------------------------------|
|              | Physical exam and biological sample | Anthropometry and obstetric exam, Wuqiang plus: venous blood and urine |
| Late-pregnancy | Questionnaires | Diet (3-day food records), nutrient supplementation, health-related behaviors, physical activity, symptoms or medicines, scale for depression, breastfeeding willingness |
|              | Physical exam and biological sample | Anthropometry and obstetric exam, Wuqiang plus: venous blood and urine |
| Delivery     | Mother-related | Enrollment participants: general characteristics of pregnant women and their husband, history of past pregnancies and diseases; Body weight before and after delivery, pre-delivery venous blood, pregnancy outcomes, Wuqiang plus: pre-delivery urine and placenta |
|              | Newborn-related | Birth outcomes, anthropometry, cord blood, Wuqiang plus: newborn’s cord and stool |

*a FFQ: food frequency questionnaire.*

After delivery, mothers were followed for 7 times in Taicang and 10 times in Wuqiang to further collect their dietary intake, supplementary intake, physical activity, mood, and anthropometric change. In addition, fasting venous blood (5 mL), breast milk (whole milk from one breast using a portable automatic breast pump), urine (20 mL), and stool samples (2 g) were collected from mothers at some visits as shown in Table 2.

After birth, children were followed for 9 times in Taicang and 10 times in Wuqiang (Table 2). General health, body growth, and motor development were assessed by doctors; child feeding practice (i.e., breast feeding, formula, and supplements), dietary intakes (by FFQ or 3-day food records), and medical history were retrospectively recalled by the caregivers. Samples of blood (5 mL), urine (10 mL), and stool (2 g) were collected at some visits as shown in Table 2. Intelligence
Quotient (IQ) test using the Gesell assessment was administered in a subset of participating children at the age of 18 and 24 months in Wuqiang.

| Time            | Subject | Data collection after delivery                                                                                  |
|-----------------|---------|------------------------------------------------------------------------------------------------------------------|
| Postpartum 28 days | Child   | Anthropometry, child feeding, general health                                                                    |
| Postpartum 42 days | Mother  | Yuezi diet (FFQ), anthropometry, general physical health, scale for depression, breast milk; Wuqiang plus: venous blood, urine |
| Postpartum 2 months | Child   | Wuqiang only: Anthropometry, child feeding, general health                                                      |
|                 | Mother  | Diet (3-day food records or FFQ), anthropometry, general physical health, breast milk; Taicang plus: venous blood |
|                 | Child   | Anthropometry, child feeding, nutrient supplementation, motor development, general health; Wuqiang plus: stool |
| Postpartum 6 months | Mother  | Anthropometry, general physical health, Wuqiang plus: breast milk                                               |
|                 | Child   | Anthropometry, child feeding, diet (3-day food records or FFQ), nutrient supplementation, motor development, general health; Wuqiang plus: urine, stool |
| Postpartum 8 months | Mother  | Wuqiang only: anthropology, general physical health                                                             |
|                 | Child   | Anthropometry, child feeding, diet (FFQ), nutrient supplementation, motor development, general health; Wuqiang plus: urine |
| Postpartum 12 months | Mother  | Anthropometry, general physical health; Wuqiang only: urine, venous blood, breast milk (subset)                   |
|                 | Child   | Anthropometry, child feeding, diet (FFQ), nutrient supplementation, motor development, general health; Wuqiang plus: urine and stool |
| Postpartum 18 months | Mother  | Anthropometry, general physical health; Wuqiang plus: IQ test (subset), urine, stool                             |
|                 | Child   | Anthropometry, child feeding, diet (3-day food records or FFQ), nutrient supplementation, motor development, general health; Wuqiang plus: IQ test (subset), urine, stool |
Postpartum 30 months  

Mother  
Wuqing only: anthropometry, general physical health

Child  
Anthropometry, child feeding, diet (FFQ), nutrient supplementation, motor development, general health

Postpartum 36 months  

Mother  
Anthropometry, general physical health

Child  
Anthropometry, child feeding, diet (3-day food records or FFQ), nutrient supplementation, motor development, general health; Wuqiang plus: venous blood, urine, stool

\(^a\) Yuezi: first month after childbirth; FFQ: food frequency questionnaire; IQ: Intelligence quotient.

**Biological samples storage and analysis**

Blood, stool, and breast milk samples were separately stored at -80°C, and urine samples were stored at -20°C. Samples of placenta and cord were fixed in neutral buffered formalin, embedded into wax blocks, and stored at room temperature. Levels of vitamins, minerals, and metabolites were measured by mass spectrometry. Blood glucose, lipid and hemoglobin were analyzed by automatic biochemical analyzer. Microbiome was analyzed by Illumina Hiseq2500 platform. Standards and pool samples were used to control the quality.

**Compliance promotion**

Five strategies had been taken to promote compliance. First, the two study sites had established standardized follow-up procedures, and the follow-up time was consistent with the local routine health cares for mothers and children. Second, all hospitals and health centers used the same electronic platform for data collection, therefore, as long as the mothers and children got health checks locally, the electronic platform could remind doctors to follow up relevant information. Third, doctors made appointments for follow-up visits by telephone and informed them of the content. For mothers and children who failed to follow on time, the doctor called again to make an appointment within one month. Fourth, regular meetings were held every three months to provide feedback on follow-up progress and carry out technical training. Fifth, the doctors fed back the results of physical examination, biochemical testing, and dietary evaluation to the mothers or child caregivers, and gave instructions on dietary intake and child feeding.

**Patient and public involvement**

None of the participants was involved in the study design, questionnaire design, biological measurements, or specimen collection and analysis. All participants were informed of the use of the
data for research in this study. There was no plan to disseminate the study results to the participants.

