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Cover Image: adapted from the United Nations, https://www.un.org/zh/observances/womens-day.
This week's issue was organized by Guest Editor Linhong Wang.

Foreword

Making Women's Health Visible: From Healthy Beginnings to System Resilience

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Women consistently outlive men in nearly all regions of the world. Yet longer life does not necessarily mean better health. Increasingly, global health discussions recognize that women's health must be understood beyond reproduction and addressed through a broader, life-course, and systems perspective. World Health Day 2025 reframes "healthy beginnings" as a process that extends across the life course, rather than a moment limited to birth (*1*). Evidence shows that adolescence, preconception, and early adulthood are critical periods when nutrition, mental health, environmental exposures, and access to preventive services shape long-term risks of noncommunicable diseases, reproductive outcomes, and even the health of the next generation (*2–3*). At the same time, women's health outcomes are strongly influenced by how health systems are organised, financed, and evaluated (*4*). The 2025 World Health Summit further highlighted that women's health is closely linked to the resilience of health systems (*5*). When women's health needs are met, health systems are better equipped to respond to pandemics, climate-related challenges, and population ageing, while maintaining prevention and continuity of care. Academic and policy debates increasingly call for making women's health more visible (*6*). This requires better sex-disaggregated data, policies that acknowledge women's multiple social roles, and service models built around continuity rather than isolated episodes of care. Together, these global developments underscore that investing in women's health is not a marginal concern, but a strategic priority aligned with equity, sustainability, and system resilience.

With socioeconomic development and rising health awareness, women's demand for comprehensive, life-course health services continues to grow. However, important gaps remain and are largely invisible in routine health data, policy discourse, and service delivery models. First, ensuring maternal safety and further reducing maternal mortality remain priorities, alongside improved management of pregnancy-related complications and expanded premarital and preconception care, including prevention of mother-to-child transmission of key infections. Second, reproductive health challenges persist, including reproductive tract infections, sexually transmitted infections, infertility, unintended pregnancy linked to inadequate contraception, and the prevention and management of induced abortion. Third, girls and adolescents face nutritional imbalance, mental health concerns, unhealthy lifestyles, risks to reproductive function, sexually transmitted infections, and exposure to injury and violence. Fourth, as population ageing accelerates, demand for health services among older women is rising, particularly for osteoporosis, malignancies, metabolic disorders, and cardiovascular and cerebrovascular diseases. Fifth, the incidence of female cancers — especially cervical and breast cancer — continues to increase, requiring strengthened primary, secondary, and tertiary prevention. Finally, mental health problems are escalating across critical life stages, while chronic diseases driven by unhealthy diets, physical inactivity, smoking, and alcohol use have become dominant long-term threats to women's health.

China has made significant progress in women's health, consistently prioritizing maternal and child health within national development strategies (*7*). A robust legal and policy framework, including legislation on maternal and child healthcare, women's rights protection and health promotion, has established institutional safeguards for women's health. National strategies such as *Healthy China 2030* and *The Outline for the Development of Chinese Women (2021–2030)* prioritize maternal and child health indicators in performance monitoring. These efforts have resulted in significant improvements in key areas. Maternal, infant, and under-five mortality rates have declined steadily and now rank among the lowest in upper-middle-income countries. China has achieved the relevant targets of the United Nation's 2030 Sustainable Development Agenda ahead of schedule, and has been recognized by the World Health Organization as a high-performing country in terms of maternal and child health. Another major advance has been made in the prevention and control of cervical and breast cancer. National screening programs have increased their reach, and free human papillomavirus (HPV) vaccination, following phased local and provincial implementation, has now been incorporated into the national immunization program (*8*). Control of mother-to-child transmission of human immunodeficiency viruses (HIV), syphilis and hepatitis B has moved from prevention to elimination strategies.

At the same time, there is a profound structural change taking place in women's health in China (*9*). Fertility patterns are changing rapidly, alongside a rapidly ageing population, while chronic diseases, mental health conditions and functional limitations are emerging earlier among women. In this special issue, we examine women's nutrition and anemia (*10*), menstrual health and abortion prevention (*11*), growth and developmental impacts of HIV-exposed children (*12*), chronic disease and management (*13*), perinatal care (*14*), and equity in service access, reflecting a life-course approach to women's health and providing multidimensional public health evidence to inform more comprehensive and equitable care. Making women's health more visible requires more than just expanding existing programs. It necessitates a change in how evidence is generated, how services are organized, and how success is measured. The launch of the 15th Five-Year Plan provides a vital chance to transition from minor adjustments to comprehensive redesign, integrating women's health throughout the life course into the fundamental principles of health system planning, quality enhancement, and equitable services.

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Perspectives

Improving Equitable Access to Antenatal Care in China: Challenges and Potential Innovative Approaches

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ABSTRACT

Achieving equitable antenatal care (ANC) is fundamental to China's 'Healthy China 2030' agenda and its universal health coverage (UHC) commitments. Despite measurable national progress, substantial urban-rural and regional disparities in ANC access persist, driven by a complex interplay of financial, geographic, institutional, and digital barriers that disproportionately affect rural, low-income, and migrant populations. This analysis examines the current landscape of ANC in China, identifying core structural challenges including the enduring legacy of the *hukou* (household registration) system, a widening digital divide, and the maldistribution of healthcare resources. We contend that piecemeal interventions are insufficient to address these deeply rooted inequities. Instead, this Viewpoint advances an integrated 'spatial-technology-institutional' strategy that synergizes innovations across three mutually reinforcing domains: optimizing tiered healthcare delivery through smart payment reforms, deploying geospatial tools for evidence-based resource allocation, constructing an inclusive digital ANC ecosystem, and establishing sustainable talent incentive mechanisms for grassroots healthcare workers. By implementing this coordinated, multi-pronged approach, China can systematically dismantle geographic inequities in maternal health and ensure equitable ANC access for all women.

Equitable access to maternal health services is a cornerstone of universal health coverage (UHC) and a key indicator of a nation's commitment to health as a fundamental human right (*1–3*). Although China has made remarkable strides in improving maternal health outcomes over recent decades, national averages obscure deep-seated and persistent inequities. The maternal mortality ratio (MMR) in rural China (17.0 per 100,000 live births) remained 1.36 times that of urban areas (12.5 per 100,000 live births) in 2023, a stark reminder that geographic location continues to be a critical determinant of survival for pregnant women (*4–5*).

Antenatal care (ANC) represents the primary and most essential mechanism for safeguarding maternal and fetal well-being. Disparities in ANC utilisation extend well beyond service statistics, reflecting a complex interplay of structural barriers that include spatial inaccessibility, socioeconomic stratification, inefficiencies in healthcare delivery, and a rapidly widening digital divide (*6–7*). This Viewpoint argues that addressing these interconnected challenges requires a paradigm shift from fragmented, project-based interventions to a systems-thinking approach. We leverage integrated innovations across infrastructure, digital technology, and institutional policy to examine how China can bridge the equity gap, with particular focus on its most vulnerable populations: those residing in remote regions and internally migrated communities.

The Challenge: Multifaceted Barriers to Equitable ANC

Geographic and socioeconomic disparities At the national level in 2023, aggregate ANC indicators appear encouraging: the prenatal examination rate (the proportion of women who received one or more antenatal checkups relative to the number of live births during the year) stood at 98.2%, the maternal system management rate at 94.5%, and the health record establishment rate (the proportion of women who had a health record account relative to the number of women who gave birth during the year) at 95.6% (*5,8*). However, a regional breakdown reveals a markedly different picture. The eastern region consistently outperforms the national average, whereas the western region lags considerably, with Xizang Autonomous Region representing a particularly pronounced outlier. In Xizang, the prenatal examination rate was only 92.1% and the system management rate only 81.9% (*5*). These disparities reflect not merely differences in service uptake, but fundamental gaps in resource capacity. Although the western region has a greater number of maternal and child health institutions, these facilities have fewer beds per institution and are substantially more dependent on government financial allocation — accounting for 21.7% of total income in the west compared with 15.2% in the east — indicating a structurally weaker capacity to generate revenue and sustain high-quality services (*8*). This financial allocation refers to fiscal utility funds (including flat-rate subsidies) provided directly to the healthcare institutions by the competent authorities, rather than direct financial assistance to patients. This dynamic perpetuates a cycle of chronic underinvestment and poorer health outcomes that aggregate national statistics consistently obscure.

Double burden of demographic shift and migration China's demographic landscape is undergoing profound transformation. The shift from the one-child policy to a three-child policy has driven a marked rise in advanced maternal age (≥35 years) pregnancies, which reached 15.8% nationally in 2019 (*9*). This trend, observed consistently across both urban and rural settings, substantially elevates the risk of obstetric complications such as preeclampsia and placental abnormalities — conditions that typically necessitate specialised, higher-level ANC (*10*–*11*). Compounding this challenge, China's internal migrant population now numbers approximately 380 million (*12*). The household registration (*hukou*) system remains a significant structural impediment to equitable service utilization, as it ties access to social services — including urban health insurance — to one's place of origin rather than current residence (*13*–*14*). As a consequence, many migrant women are compelled to return to their rural hometowns for childbirth in order to access insurance reimbursement, a phenomenon commonly referred to as 'medical return'. This return journey imposes considerable unsubsidised expenses — including long-distance transportation, accommodation, and lost income — that serve as a powerful financial deterrent to receiving continuous and timely ANC in their cities of residence (*13*).

Financial barriers and health insurance gaps Despite the dramatic expansion of health insurance coverage in China, financial barriers remain a primary obstacle to equitable ANC access. While direct medical costs for hospital delivery are heavily subsidised, the indirect costs associated with seeking care are not. For rural and migrant women, expenses related to transportation, accommodation, and lost income from informal or agricultural work can add 15%–20% to their total out-of-pocket (OOP) expenditure (*15*). The 2016 integration of rural and urban resident insurance schemes represented a meaningful policy advance; however, reimbursement rates for outpatient ANC services have not fully offset longstanding OOP gaps, particularly for advanced prenatal screenings (*16*). As a result, low-income rural households (annual income <30,000 Chinese Yuan) are 1.7 times more likely to forgo recommended ANC visits under the weight of these cumulative financial pressures (*15*).

Digital divide The rapid digitisation of healthcare holds considerable promise for bridging geographic gaps in service access, yet it simultaneously risks generating new forms of exclusion. Western and rural regions face a compounding triple burden: inadequate infrastructure, limited device access, and low digital literacy. In 2020, optical fiber density in western provinces was 42% lower than in eastern provinces, and rural internet users represented only 30.2% of the national total (*17*–*18*). Device ownership presents an additional structural constraint, with smart device ownership in rural low-income households standing at only 57% — 33 percentage points below that of urban households (*19*). Most critically, digital literacy gaps further compound these disparities. Rural women with an education level below senior high school have a 42% lower probability of effectively using online ANC services [odds ratio (*OR*)=0.58, 95% confidence interval (*CI*): 0.46–0.72, *P*<0.001] (*19*–*20*). Without systematically addressing these foundational barriers, telemedicine and digital health platforms will remain inaccessible to the populations who stand to benefit most.

Cultural and linguistic obstacles In ethnic minority regions such as Xizang, Xinjiang, and Inner Mongolia provincial-level administrative divisions (PLADs), cultural and linguistic barriers constitute a significant impediment to ANC service uptake (*21*). Traditional beliefs — including a preference for home delivery, reported by 39% of ethnic minority rural women — alongside skepticism toward modern medicine substantially reduce engagement with formal ANC (*22*).

Linguistic isolation further compounds this exclusion. Critically, 88% of telemedicine platforms operating in western ethnic regions lack multilingual support (e.g., in Tibetan or Uyghur), effectively excluding non-Mandarin-speaking women from digital health initiatives and the essential clinical information these platforms provide (*23*).

The path forward: integrated innovative solutions Addressing these deeply interconnected challenges requires China to move decisively beyond isolated, piecemeal interventions. We propose an integrated 'spatial-technology-institutional' (STI) framework (Figure 1) designed to generate synergistic, system-wide improvements in ANC equity.

Reinforcing the tiered system with targeted financial levers China has advanced a tiered service delivery model to decentralise care, establishing integrated one-stop ANC centres at the township level. By 2022, coverage of such centres in western rural areas had reached 78.3% (*24*). This structural reform is being reinforced by complementary financial innovations. The diagnosis-Intervention Packet (DIP) payment reform establishes clear reimbursement standards for basic ANC packages, incentivising primary facilities to deliver these services proactively (*25*–*26*). In addition, reimbursement rates for ANC provided at primary facilities are set 15%–20% higher than those at tertiary hospitals, creating a deliberate financial gradient to encourage care-seeking at the appropriate level.

To further advance equity, these financial mechanisms must be strengthened and more precisely targeted. Basic medical insurance could be expanded to cover high-cost ANC items — such as non-invasive prenatal DNA testing — in designated low-income counties in western China, accompanied by a firm cap on OOP expenditure for pregnant women living below the poverty line. Furthermore, the DIP reimbursement rate could be dynamically linked to a primary healthcare centre's (PHC) technical capacity — for instance, by tying higher payment levels to the proportion of staff holding certified ANC qualifications — thereby creating a direct financial incentive for quality improvement and sustained workforce investment (*27*). From a governance perspective, the draft outline of China's 15th Five-Year Plan, released in October 2025, proposed optimising fertility support policies and incentive measures, including reducing or exempting expenses associated with childbirth, reforms that may meaningfully facilitate ANC service utilisation (*28*).