**FINDINGS TO DATE**

**Baseline characteristics**

Based on the data from the early-pregnancy cohort, the two study sites effectively included pregnant mothers with different profiles, acknowledging the demographic, health- and culture-related differences in regions of China as outlined in the TAWS specific aims. The early-pregnancy cohort in Taicang and in Wuqiang enrolled 2095 and 1940 women, respectively. Compared with the study participants in Wuqiang, participants in Taicang were younger, were more likely to be enrolled at an earlier gestational age, had a greater proportion of primiparas, had a lower pre-pregnancy body mass index (BMI), were more skilled in occupations, had higher education levels, and had a higher monthly household income (Table 3).

| Indicators                  | Taicang (n=2095)       | Wuqiang (n=1940)       | Z/Chisq | P      |
|-----------------------------|------------------------|------------------------|---------|--------|
| Age (yr)                    | 25.0(24.0,28.0)        | 27.7(25.3,30.5)        | 19.09   | <0.01  |
| Gestational age (week)      | 10.0(8.0,11.0)         | 13.0(11.0,15.0)        | 37.42   | <0.01  |
| Height (cm)                 | 160.1(158.1,164.0)     | 160.0(156.5,163.0)     | 5.33    | <0.01  |
| Pre-pregnancy BMI (kg/m²)   | 20.3(18.8,22.1)        | 22.9(20.5,25.6)        | -21.32  | <0.01  |
| Primipara (%)               | 81.2                   | 8.3                    | 1803.3  | <0.01  |
| Occupation (%)              | 1025.11                | <0.01                  |
| Worker                      | 43.1                   | 1.4                    |
| Office                      | 39.0                   | 2.5                    |
| Professional                | 4.9                    | 9.4                    |
| Housewife                   | 4.0                    | 48.9                   |
| Farmer                      | 1.6                    | 23.4                   |
| Service                     | 1.9                    | 6.9                    |
| Other                       | 5.5                    | 7.5                    |
| Education (%)               | 506.14                 | <0.01                  |
| Primary school              | 0.3                    | 2.7                    |
| Junior school               | 7.0                    | 60.1                   |
| Senior school               | 20.2                   | 16.1                   |
| Monthly household income (per capita CNY\textsuperscript{d}, %) | College | 41.5 | 13.7 |
|-----------------|---------|------|------|
| University and above | 31.0 | 7.5 |

Monthly household income (per capita CNY\textsuperscript{d}, %)

| Monthly household income | Percentage (indicate with %) |
|--------------------------|------------------------------|
| ≤2000                    | 21.9                         |
| 2001-3000                | 29.7                         |
| 3001-5000                | 34.0                         |
| 5001-8000                | 9.5                          |
| 8001-12000               | 4.2                          |
| >12000                   | 0.7                          |

\textsuperscript{a} Only women with singleton births were included in the presented work.

\textsuperscript{b} Results for Wuqiang pregnancy cohort were calculated based on available data up to April 2021.

\textsuperscript{c} BMI: body mass index.

\textsuperscript{d} CNY: China yuan.

**Gestational diabetes mellitus and metabolomics**

The metabolites of mothers and newborns were compared between those diagnosed with gestational diabetes mellitus (GDM) and those with normal glucose.\textsuperscript{23} Nearly 1000 small molecular metabolites were detected, and the concentrations of 30-40 metabolites in serum were different in early pregnancy, second trimester, third trimester, and in umbilical cord blood. These results suggested abnormal metabolism occurred through the gestation and GDM affected the metabolism of offspring, which could be associated with the increased risk of long-term metabolic disorders in children.

**Folic acid and birthweight**

We analyzed the effect of folic acid levels during early pregnancy on newborns' birthweight.\textsuperscript{24} The median concentration of serum folic acid was 12.3 ng/mL for pregnancy women at an average of 13.7 weeks of gestation, there was no association between folic concentration and newborns' birthweight, but folic concentration above 14.5 ng/mL could reduce the risk of small for gestational age (\textit{OR}=0.08, 95\% \textit{CI}: 0.01-0.61).

**Future plans**
The TAWS is currently ongoing; data from the cohort is currently being collected, processed, and cleaned. A variety of biological samples will be collected and analyzed to help reveal the mechanism of early-life nutrition on children's growth and health. Data from the study could help to give evidence-based dietary instructions and primary care policies to improve the health of mothers and children.

Strengths and limitations
Strengths of the TAWS included the unique study design of mother-child pairs, detailed data on early-life exposures, particularly nutritional factors, with frequent follow-ups, and a wide range of biological samples available for analysis. Of particular importance, the two study sites had different populational characteristics: Taicang is rich and located in southern China, whereas Wuqiang is relatively poor and located in northern China; the two study sites therefore enrolled participants with different geographic and cultural profiles, aiming to reflect the diverse dietary and lifestyle patterns between regions of different economic and cultural profiles in China.

This study had several limitations. First, the study had been carried out at two major study sites to assess the research questions in different geographic regions of China. Acknowledging the broad heterogeneity of Chinese populations and regional differences, our study might not be generalizable to the general populations in China. However, our study populations’ profile was in general comparable with the obstetric characteristics reported in other studies.19-25 Second, we had some participants lost to follow-up at the two study sites, whom might not be comparable to the participants remained in the study. Reasons of loss to follow-up, if related to outcomes yet not accounted in the analysis, might lead to bias in estimating the associations of interest. Third, we prioritized to collect venous blood samples from participants at the follow-up visits, which, under some circumstances, was not feasible; we attempted to collect peripheral blood under such circumstances.