Leveraging geospatial tools for resource optimization China has made meaningful progress in leveraging geospatial analysis and telemedicine to address macro-level resource gaps. Eastern-western pairing assistance

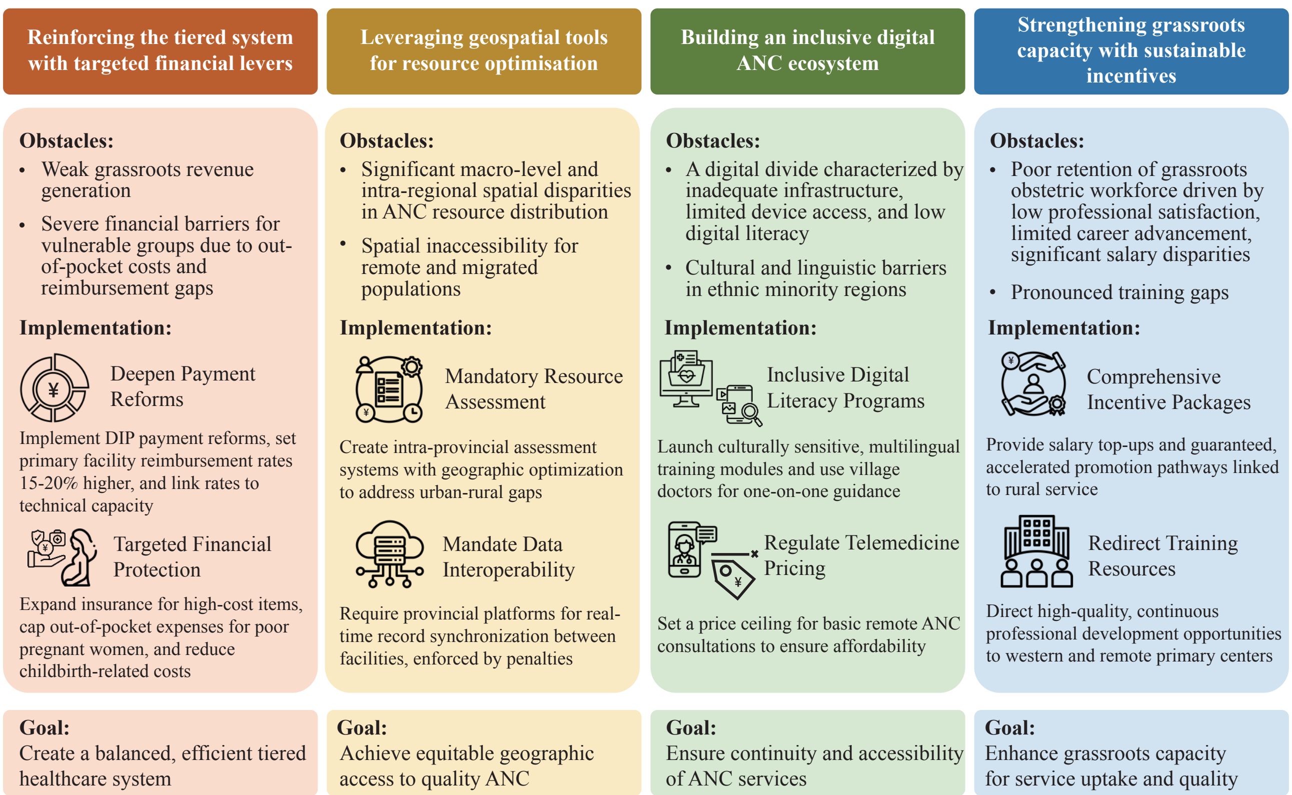

FIGURE 1. An integrated 'spatial-technology-institutional' framework.
Abbreviation: ANC=antenatal care.

programs and the construction of 'provincial-municipal-county' teleconsultation networks have demonstrated considerable success, completing over 120,000 remote ANC consultations in western counties in 2022 and reducing cross-province healthcare-seeking by 34% (*24*). National policies now mandate the application of spatial analysis to identify underserved areas for targeted resource deployment (*29*).

Attention must now shift toward intra-regional disparities, which account for over 60% of overall service gaps (*30*). We recommend establishing mandatory intra-provincial ANC resource balance assessment systems with geographic optimization capability, designed to continuously monitor and address inequities between centrally located urban areas and remote counties. This structural reform must be coupled with a requirement for provincially unified ANC data platforms that ensure real-time synchronization of prenatal examination records between PHC facilities and tertiary hospitals. To guarantee seamless care coordination and data-driven management, financial or performance-based penalties should be enforced for non-compliance (*31*).

Building an inclusive digital ANC ecosystem Initiatives to create cloud-based ANC ecosystems and distribute smart devices (e.g., fetal heart monitors) to pregnant women in remote areas show considerable promise. However, as noted above, their effectiveness is substantially undermined by persistent digital literacy gaps. Evidence indicates that even when devices are provided, only 41% of rural pregnant women in western China can operate them independently, and the effective usage rate of ANC applications plateaus at approximately 61% even following structured training (*32*).

A national commitment to 'digital inclusion' in maternal health is therefore urgently required. This entails the development and rollout of tiered, culturally sensitive digital literacy training programmes tailored to local contexts. Such programmes should employ accessible, simplified instructional formats — including short video modules delivered in local dialects, community health broadcasts, and social media content designed for low-literacy audiences — while leveraging village clinic staff to provide individualised, one-on-one guidance. This approach would simultaneously promote multilingual service delivery and help reorient traditional health-seeking behaviours. To incentivise participation, modest financial bonuses could be linked to the attainment of digital skills certification. Furthermore, given that private telemedicine platforms often demonstrate higher diagnostic accuracy (*OR*=3.85) but charge 40% more than their public counterparts, targeted regulatory measures are needed to establish a maximum price ceiling for basic remote ANC consultations, thereby ensuring that high-quality digital care remains financially accessible to low-income populations (*33*).

Strengthening grassroots capacity with sustainable incentives Initiatives such as the 'Eastern Medical Talent Pairing Assistance' programme and 'rural-oriented' medical education with compulsory service commitments play a vital role in stabilising the grassroots obstetric workforce (*34*–*35*). Nevertheless, retention remains a critical challenge, driven by persistent issues of low professional satisfaction, limited career advancement opportunities, and substantial salary disparities relative to urban hospitals. A pronounced training gap further deepens this quality divide: only 49% of western PHC staff receive annual ANC-related training, compared with 82% in the eastern region (*32*).

Incentive mechanisms must therefore be substantially strengthened and broadened in scope. Rather than relying on one-time subsidies, a comprehensive and sustained support package is required — one that encompasses salary supplements, guaranteed and accelerated promotion pathways explicitly tied to rural service tenure, and access to continuous, high-quality professional development. Targeted efforts must be made to channel training resources and opportunities toward western and remote PHCs, thereby establishing a virtuous cycle in which a well-trained workforce remains both motivated and equipped to deliver high-quality care (*36*).

Recommendations

In conclusion, achieving equitable ANC access in China requires a paradigm shift from piecemeal interventions to a systems-level, integrated approach. The proposed 'STI' framework provides a coherent logic for this transition. Its core lies in the synergistic interaction of three pillars: spatial optimization, which uses geospatial tools to identify and bridge physical access gaps; technological empowerment, which deploys inclusive digital solutions to transcend geographic distance; and institutional innovation, which crafts financial, talent, and data policies that incentivize equitable service delivery. These components are not sequential but iterative, forming a reinforcing loop in which data from one pillar informs and strengthens the others, ultimately producing a resilient system capable of adapting to diverse local needs.

Translating this framework into practice, however, presents substantial implementation challenges. First, execution fatigue and capacity gaps at the grassroots level may leave overburdened health workers without the resources or motivation to adopt new technologies and protocols. Second, high coordination and data integration costs across disparate government departments — spanning health, finance, and telecommunications — require sustained political will and investment to align objectives and systems. Third, bridging the digital divide is a long-term undertaking that involves not only infrastructure rollout but also fundamental changes in user behavior and institutional trust, with measurable returns that are often considerably delayed.

A phased, adaptive implementation strategy offers a structured pathway to address these challenges and ensure tangible progress. An initial phase (1–2 years) would establish 3–5 demonstration zones in provinces with pronounced internal disparities, such as Sichuan and Yunnan, to pilot a unified resource monitoring platform, quality-linked bundled payment reforms, and digital literacy programs, with the explicit goal of validating the approach and refining implementation toolkits. This would be followed by a scale-up phase (3–5 years) to expand successful models across western China and migrant-receiving regions, mandating equity assessments, achieving full health record interoperability, and embedding digital inclusion metrics into local government performance evaluations. In a final consolidation phase (6–10 years), these practices would be integrated nationally, establishing equitable ANC access as a core system output and normalizing digital health options in remote areas. Throughout this process, the framework itself should be continuously refined through predictive analytics and the incorporation of broader social determinants of health. Sustained commitment to this coordinated, multi-pronged strategy would enable China to move beyond documenting disparities toward systematically eliminating them, securing maternal health rights for vulnerable populations and establishing a replicable model for achieving health equity through integrated innovation.

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Vital Surveillances

Longitudinal Trajectories of Growth and Development in HIV-Exposed Uninfected Children from a Long-Term Birth Cohort — 8 Regions, 3 PLADs, China, 2017–2024

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ABSTRACT

Objective: This study examined growth and development trajectories in Human Immunodeficiency Virus (HIV) exposed children aged 0–3 years, identified key influencing factors, and generated evidence to support early developmental promotion in this population.

Methods: This prospective cohort study enrolled pregnant women who delivered between January 2017 and June 2021 and followed their infants until 3 years of age. Participants were drawn from a mother-to-child HIV transmission cohort established across Guangxi Zhuang Autonomous Region, Yunnan Province, and Xinjiang Uygur Autonomous Region. Chi-square tests were used to compare differences between groups, and generalized estimating equations (GEE) were applied to identify factors influencing growth and nutritional outcomes in HIV-exposed children.

Results: The cohort comprised 1,227 mother-child pairs: 411 in the exposed group (HIV-infected mothers) and 816 in the control group (non-HIV-infected mothers). The malnutrition rate among HIV-exposed children in the study regions was 12.00%. Relative to the control group, HIV-exposed children demonstrated significantly lower height and weight gains and a higher prevalence of malnutrition (P<0.05). GEE analysis identified a household per capita monthly income exceeding 3,000 yuan as a protective factor against malnutrition [adjusted odds ratio (a*OR*)=0.924, 95% confidence interval (*CI*): 0.877, 0.974], while a maternal history of stillbirth (a*OR*=1.055, 95% *CI*: 1.008, 1.104) and neonatal low birth weight (a*OR*=1.377, 95% *CI*: 1.267, 1.497) were independent risk factors across all follow-up periods. Female sex was also associated with a modestly elevated risk of malnutrition compared with male sex (a*OR*=1.048, 95% *CI*: 1.017, 1.079).

Conclusions: HIV-exposed children in the study regions demonstrated modestly poorer overall growth and development compared with non-exposed peers. These findings underscore the importance of targeted nutritional interventions, early developmental surveillance, and timely correction of growth abnormalities in this vulnerable population.

The global implementation of prevention of mother-to-child transmission (PMTCT) of Human Immunodeficiency Virus (HIV) programs, combined with continuous advances in antiretroviral therapy (ART), has substantially strengthened the reproductive confidence of women living with HIV (*1*). As a result, the number of HIV-infected pregnant women and their infants has risen considerably worldwide. According to data released by UNAIDS in 2023, 84% of HIV-infected pregnant women received ART to prevent mother-to-child transmission (*2*), and the World Health Organization (WHO) estimated that approximately 1.2 million women were living with HIV during pregnancy or the postpartum period in 2022 (*3*). Within this global context, China faces a growing domestic challenge: approximately 4,000 HIV-exposed infants are born in the country each year. Children's growth and development is a complex, multidimensional process shaped by the interplay between intrinsic genetic determinants and a broad range of external environmental influences. Nevertheless, the existing literature has predominantly focused on vertical transmission outcomes, with comparatively limited attention paid to the growth trajectories and developmental status of HIV-exposed children. To address this gap, the present study examines the factors affecting the growth and development of HIV-exposed children aged 0–3 years in China, providing a scientific basis for promoting their normal growth and development and reducing the burden of mother-to-child transmission of HIV.

METHODS

Data Collection

The inclusion criterion required singleton pregnancy at delivery. Exclusion criteria were as follows: 1) severe maternal illness requiring hospitalization; 2) HIV-infected children born to HIV-infected women; and 3) diagnosis of mental illness or intellectual disability based on the diagnostic criteria for neuropsychiatric diseases in China.

From January 2017 to June 2021, the study was conducted across all healthcare facilities providing maternity care and midwifery services in eight regions spanning three provinces and autonomous regions: Yunnan Province, Guangxi Zhuang Autonomous Region, and Xinjiang Uygur Autonomous Region. These regions have a well-established foundation in preventing mother-to-child transmission of HIV, syphilis, and hepatitis B, and each has a relatively large population of HIV-exposed children.

Pregnant women living with HIV were enrolled upon identification, prior to delivery, ensuring that baseline data were collected before birth. HIV-infected pregnant and postpartum women and their infants (referred to as HIV-exposed infants) were assigned to the exposed group. Following a 1:2 matching protocol, HIV-uninfected pregnant and postpartum women and their infants were selected from the same region to form the control group. Matching criteria included the same ethnicity, a gestational age at delivery within ±2 weeks, and the same neonatal sex. When more than two eligible controls were available, HIV-uninfected women with the most similar sociodemographic characteristics were selected. A prospective cohort of exposed and non-exposed children was thereby established, and follow-up assessments were subsequently conducted at 1, 3, 6, 8, 12, and 18 months, as well as at 2 and 3 years of age to evaluate growth and development in both groups.

Structured questionnaires were administered to both HIV-infected and uninfected pregnant and postpartum women to collect data on general characteristics, family background, delivery details, HIV status, and antiretroviral medication use. Data on the growth and development of their children were also obtained.

Measures

Body weight, length, and head circumference were measured for children in both the HIV-exposed and HIV-unexposed groups at each specified age interval. Growth and development were assessed according to the methods recommended by WHO in 2006 (*4*). Z-scores were calculated using WHO Anthro software (version 3.2.2, 2011) developed by WHO, Geneva, Switzerland included the following indices: Weight-for-Age Z-score (WAZ), Length-for-Age Z-score (LAZ), and Weight-for-Length Z-score (WLZ).

1) Underweight: WAZ<−2 was defined as underweight;

2) Stunting: LAZ<−2 was defined as stunting;

3) Wasting: WLZ<−2 was defined as wasting.

4) Malnutrition: Children were diagnosed with protein-energy malnutrition (PEM), hereafter referred to as malnutrition (*5*), if they presented with one or more of the following conditions: stunting, underweight, or wasting.

5) HIV-exposed children: Children born to HIV-infected women were classified as HIV-exposed. For this study, only the growth and development of HIV-exposed uninfected (HEU) children were analyzed.

6) Quality control: During the research implementation phase, relevant personnel received technical training, and investigators underwent pre-survey training. During the data entry phase, a double-entry method was employed alongside consistency checks; any forms with unclear entries were promptly clarified by contacting the responsible data collector. During the data analysis phase, sensitive identifying information was removed, and any anomalous data were cross-checked and either corrected or excluded, thereby ensuring the quality and authenticity of the dataset.

Statistical Analysis

Data were summarized, cleaned, and organized in Excel before being imported into SAS 9.4 (SAS Institute, Cary, NC, USA) for statistical analysis. Continuous variables were expressed as mean ± standard deviation ($\bar{x}$±s) and compared using Student's *t*-test, while categorical variables were expressed as frequencies and proportions and compared using the chi-square test or Fisher's exact test, as appropriate. Generalized Estimating Equations (GEE) were applied to evaluate the associations between individual or multiple variables and the nutritional status of HIV-exposed children. Given that repeated measurement data may exhibit an autocorrelated structure, an autoregressive correlation matrix was specified to account for within-subject correlations across time points. All tests were two-sided, with a significance threshold set at α=0.05; P<0.05 was considered statistically significant.

RESULTS

A total of 411 HIV-infected mother-child pairs were enrolled in the exposed group. Following a 1:2 matching protocol, 816 HIV-uninfected mother-child pairs were selected for the control group, yielding a final cohort of 1,227 mother-child pairs.

As shown in Table 1, the two groups were comparable in terms of residential region, ethnicity, household registration type, and delivery mode, with

TABLE 1. Basic characteristics of HIV-infected and uninfected pregnant and postpartum women [*n* (%)].

Variable	Total	Exposed group (*n*=411)	Control group (*n*=816)	χ^2	*P*
Region				0.011	0.995
Guangxi Zhuang Autonomous Region	504 (41.08)	168 (40.88)	336 (41.18)		
Yunnan Province	416 (33.90)	140 (34.06)	276 (33.82)		
Xinjiang Uygur Autonomous Region	307 (25.02)	103 (25.06)	204 (25.00)		
Ethnicity				0.006	0.997
Han	757 (61.70)	253 (61.56)	504 (61.76)		
Uyghur	288 (23.47)	97 (23.60)	191 (23.41)		
Others	182 (14.83)	61 (14.84)	121 (14.83)		
Educational level				2.248	0.134
Junior high school or below	970 (79.06)	335 (81.51)	635 (77.82)		
Senior high school or above	257 (20.94)	76 (18.49)	181 (22.18)		
Marital status				24.789	<0.001
Unmarried	41 (3.34)	16 (3.89)	25 (3.06)		
Married	1,174 (95.68)	383 (93.19)	791 (96.94)		
Divorced or widowed	12 (0.98)	12 (2.92)	0 (0)		
Household registration type				0.496	0.481
Rural	1,054 (85.90)	349 (84.91)	705 (86.40)		
Urban	173 (14.10)	62 (15.09)	111 (13.60)		
Delivery age				62.548	<0.001
<35 years old	1009 (82.23)	288 (70.07)	721 (88.36)		
≥35 years old	218 (17.77)	123 (29.93)	95 (11.64)		
Delivery mode				0.261	0.609
Vaginal delivery	794 (64.71)	270 (65.69)	524 (64.22)		
Cesarean section	433 (35.29)	141 (34.31)	292 (35.78)		
Occupation				9.711	0.046
Farmer	815 (66.42)	288 (70.07)	527 (64.58)		
Unemployed	228 (18.58)	77 (18.73)	151 (18.50)		
Worker	15 (1.22)	6 (1.46)	9 (1.10)		
Commercial service staff	11 (0.90)	4 (0.97)	7 (0.86)		
Cadres, staff, and others	158 (12.88)	36 (8.76)	122 (14.95)		
Per capita monthly household income (CNY)				70.989	<0.001
<500	124 (10.10)	66 (16.06)	58 (7.11)		
500–	292 (23.80)	100 (24.33)	192 (23.53)		
1,000–	432 (35.21)	173 (42.09)	259 (31.74)		
≥3,000	284 (23.15)	63 (15.33)	221 (27.08)		
Unknown	95 (7.74)	9 (2.19)	86 (10.54)		

Abbreviation: CNY=Chinese Yuan.

no statistically significant differences observed (P>0.05). In contrast, the groups differed significantly with respect to marital status, occupation, age at delivery, and average monthly household income per capita (P<0.05).

Table 2 summarizes pregnancy-related conditions in the exposed and control groups. Notably, the exposed group exhibited significantly higher incidences of adverse pregnancy outcomes, anemia, and preterm birth compared with the control group (P<0.001).

Neonatal characteristics are presented in Table 3. The two groups were similar in neonatal sex, delivery

TABLE 2. Comparison of pregnancy-related conditions among HIV-infected and uninfected pregnant and postpartum women [*n* (%)].

Variable	Total	Exposed group (*n*=411)	Control group (*n*=816)	χ^2	*P*
Adverse Pregnancy Outcomes				46.778	<0.001
Yes	287 (23.39)	144 (35.04)	143 (17.52)		
No	940 (76.61)	267 (64.96)	673 (82.48)		
Hypertensive Disorders of Pregnancy				0.056	0.812
Yes	31 (2.53)	11 (2.68)	20 (2.45)		
No	1196 (97.47)	400 (97.32)	796 (97.55)		
Anemia				20.939	<0.001
Yes	128 (10.43)	66 (16.06)	62 (7.60)		
No	1,090 (89.57)	345 (83.94)	754 (92.40)		
Preterm Birth				28.030	<0.001
Yes	99 (8.07)	57 (13.87)	42 (5.15)		
No	1,128 (91.93)	354 (86.13)	774 (94.85)		
Premature rupture of membranes				1.905	0.168
Yes	70 (6.00)	30 (7.30)	40 (5.29)		
No	1,097 (94.00)	381 (92.70)	716 (94.71)		

TABLE 3. Comparison of basic characteristics of HIV-exposed and unexposed neonates [*n* (%)].

Variable	Total	Exposed group (*n*=411)	Control group (*n*=816)	χ^2	*P*
Gender				0.007	0.936
Male	613 (49.96)	206 (50.12)	407 (49.88)		
Female	614 (50.04)	205 (49.88)	409 (50.12)		
Delivery mode				0.261	0.609
Vaginal delivery	794 (64.71)	270 (65.69)	524 (64.22)		
Cesarean section	433 (35.78)	141 (34.31)	292 (35.78)		
Birth weight (g, $\bar{x}$±s)		2925.55±511.46	3181.66±486.87	−8.462	<0.001
Birth length (cm, $\bar{x}$±s)		48.72±3.13	50.28±17.09	−1.838	0.066
Birth head circumference (cm, $\bar{x}$±s)		32.98±2.19	33.22±1.86	−4.779	0.076
Low birth weight				32.930	<0.001
Yes	99 (8.07)	59 (14.36)	40 (4.90)		
No	1,128 (91.93)	352 (85.64)	776 (95.10)		
Macrosomia				4.306	0.038
Yes	31 (2.53)	5 (1.22)	26 (3.19)		
No	1,196 (97.47)	406 (98.78)	790 (96.81)		
Neonatal asphyxia				12.862	<0.001
Yes	38 (3.10)	23 (5.60)	15 (1.84)		
No	1,189 (96.90)	388 (94.40)	801 (98.16)		

mode, mean birth length, and mean head circumference (P>0.05). However, significant between-group differences were identified in mean birth weight, incidence of macrosomia, incidence of low birth weight (LBW), and neonatal asphyxia rate (P<0.05).

Table 4 presents longitudinal comparisons of WAZ, LAZ, and WLZ, respectively, between the exposed and control groups across successive age intervals.

Univariate analysis identified ten variables significantly associated with malnutrition in HIV-exposed children. Maternal and socioeconomic factors included residential region (χ^2=7.871, P=0.020), ethnicity (χ^2=7.652, P=0.022), occupation (χ^2=16.056, P=0.003), and household monthly per capita income (χ^2=16.064, P=0.003). Obstetric and clinical factors included duration of antiretroviral therapy (ART; χ^2=11.520, P=0.021), history of stillbirth (χ^2=27.827, P<0.001), preterm birth (χ^2=24.989, P<0.001), and premature rupture of membranes (χ^2=119.856, P<0.001). Neonatal characteristics, specifically sex (χ^2=4.005, P=0.045) and LBW (χ^2=79.026, P<0.001), were also significantly associated with malnutrition. Because all HIV-exposed children received exclusive formula feeding, the influence of feeding method on growth and development could not be evaluated in this cohort.

Table 5 presents the multivariate analysis results from the generalized estimating equations, identifying several significant predictors of malnutrition across all follow-up periods. Higher household income was identified as a protective factor: compared with families earning less than 500 yuan per capita monthly, those earning more than 3,000 yuan had significantly lower odds of malnutrition in HIV-exposed children

TABLE 4. Comparison of WAZ, LAZ, and WLZ for children at different ages ($\bar{x}$±s).

Variable	Age in months	Exposed group	Control group	*t*	*P*
WAZ	0	−0.84±1.14	−0.26±1.05	−8.494	<0.001
	1	−0.11±1.09	0.25±1.09	−5.400	<0.001
	3	−0.39±1.05	−0.05±1.04	−5.380	<0.001
	6	−0.29±1.12	−0.13±1.00	−2.614	0.009
	8	−0.19±1.12	−0.03±1.01	−2.412	0.016
	12	−0.21±1.07	−0.08±0.96	−2.140	0.033
	18	−0.23±1.12	−0.11±0.97	−1.878	0.061
	24	−0.16±1.05	−0.04±0.92	−1.912	0.056
	36	−0.31±0.96	−0.15±0.88	−2.638	0.009
LAZ	0	−0.35±1.21	0.10±1.02	−6.408	<0.001
	1	−0.23±1.34	0.26±1.28	−6.113	<0.001
	3	−0.36±1.29	0.03±1.21	−5.184	<0.001
	6	−0.28±1.23	−0.04±1.19	−3.253	0.001
	8	−0.19±1.20	0.05±1.15	−3.339	0.001
	12	−0.33±1.13	−0.16±1.08	−2.525	0.012
	18	−0.57±1.15	−0.47±1.03	−1.362	0.174
	24	−0.35±1.07	−0.28±1.01	−1.092	0.275
	36	−0.53±1.05	−0.38±0.94	−2.349	0.019
WLZ	0	−0.88±1.06	−0.47±0.97	−6.550	<0.001
	1	0.10±1.23	0.02±1.18	1.017	0.309
	3	−0.06±1.11	−0.00±1.15	−0.800	0.424
	6	−0.06±1.10	−0.02±1.05	−0.563	0.574
	8	−0.01±1.13	0.03±1.05	−0.658	0.511
	12	−0.07±1.09	−0.01±1.03	−0.872	0.383
	18	0.05±1.17	0.16±1.06	−1.604	0.109
	24	−0.01±1.13	0.10±1.03	−1.666	0.096
	36	−0.05±1.10	0.06±0.98	−1.734	0.083

TABLE 5. Multivariate analysis of malnutrition in HIV-exposed children.