COLLABORATION
Data of the TAWS are not yet openly available. Researchers who are interested in potential collaboration should contact the principal investigator Jianqiang Lai (jq_lai@126.com) to complete a research plan for evaluation by Ethical Review Committee of NINH.

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Author Contributions SY, YD, JW, ZY and JQL designed the cohort. JL, FL, PZ, CL, YZ, XG
coordinated the fieldwork and supervised data collection. JW and YD performed data quality control
and statistical analysis. JY, YD and JW wrote the manuscript. ZY, CY and JQL reviewed the
manuscript. All authors have read and approved the final version of the manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study has received ethical approval from Ethical Review Committee of National
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(Study-ID: ChiCTR-OOC-16008874 and ChiCTR-OOC-16008858).

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Data availability statement Additional data are available on reasonable request.
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Figure 1 Participant recruitment and follow-ups in the TAWS Taicang subcohort
**Figure 2** Participant recruitments and follow-ups in the TAWS Wuqiang subcohort

(ongoing, data presented reflecting study period up to April 30, 2021)
Figure 1 Participant recruitment and follow-ups in the TAWS Taicang subcohort

419x506mm (57 x 57 DPI)
Figure 2  Participant recruitments and follow-ups in the TAWS Wuqiang subcohort (ongoing, data presented reflecting study period up to April 30, 2021)

From June 2016 to April 2021, pregnancy cohort recruited in early pregnancy (n=1940)

Mid-pregnancy follow-up (n=1557)

Late-pregnancy follow-up (n=1439)

Local delivery resulting live-birth(s) (n=1079)

Postpartum follow-up on mother and offspring

From November 2016 (ongoing), delivery cohort recruited at time of delivery (n=3006 as of April 31, 2021)

1 month (n=3204)
2 months (n=3085)
3 months (n=3005)
6 months (n=2793)
8 months (n=2793)
12 months (n=2339)
18 months (n=1862)
24 months (n=1415)
30 months (n=943)
36 months (n=677)
## STROBE Statement—Checklist of items that should be included in reports of cohort studies

| Item No | Recommendation |
|---------|----------------|
| **Title and abstract** | 1. *(a)* Indicate the study’s design with a commonly used term in the title or the abstract  
2. *(b)* Provide in the abstract an informative and balanced summary of what was done and what was found |
| **Introduction** | 2. | Explain the scientific background and rationale for the investigation being reported |
| **Objectives** | 3. | State specific objectives, including any prespecified hypotheses |
| **Methods** | 4. | Present key elements of study design early in the paper |
| **Setting** | 5. | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
| **Participants** | 6. *(a)* | Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up  
2. *(b)* For matched studies, give matching criteria and number of exposed and unexposed |
| **Variables** | 7. | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
| **Data sources/measurement** | 8.* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group |
| **Bias** | 9. | Describe any efforts to address potential sources of bias |
| **Study size** | 10. | Explain how the study size was arrived at |
| **Quantitative variables** | 11. | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| **Statistical methods** | 12. *(a)* | Describe all statistical methods, including those used to control for confounding  
2. *(b)* Describe any methods used to examine subgroups and interactions  
3. *(c)* Explain how missing data were addressed  
4. *(d)* If applicable, explain how loss to follow-up was addressed  
5. *(e)* Describe any sensitivity analyses |
| **Results** | 13.* | *(a)* Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed  
2. *(b)* Give reasons for non-participation at each stage  
3. *(c)* Consider use of a flow diagram |
| **Descriptive data** | 14.* | *(a)* Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders  
2. *(b)* Indicate number of participants with missing data for each variable of interest  
3. *(c)* Summarise follow-up time (eg, average and total amount) |
| **Outcome data** | 15.* | Report numbers of outcome events or summary measures over time |
| Section          | Item | Description                                                                                                                                                                                                 |
|------------------|------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Main results     | 16   | *(a)* Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included  
* *(b)* Report category boundaries when continuous variables were categorized  
* *(c)* If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
| Other analyses   | 17   | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses                                                                                                            |
| **Discussion**   | 18   | **Key results** Summarise key results with reference to study objectives                                                                                                                                 |
|                  | 19   | **Limitations** Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias  |
|                  | 20   | **Interpretation** Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence |
|                  | 21   | **Generalisability** Discuss the generalisability (external validity) of the study results                                                                                                                   |
| **Other information** | 22   | **Funding** Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based                                               |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.
# Cohort profile: the Taicang and Wuqiang mother-child cohort study (TAWS) in China

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**Primary Subject Heading:** Public health

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Cohort profile: the Taicang and Wuqiang mother-child cohort study (TAWS) in China

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ABSTRACT

Purpose The Taicang and Wuqiang cohort study (TAWS) was established to examine the association between early-life nutrition and children’s health and to explore the potential roles of maternal health, metabolites, and microbiota in children’s health in two different regions of China.

Participants A total of 7041 mother-child pairs were recruited during early pregnancy (n=4035, 57.3%) or delivery phase (n=3006, 42.5%) from health centers or hospitals in Taicang and Wuqiang. Mother-child pairs were followed up three times during pregnancy, once during delivery, and seven to ten times in the three years after delivery. Questionnaires were used to collect data on diet, supplementary intake, physical activity, depression scale, disease occurrence, feeding practice, and development quotient of children. Anthropometric measurements of mothers and their children were assessed at each visit. Pregnancy outcomes were extracted from medical records. Biospecimens were collected and stored, including venous blood, cord blood, urine, stool, breast milk, cord, and placenta.

Findings to date Data from the TAWS cohort showed different baseline characteristics of participants at the two sites of TAWS. Abnormal metabolism occurred among newborns whose mothers were diagnosed with gestational diabetes mellitus. Maternal serum folic acid above 14.5 ng/mL at early pregnancy was associated with a reduced risk of delivering small-for-gestational-age newborns.
**Future plans** The association between maternal nutrition and the health of offspring will be examined at various follow-up visits. Biomarkers will be analyzed to assess the associations between early-life nutrition and child development, immunity, and health. Strategic recommendations for optimal infant feeding practices, obesity prevention, and routine health care items will be developed and proposed based on the findings from the study. Children in this prospective cohort study will be followed up once a year until age 12 years to further examine the relationships between early-life nutrition and children’s long-term development and health.

**KEYWORDS** cohort study, early-life, nutrition, mother, child

**WORDS COUNT** 3675

**Strengths and limitations of this study**
- This ongoing study collected data from three follow-ups during pregnancy, one follow-up during the delivery phase, and seven to ten follow-ups after birth; it provides rich data with respect to dietary information and biospecimens to explore the mechanisms of associations between maternal and early-life nutrition and children’s growth and health.
- The Taicang and Wuqiang mother-child cohort in China included two study sites, one in a wealthy southern city and the other in a poor northern county; findings from this cohort may improve the understanding of diverse maternal diets and lifestyle patterns in China.
- Study participants may not be representative of the overall relevant population, as ineligibility or unwillingness information was not well documented; additionally, some participants were lost to follow-up, and biological samples were obtained from only a subset of participants, which may have led to some selection bias.

**INTRODUCTION**
Evidence from epidemiological studies and animal models has bolstered the paradigm of ‘developmental origins of health and disease’ (DOHaD) over the past decades. It is now well established that the first 1000 days of life (i.e., from conception to the age of two), is a critical time window for developmental trajectory programming. Adverse disturbances occurred during this period may lead to increased risks of chronic diseases across one’s lifespan or an epigenetic transgenerational inheritance of such risks. Of particular importance, extensive evidence suggests that maternal diets and early-life nutritional status are associated with altered risks of both short-term and long-term diseases for the offspring, including metabolic, immunological, mental, and reproductive diseases. Consequently, achieving optimal nutrition during pregnancy and early life can be one critical step to substantially lower the future disease burdens.

China has the largest population worldwide, with around 15 million babies born each year. Given the population size, addressing early-life nutrition to prevent future diseases has tremendous benefits in lowering the social and economic burdens associated with these negative long-term consequences. Since the 1990s, China has made significant improvements in maternal and child health, meeting the Millennium Development Goals and Sustainable Development Goals. In parallel with rapid economic growth and improved healthcare coverage, China is on the way further closing the gaps in maternal and newborn care across regions. Of note, studies...
have suggested heterogeneity in maternal and infant health profiles across different geographic regions in China: rates of obesity-related maternal or infant complications are higher in more developed settings, whereas rates of undernutrition-related complications are more common in less-developed settings, possibly due to differences in socioeconomic status, access to food choices, dietary patterns, or a combination of these factors.\textsuperscript{18-21}

To date, a few birth cohorts in China have examined the associations between several environmental pollutants, nutrients (e.g., folic acid and vitamin D), nutrition in pregnancy, maternal biomarkers and birth defects or children’s health.\textsuperscript{22-25} Although biospecimens were collected in some of these established cohorts, only routine sub-clinical indicators related to nutrition were assessed and examined. In addition, few Chinese cohort studies have collected up-to-date data reflecting the recent economic development and dietary intake with child growth or health. Furthermore, studies representing different Chinese subgroups are needed to account for the noted differences in maternal and infant health profiles when examining maternal and early-life nutrition. To fill in these critical gaps, we sought to establish a multi-center cohort, aiming to improve our understanding of the role of early nutrition on children’s development (anthropometric and psychological development) and health (nutritional status, the occurrence of anemia, fever, diarrhea, and allergy, etc.); and to explore potential mechanisms (metabolomics, microecology, immunology) and promote general health care across different regions of China.

**COHORT DESCRIPTION**

**Cohort setup and quality control**

The Taicang and Wuqiang Study (TAWS) consisted of two study sites, Taicang (Jiangsu Province, China) and Wuqiang (Hebei Province, China). It was designed and supervised by the National Institute for Nutrition and Health (NINH), formerly named National Institute for Nutrition and Food Safety. Study participants were screened, recruited, and followed separately at local healthcare centers and obstetric hospitals of the two study sites.

The Taicang sub-cohort was hosted by the Taicang Service Center for Mother and Child Health and Family Planning (TC-MCH). Among 22 community health centers, doctors at the prenatal clinics and child care clinics took charge of the recruitment and the follow-up during pregnancy and postpartum. Nurses at the obstetric clinics of all five hospitals were responsible for the follow-up during the delivery phase. The Wuqiang sub-cohort was hosted by the Wuqiang Center for Disease Control and Prevention (WQ-CDC). Doctors in all eight township health centers and the Maternal and Child Health Hospital were responsible for the recruitment and the follow-up during pregnancy and postpartum, and nurses at the obstetric clinic of Wuqiang County Hospital took charge of recruitment and follow-up during the delivery phase.

One month before recruitment, all the doctors and nurses involved in the study at the two study sites received 16 hours of training. Training contents included participant recruitment, questionnaire information collection (basic characteristics, supplementary intake, physical activity, depression scale, disease occurrence or medication), dietary measurements (3-day food records; food frequency questionnaire, FFQ), anthropometric measurements and assessments, child feeding, development quotient test, biological sample collection and preservation, follow-up appointment, and data entry. Since the initiation of recruitment, training sessions were held every two months for the first two years and quarterly thereafter. Training contents during the study
were designed to address the problems identified in the supervision of the principal investigators and questions raised by study doctors and/or nurses, and each training session lasted 1 hour or longer.