Variable	Wald χ^2	a*OR* (95% *CI*)	*P*	Variable	Wald χ^2	a*OR* (95% *CI*)	*P*
Region				Duration of antiviral treatment			
Guangxi Zhuang Autonomous Region	1.000			Pre-pregnancy	1.000		
Yunnan Province	0.029	0.996 (0.954–1.040)	0.865	First trimester of pregnancy	0.006	1.002 (0.958–1.047)	0.941
Xinjiang Uygur Autonomous Region	0.010	0.995 (0.910–1.088)	0.919	Second trimester of pregnancy	1.852	0.960 (0.905–1.018)	0.174
Ethnicity				Third trimester of pregnancy	0.047	1.006 (0.950–1.067)	0.828
Han	1.000			Postpartum	0.046	0.980 (0.817–1.177)	0.831
Uyghur	0.019	1.005 (0.937–1.078)	0.892	Stillbirth or neonatal death			
Others	2.135	1.038 (0.987–1.091)	0.144	No	1.000		
Occupation				Yes	5.263	1.055 (1.008–1.104)	0.022
Farmer	1.000			Preterm birth			
Unemployed	2.009	0.967 (0.923–1.013)	0.156	No	1.000		
Worker	0.059	0.989 (0.903–1.083)	0.808	Yes	0.366	0.980 (0.918–1.046)	0.545
Commercial service staff	0.134	1.012 (0.950–1.078)	0.714	Premature rupture of membranes			
Cadres, staff, and others	3.469	0.934 (0.870–1.004)	0.063	No	1.000		
Per capita monthly household income (CNY)				Yes	2.928	1.168 (0.978–1.397)	0.087
<500	1.000			Gender			
500–	0.135	0.990 (0.940–1.043)	0.713	Male	1.000		
1,000–	0.709	1.021 (0.973–1.072)	0.400	Female	9.440	1.048 (1.017–1.079)	0.002
≥3,000	8.677	0.924 (0.877–0.974)	0.003	Low birth weight			
Unknown	0.025	1.010 (0.890–1.146)	0.874	No	1.000		
				Yes	56.390	1.377 (1.267–1.497)	<0.001

[adjusted odds ratio (a*OR*)=0.924, 95% confidence interval (*CI*): 0.877, 0.974]. Regarding maternal obstetric history, children born to mothers with a prior history of stillbirth or neonatal death faced a significantly elevated risk of malnutrition across all periods compared with children of mothers without such history (a*OR*=1.055, 95% *CI*: 1.008, 1.104). Sex-based differences were also observed: HIV-exposed female infants had a consistently higher risk of malnutrition than their male counterparts at each assessment period (a*OR*=1.048, 95% *CI*: 1.017, 1.079). Finally, low birth weight emerged as a strong independent risk factor; compared with neonates of normal birth weight, those with low birth weight had 1.377 times the odds of malnutrition across all periods — representing a 37.7% increase in risk (a*OR*=1.377, 95% *CI*: 1.267, 1.497).

DISCUSSION

Neonatal birth weight serves as both a reflection of maternal health status and a key indicator of fetal well-being. LBW is associated with neonatal mortality, impaired physical growth, neurodevelopmental delays in childhood, and elevated risk of adult chronic diseases including obesity, hypertension, and diabetes (*6–8*). In the present study, the LBW rate in the exposed group was 14.36% — lower than that reported for HIV-exposed children in Kunming (19.6%) (*9*) but higher than that of the control group (4.90%), and comparable to the rate observed in Chengdu (14.17%) (*10*). These findings underscore the importance of strengthening prenatal care for HIV-infected pregnant women, enabling early detection of fetal growth restriction, and delivering evidence-based perinatal interventions to reduce the incidence of LBW and support optimal child growth and development.

The prevalence of malnutrition among HIV-exposed children varies considerably across countries and regions, likely reflecting differences in geographical environment, household socioeconomic status, health literacy, and the capacity of regional healthcare systems. In the present study, the wasting rate among HIV-exposed children exceeded that reported in comparable studies, which may be partly attributable to the study setting: county- and district-level medical institutions in economically underdeveloped western regions where urban–rural disparities and unequal distribution of healthcare resources are prevalent. Future research should examine the developmental status of HIV-exposed children across regions with varying economic conditions to better characterize these disparities. Notably, malnutrition was more pronounced among HIV-exposed children than among their non-exposed counterparts, highlighting the need for targeted intervention strategies that address the specific nutritional vulnerabilities of this population and work to reduce malnutrition rates while improving overall growth outcomes.

Prior research has demonstrated (*11*) that early-life malnutrition and stunting can have lasting adverse effects on adult stature and cognitive development. Children's growth trajectories are closely shaped by family socioeconomic background, which simultaneously reflects population health status and broader socioeconomic conditions. To support adequate nutrition during critical developmental periods, caregivers should introduce complementary foods in a timely manner and maintain a supportive feeding environment at home. Beyond dietary practices, sustained monitoring of children's growth and development is essential. Health education efforts targeting caregivers should be strengthened to raise awareness of nutritional needs, foster nurturing home environments, and ultimately promote healthy growth and development in HIV-exposed children.

The elevated risk of stunting observed in children born to mothers with a history of stillbirth or neonatal death may reflect underlying maternal health vulnerabilities, including compromised immune function or reduced engagement with child healthcare services. This hypothesis, however, remains speculative given the limited supporting data available, and further investigation is warranted. These findings nonetheless underscore the importance of strengthening pre-pregnancy and prenatal care within medical institutions, including standardized antenatal examinations and comprehensive pre-pregnancy risk assessment. Targeted perinatal interventions should be extended to high-risk populations — including women with prior adverse pregnancy outcomes and older pregnant women — through stratified clinical management protocols aimed at reducing adverse pregnancy outcomes and safeguarding maternal and infant health.

LBW serves as a key indicator of intrauterine nutritional adequacy. Suboptimal fetal nutrition disrupts postnatal growth trajectories and substantially elevates the risk of malnutrition in early childhood relative to the general pediatric population (*12*). Evidence further suggests that interventions targeting birth weight improvement may meaningfully reduce stunting rates among HIV-exposed children (*13*). Given that LBW remains disproportionately prevalent among neonates born to HIV-infected women, it is essential to strengthen antenatal care services for this population, intensify monitoring of fetal growth and development, and implement timely interventions to minimize LBW occurrence — thereby improving the overall health trajectory of HIV-exposed children.

The relationship between sex and malnutrition risk in children is inconsistent across the literature. A meta-analysis by Guo Bingbing (*14*) found that boys in China face a higher risk of malnutrition than girls, whereas a study conducted in rural China (*15*) reported the opposite pattern. Consistent with the latter, the present study found that HIV-exposed girls had a higher risk of malnutrition than boys across all assessment periods. This finding may reflect several intersecting factors, including gender-differentiated caregiving practices such as disparities in dietary allocation, healthcare-seeking behavior, and the distribution of caregiving resources. Sociocultural norms that may favor male children in certain contexts could further contribute to these disparities. Additionally, sex-based differences in morbidity patterns and healthcare access may play a role, though the underlying mechanisms remain incompletely understood and merit further investigation.

This study has several limitations. The questionnaire data lacked information on maternal pre-pregnancy and delivery weight, as well as the timing of complementary food introduction in infants, which precluded calculation of pre-pregnancy and gestational body mass index (BMI). Consequently, we were unable to evaluate the effects of these factors — including gestational weight gain — on children's growth and development. Furthermore, feeding behavior data were not collected for children in the control group, preventing a comparative assessment of the impact of feeding practices on growth outcomes across groups.

HIV-exposed children in the study regions exhibited a relatively high rate of malnutrition. Multivariate analysis identified four significant determinants of malnutrition across all follow-up periods: per capita monthly household income exceeding 3,000 yuan (protective), maternal history of stillbirth or neonatal death (risk), female sex (risk), and neonatal low birth weight (risk). These findings underscore the importance of targeted, evidence-based interventions. During pre-pregnancy and prenatal care for HIV-infected women, priority should be given to those with a history of adverse pregnancy outcomes, with close monitoring of fetal growth and timely intervention upon detection of intrauterine growth restriction to reduce the incidence of low birth weight. For HIV-exposed infants born with low birth weight, early nutritional support programs should be implemented, and families with low household income should receive integrated economic assistance alongside nutritional guidance to optimize child growth trajectories.

Conflicts of interest: No conflicts of interest.

Ethical statement: The collection of monitoring data was approved by the Ethics Committee of the National Center for Women and Children's Health, Chinese Center for Disease Control and Prevention (No. FY2015-005). This study received additional approval from the Ethics Committee of the National Center for Women and Children's Health, National Health Commission (No. 2025FY02). All surveys involving pregnant women and children were conducted in accordance with the principles of informed consent, respect, confidentiality, and beneficence. Before participation, the study purpose, significance, and procedures were clearly explained to all participants to ensure that voluntary informed consent was obtained.

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Preplanned Studies

Shifting Patterns of Anemia Prevalence and Severity Among Urban Women — China, 2019–2024

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Summary

What is already known about this topic?

The Sustainable Development Goals target a 50% reduction in anemia among women of reproductive age by 2025 and the elimination of all forms of malnutrition by 2030. However, robust evidence documenting temporal changes in anemia prevalence remains scarce.

What is added by this report?

Drawing on large-scale national health examination data, this report demonstrates overall progress in reducing anemia among urban women in China between 2019 and 2024. However, it also reveals increasing prevalence in several provinces and a growing burden of moderate-to-severe anemia specifically among women aged 40–49 years.

What are the implications for public health practice?

Risk-stratified and targeted anemia prevention and control strategies are urgently needed. Priority should be given to women aged 40–49 years, women of reproductive age residing in high-burden provinces, and geographic areas where anemia prevalence either exceeds 20% or demonstrates an upward trend.

ABSTRACT

Introduction: Anemia represents a major health burden among women globally and poses a critical challenge to achieving international targets for reducing anemia prevalence in women of reproductive age and eliminating malnutrition by 2030. Despite its public health significance, temporal trends in anemia prevalence among Chinese women remain inadequately characterized.

Methods: This study analyzed health examination data from 231 prefecture-level cities across all 31 provincial-level administrative divisions in China, encompassing 16,700,713 women examined in 2019 (*n*=7,822,489) and 2024 (*n*=8,878,224). Standardized prevalence estimates with 95% confidence intervals (*CI*s) were calculated by adjusting for provincial population structures. Temporal changes were quantified using prevalence differences with corresponding 95% *CI*s. Multivariable logistic regression models incorporating time-by-covariate interaction terms were employed to identify factors associated with anemia and moderate-to-severe anemia and to assess time-varying associations.

Results: Between 2019 and 2024, the overall prevalence of anemia among urban women and women of reproductive age in China declined from 13.7% (95% *CI*: 13.0, 14.4) and 17.0% (95% *CI*: 16.3, 17.8) to 13.2% (95% *CI*: 12.7, 13.8) and 16.7% (95% *CI*: 16.1, 17.3), respectively, while moderate-to-severe anemia prevalence remained essentially unchanged. Among women aged 40–49 years, anemia prevalence increased modestly, with a statistically significant rise in moderate-to-severe anemia of 0.32 percentage points (95% *CI*: 0.06, 0.57). Substantial regional disparities persisted: anemia prevalence decreased in 18 provincial units but increased in the remaining 13 units. Among women of reproductive age, anemia prevalence rose in 14 provincial units, with three provinces reaching or exceeding the 20% threshold indicative of moderate public health burden.

Conclusion: Although China has achieved modest progress in reducing anemia among women, the overall disease burden remains substantial, with persistently elevated or increasing prevalence observed in specific subpopulations. These findings underscore the urgent need for targeted, risk-stratified public health interventions that prioritize women aged 40–49 years and provinces where anemia prevalence has increased or exceeds 20%.

Anemia poses a widespread threat to the health of women and their offspring while also diminishing productivity and imposing substantial economic and social burdens (*1*). Recognizing this critical public health challenge, the United Nations Sustainable Development Goals (SDGs) have prioritized the reduction of maternal anemia. China has actively embraced this initiative by incorporating maternal anemia prevention and control into its national strategic planning. Continuous monitoring of anemia prevalence and its associated risk factors is essential for policymakers to develop and refine targeted intervention strategies. However, existing studies have predominantly examined anemia prevalence among Chinese women or pregnant women within specific years or geographic regions, leaving significant gaps in our understanding of temporal trends across the broader female population (*2*–*5*). To address this knowledge gap, the present study compares anemia prevalence and associated factors among urban women in China between 2019 and 2024, thereby characterizing temporal patterns and informing evidence-based public health responses.

Data for this study were obtained from Meinian Healthcare Group, China's largest health examination chain, with service networks spanning 231 prefecture-level cities across all 31 provincial-level administrative divisions (PLADs) (*6*). We extracted records from non-pregnant women aged 18 years or older who underwent physical examinations during two distinct periods: January 1 to December 31, 2019, and January 1 to December 31, 2024. The final dataset comprised 16,700,713 participants, including 7,822,489 examined in 2019 and 8,878,224 in 2024. Study participants were predominantly urban residents, including employed individuals and other city dwellers.

Demographic information, physical measurements, and laboratory tests were collected using standardized protocols and calibrated instruments across all examination centers. Following World Health Organization (WHO) criteria, anemia was defined as hemoglobin concentration <120.0 g/L (*7*). Anemia severity was further categorized as mild (110.0–119.0 g/L), moderate (80.0–109.0 g/L), or severe (<80.0 g/L). Hemoglobin concentrations were measured using automated hematology analyzers, with altitude-adjusted thresholds applied to specific prefecture-level cities according to WHO recommendations. For analytical purposes, the study population was stratified into six geographic regions: North (Beijing, Tianjin, Hebei, Shanxi, Inner Mongolia), East (Anhui, Jiangxi, Shanghai, Jiangsu, Zhejiang, Fujian, Shandong), Central (Henan, Hubei, Hunan, Guangxi, Guangdong, Hainan), Southwest (Chongqing, Sichuan, Guizhou, Yunnan, Tibet), Northwest (Shaanxi, Gansu, Qinghai, Ningxia, Xinjiang), and Northeast China (Liaoning, Jilin, Heilongjiang).

To account for demographic structure and enable valid temporal comparisons, prevalence estimates and 95% confidence intervals (*CI*s) were standardized to the population distribution reported in China's Seventh National Population Census (2020), which represents the most recent comprehensive demographic benchmark. Differences in categorical variables were assessed using the χ^2 test with Rao-Scott correction for complex survey design. Temporal changes were quantified using prevalence differences with corresponding 95% *CI*s for both overall anemia and moderate-to-severe anemia. We employed multivariable logistic regression models to identify risk factors associated with anemia and moderate-to-severe anemia, adjusting for age, body mass index (BMI), history of cesarean delivery, geographic region, per capita gross domestic product (GDP), Engel coefficient, hypertension, total cholesterol, triglycerides, hyperuricemia, diabetes, and impaired kidney function. To address the hierarchical data structure, models incorporated random intercepts at the city-level to account for within-city correlation. Furthermore, we constructed pooled models combining data from both years and included "Year×Covariate" interaction terms to investigate temporal changes in risk factor associations. A statistically significant interaction (P for interaction < 0.05) indicated that the strength of association for a given risk factor differed between 2019 and 2024. All statistical analyses were performed using SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA), with a two-sided P<0.05 threshold for statistical significance.

Table 1 presents the prevalence of anemia and moderate-to-severe anemia among urban women in China during 2019–2024. Overall anemia prevalence among urban women declined from 13.7% in 2019 to 13.2% in 2024, while moderate-to-severe anemia decreased slightly from 5.1% to 5.0%. Among women of reproductive age, anemia prevalence fell from 17.0% to 16.7%. However, none of these reductions achieved statistical significance.

Age-stratified analysis revealed significant disparities in anemia prevalence and severity across age groups. Between 2019 and 2024, anemia prevalence decreased in all age groups except women aged 40–49 years, who experienced a slight increase. The reductions were particularly pronounced and statistically significant in

TABLE 1. Prevalence of anemia by severity among urban women in China, 2019 versus 2024.

Variable	2019			2024			Prevalence difference for anemia (%, 95% *CI*)	Prevalence difference2 for moderate-severe anemia (%, 95% *CI*)
	Number (%)	Anemia (%, 95% *CI*)	Moderate-severe anemia (%, 95% *CI*)	Number (%)	Anemia (%, 95% *CI*)	Moderate-severe anemia (%, 95% *CI*)		
Overall	7,822,489 (100.0)	13.7 (13.0, 14.4)	5.1 (4.8, 5.4)	8,878,224 (100.0)	13.2 (12.7, 13.8)	5.0 (4.8, 5.3)	−0.49 (−1.03, 0.06)	−0.06 (−0.23, 0.11)
Age group (years)								
18–29	1,577,832 (20.2)	11.9 (11.1, 12.6)	3.9 (3.6, 4.2)	1,521,094 (17.1)	11.8 (11.2, 12.4)	4.1 (3.9, 4.3)	−0.08 (−0.75, 0.60)	0.18 (−0.02, 0.38)
30–39	2,132,587 (27.3)	16.8 (16.0, 17.6)	6.6 (6.3, 7.0)	2,634,552 (29.7)	15.9 (15.3, 16.6)	6.5 (6.2, 6.8)	−0.84 (−1.47, −0.20)*	−0.15 (−0.39, 0.08)
40–49	1,732,054 (22.1)	19.5 (18.7, 20.3)	9.3 (8.9, 9.8)	1,932,893 (21.8)	19.6 (18.9, 20.4)	9.7 (9.2, 10.1)	0.15 (−0.41, 0.71)	0.32 (0.06, 0.57)*
50–59	1,497,049 (19.1)	9.5 (8.9, 10.0)	3.1 (2.9, 3.3)	1,657,106 (18.7)	8.9 (8.5, 9.4)	2.8 (2.7, 3.0)	−0.56 (−0.99, −0.14)*	−0.25 (−0.36, −0.13)*
60–69	677,413 (8.7)	8.4 (7.7, 9.1)	1.6 (1.4, 1.7)	837,762 (9.4)	7.6 (7.1, 8.2)	1.4 (1.2, 1.6)	−0.76 (−1.35, −0.17)*	−0.17 (−0.32, −0.02)*
70+	205,554 (2.6)	14.3 (13.3, 15.3)**	3.8 (3.4, 4.2)**	294,817 (3.3)	13.4 (12.4, 14.4)**	3.5 (3.0, 4.0)**	−0.94 (−2.12, 0.25)	−0.31 (−0.87, 0.25)
Age group 2 (years)								
18–49	5,442,473 (69.6)	17.0 (16.3, 17.8)	7.2 (6.9, 7.6)	6,088,539 (68.6)	16.7 (16.1, 17.3)	7.3 (7.0, 7.7)	−0.31 (−0.89, 0.26)	0.09 (−0.12, 0.30)
50+	2,380,016 (30.4)	10.0 (9.4, 10.7)**	2.7 (2.5, 2.9)**	2,789,685 (31.4)	9.3 (8.8, 9.9)**	2.5 (2.3, 2.7)**	−0.70 (−1.29, −0.10)*	−0.23 (−0.41, −0.05)*
BMI								
Underweight	439,078 (5.6)	16.6 (15.7, 17.5)	5.5 (5.1, 5.8)	433,134 (4.9)	17.0 (16.2, 17.7)	5.7 (5.5, 6.0)	0.34 (−0.40, 1.09)	0.27 (0.03, 0.52)*
Normal	4,535,052 (58.0)	15.5 (14.7, 16.3)	5.7 (5.4, 6.0)	4,970,298 (56.0)	14.9 (14.3, 15.5)	5.6 (5.3, 5.9)	−0.60 (−1.20, 0.00)	−0.11 (−0.30, 0.08)
Overweight	2,168,776 (27.7)	11.7 (11.1, 12.2)	4.4 (4.2, 4.7)	2,582,885 (29.1)	11.3 (10.8, 11.8)	4.4 (4.2, 4.6)	−0.36 (−0.85, 0.12)	−0.03 (−0.19, 0.13)
Obesity	679,583 (8.7)	9.6 (9.2, 10.1)**	3.8 (3.6, 4.0)**	891,907 (10.0)	9.9 (9.5, 10.3)**	4.1 (3.9, 4.3)**	0.25 (−0.21, 0.70)	0.27 (0.10, 0.44)*
History of cesarean delivery								
Yes	321,881 (4.1)	17.0 (15.8, 18.3)	7.2 (6.6, 7.8)	1,116,428 (12.6)	16.3 (15.5, 17.0)	7.3 (6.9, 7.7)	−0.78 (−1.96, 0.41)	0.11 (−0.40, 0.63)
No	7,500,608 (95.9)	13.6 (12.9, 14.2)**	5.0 (4.8, 5.3)**	7,761,796 (87.4)	12.9 (12.3, 13.4)**	4.8 (4.5, 5.0)**	−0.73 (−1.25, −0.20)*	−0.25 (−0.41, −0.09)*
Per capita GDP								
Lowest	2,010,724 (25.7)	14.0 (13.2, 14.9)	5.3 (5.0, 5.6)	2,021,530 (22.8)	13.7 (12.9, 14.5)	5.4 (5.0, 5.7)	−0.32 (−1.16, 0.52)	0.08 (−0.22, 0.38)
Up to median	2,156,418 (27.6)	13.0 (11.7, 14.2)	4.9 (4.4, 5.4)	2,025,231 (22.8)	12.7 (11.7, 13.7)	5.0 (4.5, 5.4)	−0.30 (−1.19, 0.59)	0.08 (−0.20, 0.36)
Above median	1,805,148 (23.1)	14.2 (12.6, 15.9)	5.2 (4.5, 5.9)	2,068,072 (23.3)	12.7 (11.7, 13.8)	4.8 (4.3, 5.3)	−1.51 (−3.04, 0.02)	−0.40 (−0.83, 0.02)
Highest	1,850,199 (23.7)	13.9 (12.5, 15.4)	5.1 (4.5, 5.6)	2,763,391 (31.1)	13.9 (12.5, 15.3)	5.0 (4.5, 5.5)	−0.04 (−1.03, 0.94)	−0.12 (−0.44, 0.20)
Engel coefficient								
Highest	2,341,106 (29.9)	13.8 (12.7, 14.9)	4.9 (4.5, 5.3)	2,504,518 (28.2)	13.5 (12.4, 14.5)	4.9 (4.5, 5.4)	−0.35 (−1.24, 0.54)	0.06 (−0.25, 0.36)
Above median	1,608,892 (20.6)	13.8 (12.0, 15.6)	5.0 (4.2, 5.8)	1,843,720 (20.8)	13.2 (12.0, 14.3)	4.9 (4.3, 5.4)	−0.60 (−1.69, 0.49)	−0.16 (−0.50, 0.18)
Up to median	2,026,962 (25.9)	13.9 (12.7, 15.2)	5.3 (4.9, 5.7)	2,292,146 (25.8)	13.3 (12.4, 14.2)	5.2 (4.8, 5.6)	−0.65 (−1.62, 0.31)	−0.08 (−0.36, 0.21)
Lowest	1,845,529 (23.6)	13.2 (12.1, 14.3)	5.3 (4.9, 5.8)	2,237,840 (25.2)	12.8 (11.7, 13.9)	5.3 (4.7, 5.8)	−0.42 (−1.97, 1.12)	−0.08 (−0.55, 0.39)
Geographic region								
North	857,401 (11.0)	11.9 (10.8, 13.0)	5.1 (4.7, 5.5)	1,474,737 (16.6)	12.7 (11.4, 14.0)	5.3 (4.7, 6.0)	0.81 (−0.65, 2.28)	0.26 (−0.26, 0.77)

Continued

Variable	2019			2024			Prevalence difference for anemia (%, 95% *CI*)	Prevalence difference2 for moderate-severe anemia (%, 95% *CI*)
	Number (%)	Anemia (%, 95% *CI*)	Moderate-severe anemia (%, 95% *CI*)	Number (%)	Anemia (%, 95% *CI*)	Moderate-severe anemia (%, 95% *CI*)		
East	2,748,022 (35.1)	13.7 (12.7, 14.7)	5.1 (4.8, 5.5)	3,133,161 (35.3)	13.7 (13.0, 14.4)	5.1 (4.8, 5.4)	−0.02 (−0.86, 0.82)	0.03 (−0.21, 0.26)
Central	2,031,347 (26.0)	16.1 (14.8, 17.4)	5.8 (5.3, 6.3)	2,254,437 (25.4)	15.0 (14.1, 15.9)	5.6 (5.2, 5.9)	−1.11 (−2.39, 0.18)	−0.23 (−0.65, 0.18)
Southwest	1,001,486 (12.8)	11.3 (10.1, 12.5)	3.8 (3.4, 4.2)	794,601 (9.0)	10.6 (9.5, 11.6)	3.7 (3.3, 4.0)	−0.75 (−1.71, 0.20)	−0.13 (−0.38, 0.12)
Northwest	443,920 (5.7)	14.1 (12.0, 16.2)	6.0 (5.3, 6.6)	448,662 (5.1)	12.9 (11.7, 14.0)	5.8 (5.4, 6.2)	−1.23 (−3.01, 0.55)	−0.16 (−0.77, 0.45)
Northeast	740,313 (9.5)	11.7 (11.0, 12.4)**	4.1 (3.7, 4.4)**	772,626 (8.7)	10.4 (9.7, 11.2)**	4.0 (3.8, 4.2)**	−1.23 (−2.35, −0.12)*	−0.07 (−0.54, 0.37)

Note: The prevalence difference and *P* represent comparisons for the overall anemia rate.
Abbreviation: *CI*=confidence interval; GDP=gross domestic product; BMI=body mass index.
* *P*<0.05;
** *P*<0.01.

the 30–39 and 50–69 age groups. For moderate-to-severe anemia, prevalence among women aged 40–49 years increased significantly over the five-year period [odds ratio (*OR*)=0.32, 95% *CI*: 0.06, 0.57], whereas prevalence among women aged 50–59 and 60–69 years decreased significantly (*OR*=−0.25, 95% *CI*: −0.36, −0.13; *OR*=−0.17, 95% *CI*: −0.32, −0.02).

Regional analysis revealed statistically significant differences in both overall anemia and moderate-to-severe anemia prevalence among Chinese urban women in both 2019 and 2024. Notably, only women in Northeast China demonstrated a significant decline in anemia prevalence during this period. Figure 1 provides detailed provincial-level data. Among all age groups, anemia prevalence decreased in 18 provincial-level administrative divisions (PLADs) while increasing in 13 PLADs, including Hebei, Guizhou, and Tibet. Among women of reproductive age specifically, 17 PLADs experienced declining prevalence whereas 14 PLADs showed increases, with Tibet, Shandong, and Hebei reaching the 20% threshold.

Multivariate analysis identified several factors significantly associated with anemia and moderate-to-severe anemia risk among Chinese urban women (Table 2). Relative to women aged 18–29 years, all other age groups except those aged 60–69 years demonstrated significantly elevated anemia risk. Age-year interaction analysis, however, revealed a significant temporal decline in anemia and moderate-to-severe anemia risk across all age groups except women aged 40–49 years (interaction *OR*=0.99, 95% *CI*: 0.99, 1.01). Underweight women exhibited significantly increased anemia risk that intensified over time, whereas obese women showed significantly reduced risk (*OR*=0.80, 95% *CI*: 0.78, 0.82), with this protective effect strengthening over time (*OR*=1.01, 95% *CI*: 1.00, 1.01). A history of cesarean section was associated with elevated anemia risk (*OR*=1.07, 95% *CI*: 1.04, 1.10), and this association with moderate-to-severe anemia strengthened over time (*OR*=1.02, 95% *CI*: 1.00, 1.03). Women residing in areas with the lowest per capita GDP demonstrated significantly higher anemia risk compared to those in the highest GDP areas (*OR*=1.15, 95% *CI*: 1.03, 1.28), though this association remained stable over time.

DISCUSSION

Although anemia among women remains a major public health concern, comprehensive data on the prevalence, severity, and temporal trends of anemia among Chinese women have been limited. To address this gap, the present study leveraged national-level health examination data to characterize recent changes in anemia prevalence and its associated risk factors. Our findings provide a detailed portrait of anemia burden among urban women at both provincial and national levels, revealing substantial temporal, demographic, and regional heterogeneity. These results offer robust scientific evidence to inform the identification of high-risk subpopulations and the development of targeted, stratified anemia prevention and control strategies.