Participants were recruited from May 2013 to December 2017 in Taicang and from June 2016 to December 2021 in Wuqiang. Pregnant women less than 16 weeks of gestation were invited to participate in the early-pregnancy cohort at both study sites. A delivery cohort was additionally set up in Wuqiang, and pregnant women coming to the Wuqiang County Hospital for delivery were invited to participate in the delivery cohort. We compared data from the two early-pregnancy sub-cohorts for differences in maternal and childhood nutrition and health at the two study sites. Figure 1 and Figure 2 illustrate the enrollment and follow-up schedule of the study in Taicang and Wuqiang, respectively.

Participants

Participants were recruited at two stages: (1) early pregnancy (n=4035, early-pregnancy cohort) and (2) during delivery (n=3006, delivery cohort, Wuqiang site). Pregnant women coming for prenatal care were considered potential participants and were approached by trained doctors or nurses for eligibility screening. They were eligible if: 1) aged 18-45 years, 2) less than 16 weeks of gestation, 3) had no history of recurrent abortion, 4) self-reported to be overall healthy without significant medical history (i.e., hypertension, diabetes, mental disorders, cancer, and other malignant diseases), 5) plan to receive prenatal care and deliver at local hospitals, 6) plan to stay in Taicang/Wuqiang in the next four years, 7) be willing to cooperate, 8) be able to write and communicate well. For the delivery cohort in Wuqiang, pregnant women coming for labor were approached and screened by nurses before delivery, with the identical eligibility criteria outlined above, except 2) and 5). Women who agreed to be enrolled in the study provided written informed consent.

For participants in the early-pregnancy cohort, baseline data were collected using questionnaires at enrollment, including information on general characteristics of the pregnant women and their husbands, pre-pregnancy dietary and supplementary intake, pregnancy history, and health history. For participants in the delivery cohort, similar baseline data were collected except pre-pregnancy dietary intake.

Cohort follow-up and data collection

Pregnant women received one face-to-face visit at outpatient clinics in each early, mid-, and late pregnancy. Dietary intake was collected using 3-day food records; information on supplementary intake, physical activity (by mobile monitoring devices or self-reported), depression scale, and symptoms or medicines used during pregnancy were queried too. Doctors administered physical and obstetric examinations to check the health status of the mother and the development of her fetus. Twenty milliliters of urine samples and 5 mL of venous blood were collected from mothers at each follow-up during pregnancy at the Wuqiang site (Table 1).

| Time               | Methods     | Data contents                                                                 |
|--------------------|-------------|-------------------------------------------------------------------------------|
| Early pregnancy    | Questionnaire| Recruitment: Demographics, pre-pregnancy diet (FFQ), pre-pregnancy supplementary intake, pregnancy history, health history, husband-related information (body weight, height, smoking) |
During the delivery phase, pregnancy outcomes (e.g., gestational week at delivery, delivery mode, gestational diseases, postpartum hemorrhage, birthweight and length of the newborn, Apgar score) were extracted from medical records. We collected maternal venous blood (5 mL) and neonatal cord blood (5 mL) in both Taicang and Wuqiang. We additionally collected maternal urine (20 mL), placenta (4 sites), umbilical cord (3 cm), and meconium (2 g) at the Wuqiang study site (Table 1).

After delivery, mothers were followed seven times in Taicang and ten times in Wuqiang. Information on dietary intake, supplementary intake, physical activity, and mental health was self-reported; and anthropometrics were measured on-site. Fasting venous blood (5 mL) and breast milk (whole milk from one breast using a portable automatic breast pump) were collected from mothers by nurses. Sampling tubes for urine (20 mL) and stool (2 g) were distributed to the mothers, and they were instructed by doctors to collect, store, and carry the samples to the clinics at the designated follow-up visits as shown in Table 2.

After birth, children were followed nine times in Taicang and ten times in Wuqiang (Table 2). General health, growth, and motor development were assessed by doctors; child feeding practice (e.g., breastfeeding, formula, complementary feeding, and supplementary intake), dietary intake (using FFQ or 3-day food records), and disease occurrence during the previous 14 days were retrospectively recalled by the caregivers. Samples of blood (5 mL), urine (10 mL), and stool (2 g) were collected at some visits as shown in Table 2. To assess child development, the Development Quotient (DQ) test using the Gesell assessment was administered for a part of children aged 18 and 24 months in Wuqiang.

| Physical examination | Biological sample | Follow-up: early pregnancy diet (3-day food records), nutrient supplementation, physical activity, depression scale, symptoms, medicines used. Anthropometry and obstetric examination. Wuqiang site: venous blood and urine. |
|---------------------|------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mid-pregnancy       | Questionnaires   | Diet (3-day food records), nutrient supplementation, physical activity, depression scale, symptoms, medicines used. Anthropometry and obstetric examination. Wuqiang site: venous blood and urine. |
|                     | Physical examination | Anthropometry and obstetric examination. Wuqiang site: venous blood and urine.                                                                                                               |
|                     | Biological sample | Anthropometry and obstetric examination. Wuqiang site: venous blood and urine.                                                                                                                  |
| Late-pregnancy      | Questionnaire    | Diet (3-day food records), nutrient supplementation, physical activity, depression scale, symptoms, medicines used. Anthropometry and obstetric examination. Wuqiang site: venous blood and urine. |
|                     | Physical examination | Anthropometry and obstetric examination. Wuqiang site: venous blood and urine.                                                                                                                  |
| Delivery            | Questionnaire    | Recruitment (Wuqiang site): general characteristics of pregnant women and their husbands, pre-pregnancy supplementary intake, pregnancy history, health history.                                       |
|                     | Physical examination | Maternal body weight before and after delivery, birth weight and length of newborns.                                                                                                              |
|                     | Biological sample | Pre-delivery venous blood and cord blood. Wuqiang site: maternal pre-delivery urine, placenta, and newborn’s stool.                                                                                      |

*a* FFQ: food frequency questionnaire; Wuqiang site: indicators or samples were collected only at the Wuqiang study site.

Table 2. Data collection after delivery in the TAWS*
| Time    | Subject | Data collection after delivery                                                                 |
|---------|---------|-----------------------------------------------------------------------------------------------|
| 28 days | Child   | Anthropometry, child feeding, general health                                                   |
| 42 days | Mother  | Diet (FFQ), anthropometry, general health, depression scale, breast milk; Wuqiang site: venous blood, urine |
| 2 months| Child   | Wuqiang site: Anthropometry, child feeding, general health                                    |
| 3 months| Mother  | Diet (3-day food records or FFQ), anthropometry, general health, breast milk; Taicang site: venous blood |
|         | Child   | Anthropometry, child feeding, nutrient supplementation, motor development, general health; Wuqiang site: stool |
| 6 months| Mother  | Anthropometry, general health; Wuqiang site: breast milk                                       |
|         | Child   | Anthropometry, child feeding, diet (3-day food records or FFQ), nutrient supplementation, motor development, general health; Wuqiang site: urine, stool |
| 8 months| Mother  | Wuqiang site: anthropometry, general health                                                   |
|         | Child   | Anthropometry, child feeding, diet (FFQ), nutrient supplementation, motor development, general health; Wuqiang site: urine |
| 12 months| Mother | Anthropometry, general health                                                                |
|         | Child   | Wuqiang site: urine, venous blood, breast milk; Anthropometry, child feeding, diet (FFQ), nutrient supplementation, motor development, general health; Wuqiang site: urine and stool |
| 18 months| Mother | Anthropometry, general health                                                                |
|         | Child   | Anthropometry, child feeding, diet (3-day food records or FFQ), nutrient supplementation, motor development, general health; Wuqiang site: DQ test, urine, stool |
| 24 months| Mother | Anthropometry, general health                                                                |
|         | Child   | Anthropometry, child feeding, diet (FFQ), nutrient supplementation, motor development, general health; Wuqiang site: DQ test, urine, stool |
| 30 months| Mother | Wuqiang site: anthropometry, general health                                                   |
|         | Child   | Anthropometry, child feeding, diet (FFQ), nutrient supplementation, motor development, general health |
| 36 months| Mother | Anthropometry, general health                                                                |
|         | Child   | Anthropometry, child feeding, diet (3-day food records or FFQ), nutrient supplementation, motor development, general health; Wuqiang site: venous blood, urine, stool |

* FFQ: food frequency questionnaire; DQ: Development quotient; Wuqiang site: indicators or samples were collected only at the Wuqiang study site; Taicang site: indicators or samples were collected only at the Taicang study site.

Biological samples storage and analysis

Blood, stool, and breast milk samples were separately stored at -80°C, and urine samples were stored at -20°C. Samples of placenta and cord were fixed in neutral buffered formalin, embedded into wax blocks, and stored at room temperature. Levels of vitamins, minerals, and metabolites were measured by mass spectrometry. Blood glucose, lipid, and hemoglobin were analyzed by an automatic biochemical analyzer. Microbiome was analyzed by the Illumina Hiseq2500 platform. Laboratory quality control materials were run at the beginning and during sample testing.

Compliance promotion

We adopted five strategies to promote participant compliance. First, the two study sites had established standardized follow-up procedures according to the local routine health care schedule, which lowered the participants’ burden of transportation and time. Second, all hospitals and health centers worked with the same electronic platform for routine care and follow-up, which has an
alarming system to remind doctors to collect data for the study as long as the participants came for care. Third, doctors scheduled appointments for the subsequent follow-up visits via the telephone and informed participants of the contents ahead of the visits. For mothers and children who failed to follow up on time, doctors would call again to make an appointment within a month. Fourth, the principal investigators documented all the issues and provided relevant updated training and feedback to doctors at the regular training sessions every two to three months. Fifth, doctors provided mothers or child caregivers with instructions on dietary intake and child feeding practice based on results of physical examination, biochemical testing, and dietary evaluation, which would benefit the participants.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research. All participants were informed that the data from this study were used only for research purposes. There were no plans to disseminate the findings to the participants.

FINDINGS TO DATE

Baseline characteristics

The early-pregnancy cohort in Taicang and Wuqiang enrolled 2095 and 1940 women, respectively. Based on data from the early-pregnancy cohorts, the two study sites included pregnant women with different profiles, acknowledging the demographic, health- and culture-related differences in regions of China as outlined in the TAWS specific aims. Compared with the study participants in Wuqiang, participants in Taicang were younger and more likely to be enrolled at an earlier gestational age, be primiparas, and have a lower pre-pregnancy body mass index (BMI); they were more likely to be workers or office clerks and to have higher education and higher household income (Table 3).