The WHO classifies anemia prevalence below 20% as a mild public health burden, 20%–40% as moderate, and above 40% as severe (*7*). By this criterion, the overall anemia burden among Chinese urban women remains mild. While the latest WHO

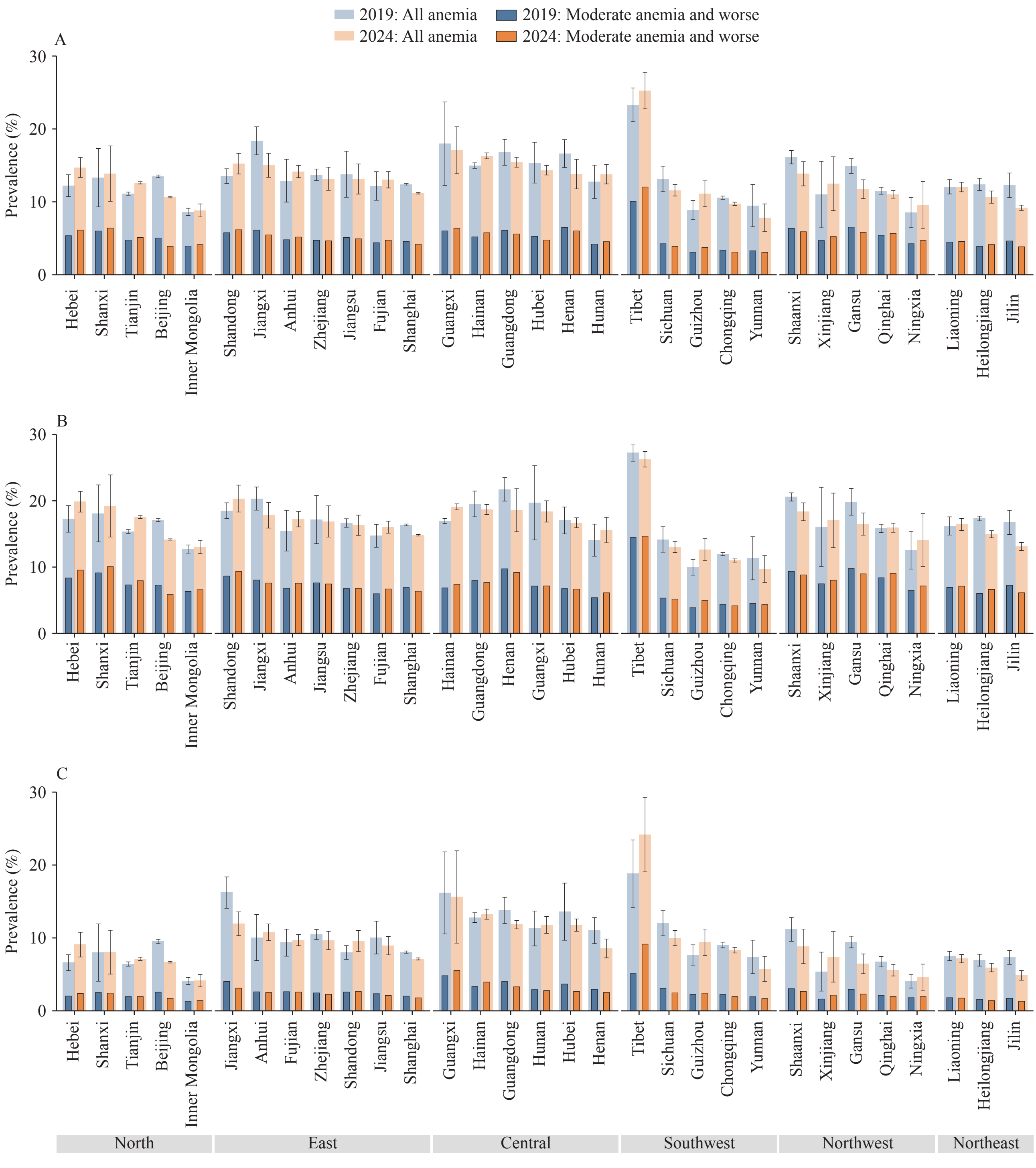

FIGURE 1. Regional disparities in the prevalence of anemia among urban women in China, standardized by age, 2019 versus 2024. (A) Anemia among all urban women; (B) Anemia among urban women aged 18–49 years; (C) Anemia among urban women aged 50 years and over.

global anemia assessment report indicates a stagnation in progress toward reducing anemia among women of reproductive age worldwide, anemia prevalence among urban Chinese women of reproductive age declined from 2019 to 2024, with decreases observed in most PLADs. This trend demonstrates that China has achieved measurable progress in maternal anemia prevention and control, likely attributable to the implementation of national nutrition and health policies. These include the *Healthy China Initiative (2019–2030)*, which explicitly outlines targeted actions for rational dietary practices, and the *National*

TABLE 2. Multilevel logistic regression analysis of factors associated with anemia among urban women in China: Overall effects and interactions with year (2019 versus 2024).

Variable	Anemia			Moderate-severe anemia		
	Overall *OR* (95% *CI*)	Interaction *OR* (95% *CI*)	*P* for interaction	Overall *OR* (95% *CI*)	Interaction *OR* (95% *CI*)	*P* for interaction
Year						
2019	Reference	—	—	Reference	—	—
2024	0.98 (0.93, 1.02)	—	—	1.01 (0.97, 1.05)	—	—
Age group (years)						
18–29	Reference	Reference	—	Reference	Reference	—
30–39	1.52 (1.48, 1.56)**	0.987 (0.980, 0.995)	<0.001	1.71 (1.66, 1.76)**	0.984 (0.978, 0.991)	<0.001
40–49	2.16 (2.11, 2.22)**	0.999 (0.991, 1.008)	0.908	2.88 (2.79, 2.97)**	0.994 (0.987, 1.002)	0.159
50–59	1.09 (1.04, 1.14)**	0.982 (0.973, 0.990)	<0.001	1.01 (0.97, 1.06)	0.969 (0.961, 0.977)	<0.001
60–69	1.01 (0.94, 1.09)	0.923 (0.961, 0.985)	<0.001	0.53 (0.47, 0.59)**	0.961 (0.943, 0.980)	<0.001
70+	1.76 (1.64, 1.88)**	0.979 (0.962, 0.995)	0.013	1.15 (1.02, 1.30)*	0.969 (0.940, 0.998)	0.038
BMI						
Underweight	1.12 (1.10, 1.15)**	1.015 (1.010, 1.020)	<0.001	1.02 (0.99, 1.04)	1.013 (1.006, 1.021)	<0.001
Normal	Reference	Reference	—	Reference	Reference	—
Overweight	0.86 (0.85, 0.87)**	0.998 (0.995, 1.001)	0.205	0.97 (0.96, 0.99)**	0.998 (0.994, 1.001)	0.156
Obesity	0.80 (0.78, 0.82)**	1.009 (1.004, 1.014)	<0.001	0.98 (0.96, 1.01)	1.007 (1.002, 1.013)	0.010
History of cesarean delivery						
Yes	1.07 (1.04, 1.10)**	1.006 (0.993, 1.020)	0.349	1.10 (1.07, 1.14)**	1.015 (1.003, 1.027)	0.015
No	Reference	Reference	—	Reference	Reference	—
Per capita GDP						
Lowest	1.15 (1.03, 1.28)*	0.998 (0.976, 1.020)	0.856	1.20 (1.08, 1.34)**	1.011 (0.991, 1.030)	0.284
Up to median	1.05 (0.95, 1.17)	0.995 (0.972, 1.018)	0.680	1.10 (1.00, 1.22)*	1.007 (0.988, 1.026)	0.468
Above median	1.08 (0.95, 1.22)	0.976 (0.947, 1.006)	0.121	1.13 (1.00, 1.27)*	0.987 (0.966, 1.009)	0.258
Highest	Reference	Reference	—	Reference	Reference	—
Engel coefficient						
Highest	1.08 (0.99, 1.17)	1.005 (0.974, 1.037)	0.755	0.97 (0.89, 1.06)	1.011 (0.988, 1.035)	0.350
Above median	1.05 (0.94, 1.17)	0.999 (0.966, 1.033)	0.968	0.95 (0.86, 1.05)	0.999 (0.976, 1.024)	0.958
Up to median	1.07 (0.97, 1.19)	1.004 (0.972, 1.037)	0.828	0.99 (0.90, 1.09)	1.009 (0.987, 1.032)	0.432
Lowest	Reference	Reference	—	Reference	Reference	—
Geographic region						
North	1.13 (1.01, 1.27)*	1.035 (0.999, 1.072)	0.056	1.21 (1.09, 1.35)**	1.007 (0.973, 1.042)	0.696
East	1.25 (1.15, 1.35)**	1.024 (0.998, 1.050)	0.075	1.23 (1.15, 1.31)**	1.001 (0.974, 1.029)	0.934
Central	1.41 (1.29, 1.55)**	1.005 (0.976, 1.036)	0.728	1.35 (1.24, 1.46)**	0.991 (0.960, 1.022)	0.563
Southwest	0.90 (0.81, 1.01)	1.007 (0.978, 1.036)	0.654	0.83 (0.76, 0.91)**	0.990 (0.961, 1.020)	0.506
Northwest	1.10 (0.95, 1.28)	0.998 (0.962, 1.035)	0.914	1.26 (1.13, 1.40)**	0.991 (0.958, 1.025)	0.585
Northeast	Reference	Reference	—	Reference	Reference	—

Note: "—" means not applicable.
Abbreviation: *OR*=odds ratio; *CI*=confidence interval; GDP=gross domestic product; BMI=body mass index.
* *P*<0.05;
** *P*<0.01.

Nutrition Plan (2017–2030), which establishes specific goals for reducing population anemia prevalence (*8–9*). Nevertheless, anemia prevalence among urban women has risen over the past five years in several provinces, with prevalence reaching or exceeding the 20% threshold in Tibet, Shandong, and Hebei—indicating a moderate disease burden in these regions that warrants heightened public health attention.

This study confirmed age as an independent risk factor for anemia, consistent with previous findings. Although overall anemia prevalence did not differ significantly between 2019 and 2024, age-year interaction effects revealed substantial heterogeneity in temporal risk patterns across age groups. Anemia risk decreased significantly over time among women aged 30–39, 50–59, 60–69, and 70+ years, while remaining stable in the 40–49 age group. This distinctive pattern likely reflects the higher susceptibility to abnormal uterine bleeding in women aged 40–49 years — often attributable to conditions such as uterine fibroids and perimenopausal endocrine disorders (*10–12*). These findings underscore the need for age-differentiated anemia prevention and control strategies, with particular emphasis on strengthening health management for women aged 40–49 years to further reduce the overall anemia burden.

Women with a history of cesarean section demonstrated a significantly elevated anemia risk, consistent with previous research (*2*). This association likely stems from both greater perinatal blood loss and increased risk of uterine impairment associated with cesarean delivery, either of which can substantially increase anemia susceptibility (*13–14*). Moreover, this study revealed that the association between cesarean section history and anemia risk strengthened significantly over time. These findings highlight the importance of increasing clinical awareness of cesarean section history as an anemia risk factor and reducing unnecessary cesarean deliveries.

This study has several limitations. First, the cross-sectional design precludes definitive causal inferences regarding factors contributing to anemia in women. Second, due to practical constraints on data processing timelines, this study compared anemia prevalence at only two discrete time points, failing to capture potential fluctuations during the intervening period—a limitation that may affect the precision of temporal trend assessments. Third, although automated hematology analyzers were used to measure hemoglobin levels at all examination centers with standardized calibration protocols, variations in specific instrument models and testing reagents across sites may have introduced measurement variability.

In conclusion, China has made measurable progress in maternal anemia prevention and control, yet substantial disease burden persists in certain provinces and population subgroups. Targeted and risk-stratified public health interventions are warranted, with priority given to women aged 40–49 years, women with a history of cesarean section, and provinces where anemia prevalence has increased or exceeded 20%.

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Preplanned Studies

Menstrual Characteristics and the Risk of Spontaneous Abortion — 9 PLADs, China, 2013–2024

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Summary

What is already known about this topic?

Menstrual irregularity is a hallmark clinical feature of polycystic ovary syndrome (PCOS), which is an established risk factor for spontaneous abortion. However, robust population-level evidence directly linking specific patterns of menstrual irregularity to spontaneous abortion risk remains lacking, as prior studies have been limited by small sample sizes.

What is added by this report?

This nationwide study of 3.9 million women demonstrates that abnormal menstrual characteristics — including irregular menstrual cycles and abnormal menstrual period duration — are independent risk factors for spontaneous abortion, each exhibiting a dose-response relationship. The co-occurrence of long cycles and prolonged periods confers the highest overall risk.

What are the implications for public health practice?

These findings offer a scientific basis for formulating public health policies aimed at reducing spontaneous abortion (SA) risk, particularly in resource-limited settings. Menstrual characteristics constitute a simple, low-cost, and readily accessible tool for stratifying SA risk across the perinatal continuum — from preconception counseling through early pregnancy management.

ABSTRACT

Introduction Menstrual irregularity is a hallmark clinical feature of polycystic ovary syndrome (PCOS), a well-established risk factor for spontaneous abortion (SA). However, robust population-level evidence directly linking specific menstrual patterns to SA risk remains lacking, as prior studies have been limited by small sample sizes and single-center designs.

Methods We analyzed data from 3.9 million women across nine Chinese provinces who participated in the National Free Preconception Care Project (NFPCP) between 2013 and 2024. Logistic regression was used to examine associations between menstrual characteristics and SA risk. Multilevel models, restricted cubic splines, and subgroup analyses were employed as extended analytical approaches to confirm the robustness of findings.