### Table 3. Baseline characteristics of participants in the early-pregnancy cohort of the TAWS

| Indicators         | Taicang (n=2095) | Wuqiang (n=1940) | Z/Chisq | P    |
|--------------------|------------------|------------------|---------|------|
| Age (yr)           | 25.0(24.0,28.0)  | 27.7(25.3,30.5)  | 19.09   | <0.01|
| Gestational age (week) | 10.0(8.0,11.0)  | 13.0(11.0,15.0)  | 37.42   | <0.01|
| Height (cm)        | 160.1(158.1,164.0) | 160.0(156.5,163.0) | 5.33   | <0.01|
| Pre-pregnancy BMI (kg/m²) | 20.3(18.8,22.1) | 22.9(20.5,25.6) | -21.32  | <0.01|
| Primipara (%)      | 81.2             | 8.3              | 1803.3  | <0.01|
| Occupation (%)     |                  |                  | 1025.11 | <0.01|
| Worker             | 43.1             | 1.4              |
| Office clerk       | 39.0             | 2.5              |
| Professional       | 4.9              | 9.4              |
| Housewife          | 4.0              | 48.9             |
| Farmer             | 1.6              | 23.4             |
| Service            | 1.9              | 6.9              |
| Other              | 5.5              | 7.5              |
| Education (%)      |                  |                  | 506.14  | <0.01|
| Primary school     | 0.3              | 2.7              |
| Junior school      | 7.0              | 60.1             |
| Senior school      | 20.2             | 16.1             |
| College            | 41.5             | 13.7             |
Gestational diabetes mellitus and metabolomics
Metabolites of mothers and newborns were compared between those diagnosed with gestational diabetes mellitus (GDM) and those with normal glucose. Nearly 1000 small molecular metabolites were assessed, and concentrations of 30-40 serum metabolites were different in early pregnancy, second trimester, third trimester, and in umbilical cord blood between women with GDM and those with normal glucose. These results suggested abnormal metabolism occurred through gestation in mothers and their newborns.

Folic acid and birthweight
We analyzed the association between folic acid levels during early pregnancy with newborns’ birthweight. Median concentration of serum folic acid was 12.3 ng/mL for pregnant women at an average of 13.7 weeks of gestation. There was no association observed between serum folic concentration and newborns’ birthweight. However, maternal serum folic concentration above 14.5 ng/mL was associated with a lower risk of delivering small-for-gestational-age newborns ($OR=0.08$, 95%CI: 0.01-0.61).

Future plans
The TAWS is currently ongoing. Data from the cohort are being collected, processed, and cleaned. The association between maternal nutrition and the health of their offspring will be examined at various follow-up visits. Biomarkers will be analyzed to assess the associations between early-life nutrition and child development, immunity, and health. Strategic recommendations for optimal infant feeding practices, obesity prevention, and routine health care items will be developed and proposed based on the findings from the study. Children in this prospective cohort study will be followed up once a year until the age of 12 years to further examine the relationships between early-life nutrition and children’s long-term development and health.

Strengths and limitations

| University and above | Monthly household income (per capita CNYd, %) | 31.0 | 7.5 | 36.73 | <0.01 |
|----------------------|-----------------------------------------------|------|-----|--------|-------|
| ≤2000                |                                               | 21.9 | 19.5|        |       |
| 2001-3000            |                                               | 29.7 | 40.7|        |       |
| 3001-5000            |                                               | 34.0 | 35.0|        |       |
| 5001-8000            |                                               | 9.5  | 4.2 |        |       |
| 8001-12000           |                                               | 4.2  | 0.5 |        |       |
| >12000               |                                               | 0.7  | 0.1 |        |       |

a Only women with singleton births were included in the presented results.
b Results for the Wuqiang pregnancy cohort were calculated based on available data up to April 2021.
c BMI: body mass index.
d CNY: China yuan.
Strengths of the TAWS included detailed data on early-life exposures, particularly nutritional information, frequent follow-ups, and a wide range of biospecimens available for exploring potential mechanisms of early nutrition on children’s growth and health. Of particular importance, the two study sites had different populational characteristics: Taicang is economically more developed and located in southern China, whereas Wuqiang is relatively less developed compared with Taicang and located in northern China; the two study sites, therefore, represent participants with different geographic and cultural profiles, aiming to better reflect and acknowledge the diverse dietary and lifestyle patterns in China. In addition, given the overall economic status of Wuqiang as less developed, nearly half of the pregnant women in Wuqiang did not receive prenatal care; as a result, we established an early-pregnancy cohort and a delivery cohort to better represent profiles of the local pregnant women.

This study has several potential limitations. Similar to other Chinese pregnancy or birth cohorts, generalizability to the diverse Chinese population is a concern. However, our study population’s profile was in general comparable with obstetric characteristics reported in earlier studies. Second, we had some participants lost to follow-up, who might not be comparable to the participants who remained in the study. Baseline characteristics will be compared between subjects who remained in the cohort and those lost to follow-up to assess the degree of concern due to loss to follow-up. Reasons for loss to follow-up, if related to outcomes yet not accounted in the analysis, might lead to bias in estimating the associations of interest. Third, we prioritized collecting venous blood samples from participants at the follow-up visits, which, under some circumstances, was not feasible, especially for children; we attempted to collect peripheral blood under such circumstances, which may limit the understanding of children’s micronutrient status. Fourth, we did not record the number and the specific reasons for pregnant women who did not meet the inclusion criteria or who were unwilling to participate in this study. Based on our communication with doctors during the training sessions, the main reason for not meeting the inclusion criteria was exceeding the gestational age criteria for the early-pregnancy cohort, and some pregnant women were unwilling to participate because of the large content and the long duration of the study.

COLLABORATION
Data of the TAWS are not openly available yet. Researchers who are interested in potential collaboration should contact the principal investigator Jianqiang Lai (jq_lai@126.com) to submit a research plan for evaluation by the Ethical Review Committee of NINH.

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We are grateful to all the collaborating organizations and staff of the TAWS whose hard work has made this study possible. We would like to thank the 22 community health centers in Taicang for their follow-ups during pregnancy and postpartum, and five hospitals in Taicang for the follow-up during delivery. We would like to thank Wuqiang Maternal and Child Health Care Hospital and the eight township health centers for follow-ups during pregnancy and postpartum, and Wuqiang County Hospital for the follow-up at delivery. We would like to thank all the study participants and their families for their voluntary participation and ongoing support for the TAWS.
Contributors
SY, YD, JW, ZY, and JQL designed the cohort. JL, FL, PZ, CL, YZ, and XG coordinated the fieldwork and supervised data collection. JW took charge of the training and quality control in the Taicang sub-cohort, and YD was responsible for the Wuqiang sub-cohort. JW and YD performed data process and statistical analysis. JY, YD, and JW wrote the manuscript. ZY, CY, and JQL reviewed the manuscript. All authors have read and approved the final version of the manuscript.

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Competing interests
None declared.

Ethics approval
The study has received ethical approval from the Ethical Review Committee of National Institute for Nutrition and Health, Chinese Center for Disease Control and Prevention (Approval number: 2013-001 and 2016-014). We registered the study at the Chinese Clinical Trial Registry (Study-ID: ChiCTR-OOC-16008874 and ChiCTR-OOC-16008858).

Patient consent for publication
Not required.

Data availability statement
Data are available on reasonable request, including anthropometric data and micronutrient status data of mothers and children.

Provenance and peer review
Not commissioned; externally peer reviewed.

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Figure 1. Participant recruitment and follow-ups in the TAWS Taicang sub-cohort

Figure 2. Participant recruitments and follow-ups in the TAWS Wuqiang sub-cohort 
(ongoing, data presented reflecting study period up to April 30, 2021)
Early-pregnancy cohort from 2013 to 2017 in Taicang, Pregnant women recruited in early pregnancy (n=2095)

Mid-pregnancy follow-up (n=2085)

Late-pregnancy follow-up (n=2081)

Local delivery (n=1797)

Postpartum follow-ups

Mothers

Children

42 days (n=1741)
3 months (n=1477)
6 months (n=1351)
12 months (n=782)
18 months (n=589)
24 months (n=478)
36 months (n=351)

28 days (n=1937, including local births (n=1797) and children returned to local place after birth (n=140))
3 months (n=2045, including local births (n=1797) and children returned to local place after birth (n=248))
   6 months (n=2005)
   8 months (n=2018)
   12 months (n=1991)
   18 months (n=1995)
   24 months (n=1957)
   30 months (n=1830)
   36 months (n=1487)

Figure 1. Participant recruitment and follow-ups in the TAWS Taicang sub-cohort
From June 2016 to April 2021, early-pregnancy cohort recruited in early pregnancy (n=1940)

Mid-pregnancy follow-up (n=1559)

Late-pregnancy follow-up (n=1439)

Local delivery (n=1100)

Postpartum follow-ups of mothers and children

From November 2016 (ongoing), delivery cohort recruited at the time of delivery (n=3006 as of April 30, 2021)

Miscarriage n=39
Not reaching the next time n=34
Move out n=308

Miscarriage n=5
Not reaching the next time n=58
Move out n=57

Move out n=339

1 month (n=3204)
2 months (n=3085)
3 months (n=3005)
6 months (n=2793)
8 months (n=2571)
12 months (n=2339)
18 months (n=1862)
24 months (n=1415)
30 months (n=943)
36 months (n=677)

Figure 2. Participant recruitments and follow-ups in the TAWS Wuqiang sub-cohort (ongoing, data presented reflecting study period up to April 30, 2021)
STROBE Statement—Checklist of items that should be included in reports of cohort studies

| Item No | Recommendation                                                                 | Page No |
|---------|-------------------------------------------------------------------------------|---------|
| **Title and abstract** | (a) Indicate the study’s design with a commonly used term in the title or the abstract  
(b) Provide in the abstract an informative and balanced summary of what was done and what was found | 3, 4 |
| **Introduction** | | 3, 4 |
| **Background/rationale** | Explain the scientific background and rationale for the investigation being reported | 4, 5 |
| **Objectives** | State specific objectives, including any prespecified hypotheses | 5 |
| **Methods** | | 6 |
| Study design | Present key elements of study design early in the paper | 6 |
| Setting | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 6 |
| Participants | (a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up  
(b) For matched studies, give matching criteria and number of exposed and unexposed | 7 |
| Variables | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 7-10 |
| Data sources/measurement | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 7-10 |
| Bias | Describe any efforts to address potential sources of bias | 10, 11 |
| Study size | Explain how the study size was arrived at | 7 |
| Quantitative variables | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 12, 13 |
| Statistical methods | (a) Describe all statistical methods, including those used to control for confounding  
(b) Describe any methods used to examine subgroups and interactions  
(c) Explain how missing data were addressed  
(d) If applicable, explain how loss to follow-up was addressed  
(e) Describe any sensitivity analyses | 11 |
| **Results** | | 19, 20 |
| Participants | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed  
(b) Give reasons for non-participation at each stage  
(c) Consider use of a flow diagram | 19, 20 |
| Descriptive data | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders  
(b) Indicate number of participants with missing data for each variable of interest  
(c) Summarise follow-up time (eg, average and total amount) | 11, 12, 19, 20 |
| Outcome data | Report numbers of outcome events or summary measures over time | 7-10 |
Main results

16. (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included.

(b) Report category boundaries when continuous variables were categorized.

(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.

Other analyses

17. Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses.

Discussion

Key results

18. Summarise key results with reference to study objectives.

Limitations

19. Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.

Interpretation

20. Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.

Generalisability

21. Discuss the generalisability (external validity) of the study results.

Other information

Funding

22. Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.