Results Irregular menstrual cycles [adjusted odds ratio (a*OR*)=1.11, 95% confidence interval (*CI*): 1.05, 1.17] and irregular periods (a*OR*=1.23, 95% *CI*: 1.15, 1.32) were independently associated with SA. The combination of long cycles (38-53 days) and prolonged periods (>7 days) conferred the highest risk (a*OR*=1.82, 95% *CI*: 1.33, 2.49). Dose-response relationships and subgroup analyses yielded patterns consistent with the primary analysis.

Conclusions These findings support the utility of menstrual characteristic assessment as an effective tool for SA risk stratification before and during pregnancy. Greater clinical attention should be directed toward women with abnormal menstrual cycles and/or periods, who warrant targeted monitoring and intervention — measures that offer meaningful benefit even for those who have already achieved conception.

Spontaneous abortion (SA), defined as pregnancy loss before viability, affects approximately 23 million women each year. Polycystic ovary syndrome (PCOS), a common endocrinopathy affecting up to 13% of reproductive-age women, is associated with a 49–53% increased risk of SA (*1*). PCOS is frequently underdiagnosed (*2*), and its complex diagnostic criteria can delay confirmation by more than 2 years (*3*). Since anovulation — affecting 75%–85% of PCOS patients (*4*–*5*) — is central to the condition and is closely associated with menstrual dysfunction, the characteristic patterns of these menstrual abnormalities may themselves serve as simple, accessible early warning signs. Menstrual characteristics (cycle length, bleeding duration) directly reflect endocrine health in women of reproductive age (*6*). Accordingly, assessment of menstrual characteristics represents a simple, low-cost, and clinically accessible tool for stratifying SA risk during preconception and early pregnancy. Incorporating this assessment into routine care could enable earlier identification of high-risk women, facilitating targeted monitoring and timely intervention.

Current research on menstrual characteristics has focused predominantly on fertility assessment during preconception, with limited robust evidence linking specific menstrual patterns to SA risk — a gap attributable in part to the small sample sizes and single-center designs of prior studies (*7–9*). To address this limitation, we analyzed data from over 3 million reproductive-aged women across nine Chinese regions within the National Free Preconception Checkups Project (NFPCP) to investigate the independent and combined associations of menstrual characteristics with SA risk.

This retrospective cohort study drew on data from the NFPCP, a population-based initiative launched in 2010 by the National Health and Family Planning Commission and the Ministry of Finance to provide free preconception health check-ups to rural and urban couples throughout mainland China. The project encompasses free health examinations, risk assessments, consultations, early pregnancy follow-ups, and pregnancy outcome follow-ups; its design, organization, and implementation have been described previously (*8*,*10*). The present study included women aged 20–49 years from nine provinces spanning eastern, central, and western China (Supplementary Table S1, available at https://weekly.chinacdc.cn/) who participated in the NFPCP between January 1, 2013, and December 31, 2024. Women were excluded if they met any of the following criteria: 1) multiple births; 2) ectopic pregnancy; 3) medically induced abortion; or 4) missing data on both menstrual cycle and menstrual period. After applying these exclusion criteria, a final cohort of 3,865,348 women was retained for analysis (Figure 1).

Menstrual characteristics (cycle length and period length) were assessed by trained health workers through structured interviews using a standardized household health questionnaire; data were entered directly into a web-based electronic collection system and transmitted to the national database center. Based on self-reported averages, menstrual cycles were categorized as regular (24–38 days) or irregular (≤24 days, 39–53 days, or >53 days), and menstrual period

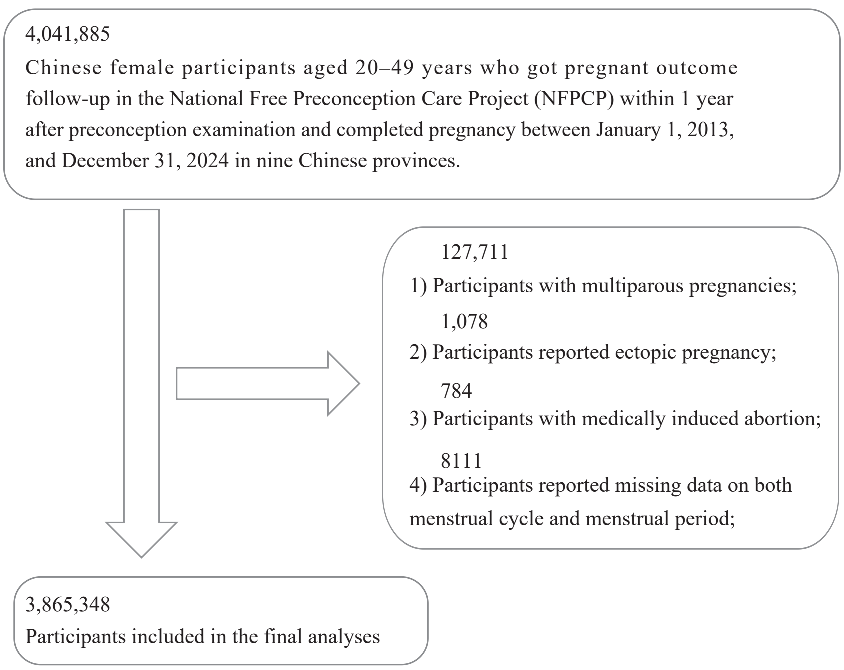

FIGURE 1. Flowchart of the study population selection.
Abbreviation: NFPCP=National Free Preconception Checkups Project.

as normal (3–7 days) or abnormal (<3 days or >7 days) (*11*–*12*). The primary outcome was SA, defined as fetal death or pregnancy loss before 28 weeks of gestation. Baseline characteristics were compared across menstrual regularity groups using descriptive statistics and chi-square (χ^2) tests.

The primary analysis employed logistic regression models to estimate odds ratios (*OR*s) and 95% confidence intervals (95% *CI*s) for associations between menstrual characteristics and SA. To minimize confounding, we adjusted for a comprehensive set of covariates spanning demographic, physiological, and lifestyle factors across three sequential models: unadjusted (Model 1), adjusted for high-risk factors (Model 2), and fully adjusted (Model 3); detailed covariate definitions are provided in Supplementary Table S2 (available at https://weekly.chinacdc.cn/). As an extended analytical approach, multilevel logistic regression models incorporating random intercepts at the economic region level were fitted to account for the clustering of nine provinces within three economic regions (Model 4). Dose–response relationships were evaluated using restricted cubic splines with four knots. Subgroup analyses stratified by age, body mass index (BMI), and adverse pregnancy history were performed to assess the robustness of the primary findings. Baseline characteristics were compared across menstrual regularity groups using descriptive statistics and chi-square tests. All analyses were performed in R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria); two-sided *P*<0.05 was considered statistically significant.

The final analysis included 3,865,348 reproductive-age women (mean age 27±4.28 years), among whom 64,834 SA events were recorded (incidence: 1.68%). Complete menstrual cycle and menstrual period data were available for 3,860,915 and 3,791,110 women, with irregularity prevalences of 3.05% and 1.63%, respectively. Women with irregular menstrual cycles had higher rates of overweight or obesity and adverse pregnancy history. Women with abnormal menstrual periods showed higher prevalences of scanty menstrual flow and adverse pregnancy history (all *P*<0.001; Table 1 and Supplementary Table S3, available athttps://weekly.chinacdc.cn/).

Logistic regression models confirmed that both irregular menstrual cycles [adjusted *OR* (a*OR*)=1.11, 95% *CI*: 1.05, 1.17] and abnormal menstrual periods (a*OR*=1.23, 95% *CI*: 1.15, 1.32) were independently associated with increased SA risk after full covariate adjustment (Model 3), with consistent estimates obtained from multilevel models (Model 4). Further categorization revealed dose-response relationships for both menstrual characteristics. Very long cycles (>53 days) conferred the highest cycle-related risk (a*OR*=1.25, 95% *CI*: 1.06, 1.48), and prolonged menstrual periods (>7 days) were also a significant risk factor (a*OR*=1.31, 95% *CI*: 1.20, 1.42) (Table 2). Restricted cubic spline (RCS) analyses revealed a J-shaped relationship for cycle length and a U-shaped relationship for menstrual period duration (both *P* for nonlinearity <0.001; Figure 2). In joint analyses, isolated irregularities in either dimension were each significantly associated with SA risk (cycles only: a*OR*=1.10; period only: a*OR*=1.24). Combined abnormalities showed an elevated point estimate (a*OR*=1.14, 95% *CI*: 0.90, 1.44) that did not reach statistical significance, a result likely attributable to the limited number of women in this category yielding wide confidence intervals. Notably, the combination of long cycles (39–53 days) and prolonged periods (>7 days) conferred the highest overall risk (Model 3: a*OR*=1.82, 95% *CI*: 1.33, 2.49), with multilevel models (Model 4) producing consistent estimates across all joint exposure categories (Table 3). Finally, stratified analyses suggested potentially enhanced associations among women aged ≥35 years, those with overweight or obesity, and those with a history of adverse pregnancy outcomes (Figure 3).

DISCUSSION

In this cohort of 3 million reproductive-age women spanning more than a decade, we demonstrated that deviations in menstrual characteristics — both cycle length and bleeding duration — are independently and dose-dependently associated with SA risk, following a J-shaped relationship for cycle length and a U-shaped relationship for period duration. The combination of long cycles and prolonged periods conferred the highest risk, a pattern that remained consistent across all subgroups examined.

These findings extend prior evidence linking menstrual irregularities to adverse pregnancy outcomes. We confirmed that longer menstrual cycles are associated with increased SA risk, consistent with existing literature connecting cycle irregularity to miscarriage and ovulatory dysfunction (*13*–*14*). We further identified prolonged menstrual periods (>7 days) as a significant independent risk factor for SA. Both patterns are consistent with underlying oligo-

TABLE 1. Baseline characteristics of the study population by menstrual cycle and menstrual period.

Maternal characteristic	Menstruation: Menstrual cycle regularity		*P*	Menstruation: Menstrual period regularity		*P*
	Regularity (*N*=3,743,087)	Irregularity (*N*=117,828)		Regularity (*N*=3,729,300)	Irregularity (*N*=61,810)	
Age at last menstrual period, years (*n*, %)			<0.001			<0.001
20–24	1,478,896 (39.51)	42,220 (35.83)		1,476,231 (39.58)	18,311 (29.62)	
25–29	1,561,268 (41.71)	51,791 (43.95)		1,556,429 (41.73)	26,447 (42.79)	
30–34	506,842 (13.54)	18,032 (15.30)		503,009 (13.49)	11,900 (19.25)	
35–49	196,081 (5.24)	5,785 (4.91)		193,661 (5.19)	5,152 (8.34)	
BMI (kg/m^2)			<0.001			<0.001
Underweight	375,595 (10.03)	11,720 (9.95)		373,815 (10.02)	7,173 (11.60)	
Normal weight	2,672,162 (71.39)	74,583 (63.30)		2,658,515 (71.29)	41,536 (67.20)	
Overweight	551,434 (14.73)	22,657 (19.23)		551,471 (14.79)	10,120 (16.37)	
Obesity	139,047 (3.71)	8,590 (7.29)		140,861 (3.78)	2,896 (4.69)	
Unknown	4,849 (0.13)	278 (0.24)		4,668 (0.13)	85 (0.14)	
Blood sugar status (*n*, %)			<0.001			<0.001
Normal glucose level	3,216,942 (85.94)	100,104 (84.96)		3,204,832 (85.94)	52,510 (84.95)	
Pre-diabetes	479,579 (12.81)	15,870 (13.47)		477,901 (12.81)	8,490 (13.74)	
Diabetes	29,522 (0.79)	1,204 (1.02)		29,639 (0.79)	504 (0.82)	
Unknown	17,044 (0.46)	650 (0.55)		16,958 (0.45)	306 (0.50)	
Blood pressure status (*n*, %)			<0.001			<0.001
Normal	3,332,227 (89.02)	100,573 (85.36)		3,319,996 (89.02)	53,053 (85.83)	
Hypertension	39,778 (1.06)	2,118 (1.80)		39,659 (1.06)	1,035 (1.67)	
Unknown	371,082 (9.91)	15,137 (12.85)		369,675 (9.91)	7,722 (12.49)	
Education level (*n*, %)			<0.001			<0.001
Junior high school or below	2,426,323 (64.82)	66,952 (56.82)		2,408,328 (64.58)	39,942 (64.62)	
Senior high school or above	1,181,982 (31.58)	46,838 (39.75)		1,188,935 (31.88)	20,604 (33.33)	
Unknown	134,782 (3.60)	4,038 (3.43)		132,067 (3.54)	1,264 (2.04)	
Ethnicity (*n*, %)			<0.001			<0.001
Han	3,610,322 (96.45)	114,083 (96.82)		3,599,376 (96.52)	58,988 (95.43)	
Others	78,800 (2.11)	2,118 (1.80)		77,690 (2.08)	2,384 (3.86)	
Unknown	53,965 (1.44)	1,627 (1.38)		52,264 (1.40)	438 (0.71)	
Residence type (*n*, %)			<0.001			<0.001
Urban	233,895 (6.25)	12,246 (10.39)		234,371 (6.28)	6,240 (10.10)	
Rural	3,509,192 (93.75)	105,582 (89.61)		3,494,959 (93.72)	55,570 (89.90)	
Dysmenorrhea status (*n*, %)			<0.001			<0.001
None	2,902,978 (77.56)	76,971 (65.32)		2,886,189 (77.39)	44,034 (71.24)	
Mild	801,085 (21.40)	36,225 (30.74)		803,670 (21.55)	16,268 (26.32)	
Severe	29,654 (0.79)	2,903 (2.46)		30,188 (0.81)	1,347 (2.18)	
Unknown	9,370 (0.25)	1,729 (1.47)		9,283 (0.25)	161 (0.26)	
Menstrual flow (*n*, %)			<0.001			<0.001
Slight	72,082 (1.93)	6,726 (5.79)		69,712 (1.87)	6,110 (9.90)	
Moderate	3,594,677 (96.22)	104,608 (90.03)		3,584,151 (96.30)	52,417 (84.93)	
Large	69,000 (1.85)	4,857 (4.18)		68,144 (1.83)	3,188 (5.17)	

Continued

Maternal characteristic	Menstruation: Menstrual cycle regularity: Regularity (*N*=3,743,087)	Menstruation: Menstrual cycle regularity: Irregularity (*N*=117,828)	*P*	Menstruation: Menstrual period regularity: Regularity (*N*=3,729,300)	Menstruation: Menstrual period regularity: Irregularity (*N*=61,810)	*P*
Adverse pregnancy history (*n*, %)			<0.001			<0.001
No	3,186,350 (85.13)	90,078 (76.45)		3,173,876 (85.11)	44,634 (72.21)	
Yes	556,737 (14.87)	27,750 (23.55)		555,454 (14.89)	17,176 (27.79)	
Parity (*n*, %)			<0.001			<0.001
Nulliparous	2,085,449 (55.71)	61,670 (52.34)		2,081,289 (55.81)	25,327 (40.98)	
Parous	1,657,638 (44.29)	56,158 (47.66)		1,648,041 (44.19)	36,483 (59.02)	

Note: All variables are presented as *N* (%). All *P*<0.001. Baseline characteristics were stratified by menstrual cycle regularity — regular (24–38 days) versus irregular (<24 days, 39–53 days, or >53 days) — and by menstrual bleeding duration (menstrual period) — normal (3–7 days) versus abnormal (<3 or >7 days). All variables were classified into appropriate categories, and chi-square (χ^2) tests were used to calculate *P*.
Abbreviation: BMI=body mass index.

TABLE 2. Individual associations between menstrual characteristics and SA risk.

Characteristic	Total participants	SA cases *n* (%)	*OR* (95% *CI*): Model 1	Model 2	Model 3	Model 4
Menstrual cycle						
Binary classification						
Regular (24–38 days)	3,743,087	62,165 (1.66)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Irregular	117,828	2,559 (2.17)	1.31 (1.26, 1.37)	1.23 (1.18, 1.29)	1.11 (1.05, 1.17)	1.11 (1.05, 1.17)
Detailed classification						
24D–38D	3,743,087	62,165 (1.66)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
<24D	69,579	1,454 (2.09)	1.26 (1.20, 1.33)	1.22 (1.15, 1.29)	1.12 (1.04, 1.20)	1.10 (1.02, 1.17)
39D–53D	38,707	865 (2.23)	1.35 (1.26, 1.45)	1.22 (1.13, 1.32)	1.06 (0.97, 1.17)	1.09 (0.99, 1.12)
>53D	9,542	240 (2.52)	1.53 (1.34, 1.74)	1.40 (1.21, 1.61)	1.25 (1.06, 1.48)	1.25 (1.06, 1.48)
Menstrual period						
Binary classification						
Regular (3D–7D)	3,729,330	61,780 (1.66)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Irregular	61,810	1,643 (2.66)	1.62 (1.54, 1.70)	1.44 (1.36, 1.52)	1.23 (1.15, 1.32)	1.26 (1.17, 1.35)
Detailed classification						
3D–7D	3,729,330	61,780 (1.66)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
<3D	29,729	743 (2.50)	1.52 (1.41, 1.64)	1.35 (1.25, 1.46)	1.11 (0.99, 1.25)	1.18 (1.05, 1.32)
>7D	32,081	900 (2.81)	1.71 (1.60, 1.83)	1.53 (1.42, 1.64)	1.31 (1.20, 1.42)	1.31 (1.20, 1.42)

Note: Data are presented as odds ratio (95% *CI*). Estimates with 95% *CI*s excluding 1 are considered statistically significant at *P*<0.05. Models examined associations between menstrual cycle regularity (regular: 24–38 days; irregular: <24, 39–53, or >53 days) and menstrual period duration (normal: 3–7 days; abnormal: <3 or >7 days) with SA risk. Four models were fitted: Model 1 (unadjusted), Model 2 (adjusted for high-risk factors), and Model 3 (fully adjusted) using conventional logistic regression; Model 4 (fully adjusted) using multilevel logistic regression as an extended analytical approach. All covariates are listed in Supplementary Table S2.
Abbreviation: *OR*=odds ratio; *CI*=confidence interval; SA=spontaneous abortion.

anovulation or luteal-phase deficiency — conditions relevant to PCOS, in which hyperandrogenism and progesterone insufficiency may compromise endometrial receptivity and impair early pregnancy maintenance (*15–16*). Direct mechanistic verification was beyond the scope of the present study. Nevertheless, our findings provide a scientific basis for public health policies targeting SA prevention, particularly in resource-limited settings. Menstrual characteristics represent a simple, low-cost, and readily accessible tool for stratifying SA risk across the perinatal continuum — from preconception counseling through early pregnancy. Early identification of women with menstrual abnormalities

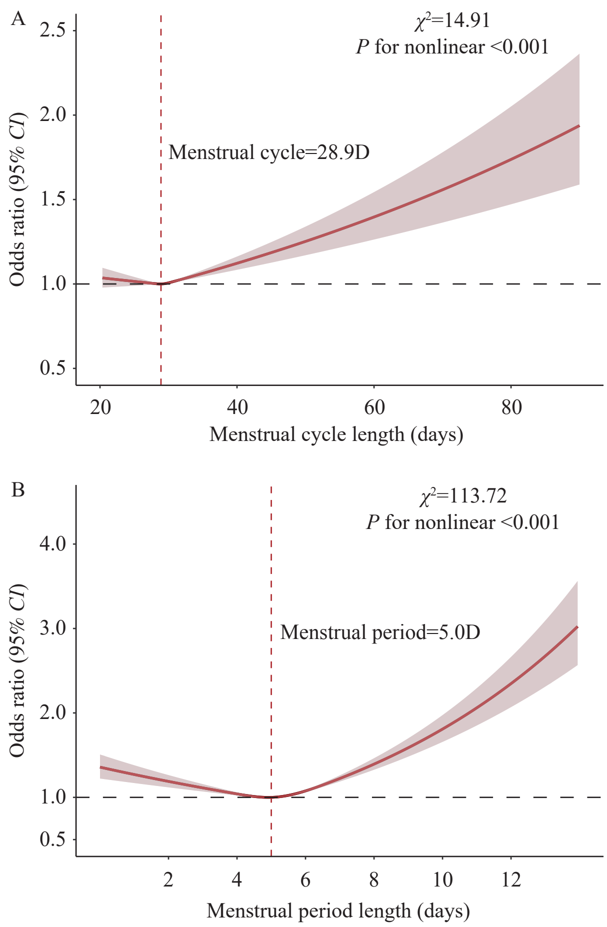

FIGURE 2. Dose-response relationship between menstrual characteristics and SA risk (restricted cubic spline analysis). (A) Menstrual cycle length (RCS-adjusted logistic regression); (B) Menstrual period length (RCS-adjusted logistic regression).

Note: This figure displays restricted cubic spline (RCS) curves from logistic regression models examining the dose–response relationships between menstrual cycle length and menstrual period duration with spontaneous abortion (SA) risk. The red dashed horizontal line represents an *OR* of 1.0, indicating no difference in risk relative to the reference. Solid red lines indicate the estimated *OR*s, and shaded ribbons denote the corresponding 95% *CI*s. Logistic regression models were adjusted for all covariates listed in Supplementary Table S2. Bolded values indicate statistical significance (P<0.05). The χ^2 and P for nonlinearity are reported in each panel to evaluate the significance of the non-linear association.

Abbreviation: RCS=Restricted Cubic Spline; SA=Spontaneous Abortion; χ^2=Chi-square statistic; *OR*=odds ratio; *CI*=confidence interval.

facilitates timely intervention for underlying conditions such as PCOS or obesity-related anovulation, before pregnancy complications emerge. Evidence supports that lifestyle modification and low-cost pharmacological interventions can restore ovulatory cycles, improve metabolic health, and enhance reproductive outcomes (*5,11*). Although menstrual data are routinely recorded in clinical practice, they remain substantially underutilized in pregnancy risk assessment. Greater clinical attention should therefore be directed toward women with abnormal cycles or periods — not only during preconception counseling, but also after conception has occurred — as both groups stand to benefit from targeted monitoring and timely intervention. Embedding this risk-aware approach throughout the perinatal continuum has the potential to meaningfully improve pregnancy outcomes.

This study has several notable strengths. First, the large-scale design, drawing on long-term data from nine Chinese regions, provided sufficient statistical power to detect moderate yet clinically meaningful associations between menstrual characteristics and *SA* risk — associations that prior smaller studies were underpowered to establish. Second, the application of multiple analytical approaches to evaluate distinct menstrual dimensions, combined with detailed exposure categorization, enhanced both the robustness and granularity of our findings. Importantly, all menstrual characteristics were ascertained prior to pregnancy, which minimizes recall bias and establishes a clear temporal sequence between exposure and outcome. Finally, the availability of comprehensive individual-level covariate data enabled well-powered and informative subgroup analyses across key demographic and clinical strata.

This study has several limitations that warrant consideration. First, menstrual characteristics were self-reported at the preconception health visit, which may introduce misclassification arising from recall or reporting inaccuracies. Second, the absence of biochemical or hormonal biomarkers precluded direct verification of ovulatory status or quantification of endocrine dysfunction. Third, residual confounding cannot be excluded, as certain variables remained unmeasured or unidentified — including genetic factors (such as embryonic or parental chromosomal abnormalities) and environmental exposures at the population level (e.g., air pollution, climate, temperature, humidity, and atmospheric pressure). Fourth, although participants were drawn from nine provinces, the majority were rural residents; consequently, our findings may not be fully generalizable to all reproductive-age women in China, particularly those of higher socioeconomic status or those who do not seek preconception care.

TABLE 3. Combined associations between menstrual characteristics and SA risk.

Menstrual Characteristic Pattern	Total participants	SA cases *n* (%)	*OR* (95% *CI*)			
			Model 1	Model 2	Model 3	Model 4
Binary joint classification						
Both normal	3,657,947	60,231 (1.62)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Irregular cycle only	67,043	1,444 (2.11)	1.31 (1.25, 1.39)	1.20 (1.13, 1.27)	1.10 (1.01, 1.17)	1.11 (1.03, 1.20)
Irregular period only	56,991	1,498 (2.56)	1.61 (1.53, 1.70)	1.42 (1.34, 1.50)	1.24 (1.16, 1.34)	1.27 (1.18, 1.37)
Both abnormal	4,726	140 (2.88)	1.82 (1.54, 2.16)	1.45 (1.20, 1.76)	1.14 (0.90, 1.44)	1.18 (0.93, 1.49)
Detailed joint classification						
Both normal	3,657,947	60,231 (1.62)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Short cycle & short period	1,414	33 (2.28)	1.43 (1.01, 2.02)	1.01 (0.67, 1.51)	0.97 (0.65, 1.47)	0.68 (0.38, 1.20)
Short cycle & regular period	21,392	420 (1.93)	1.20 (1.09, 1.32)	1.11 (1.00, 1.23)	1.07 (0.97, 1.20)	1.12 (0.97, 1.29)
Short cycle & long period	804	30 (3.60)	2.23 (1.61, 3.33)	1.75 (1.15, 2.66)	1.52 (0.99, 2.32)	1.44 (0.90, 2.31)
Regular cycle & short period	27,655	690 (2.43)	1.53 (1.42, 1.65)	1.34 (1.24, 1.46)	1.31 (1.20, 1.42)	1.22 (1.08, 1.38)
Regular cycle & long period	29,336	808 (2.68)	1.69 (1.58, 1.82)	1.50 (1.39, 1.62)	1.39 (1.29, 1.50)	1.30 (1.19, 1.42)
Long cycle & short period	472	15 (3.08)	1.96 (1.17, 3.28)	1.36 (0.75, 2.48)	1.37 (0.75, 2.51)	1.31 (0.61, 2.79)
Long cycle & regular period	36,704	802 (2.14)	1.33 (1.24, 1.43)	1.20 (1.11, 1.29)	1.19 (1.10, 1.29)	1.07 (0.97, 1.17)
Long cycle & long period	1,463	46 (3.05)	1.94 (1.45, 2.60)	1.98 (1.46, 2.69)	1.82 (1.33, 2.49)	1.64 (1.15, 2.34)
Very long cycle & short period	146	2 (1.35)	0.83 (0.21, 3.35)	0.78 (0.19, 3.17)	0.75 (0.18, 3.04)	0.58 (0.08, 4.21)
Very long cycle & regular period	8,947	222 (2.42)	1.52 (1.33, 1.74)	1.41 (1.22, 1.63)	1.40 (1.21, 1.62)	1.29 (1.08, 1.53)
Very long cycle & long period	427	14 (3.17)	2.02 (1.19, 3.45)	1.08 (0.51, 2.28)	1.04 (0.50, 2.21)	0.59 (0.19, 1.86)

Note: Exposure categories were defined based on combinations of menstrual cycle length and menstrual period duration. The reference group comprised women with both normal cycle length and normal period duration. Both normal: normal menstrual cycle length (24–38 days) and normal period duration (3–7 days). Irregular cycle only: irregular menstrual cycle (<24 or >38 days) with normal period duration. Irregular period only: normal menstrual cycle with irregular period duration (<3 or >7 days). Both abnormal: irregular menstrual cycle and irregular period duration. Four models were constructed: Model 1 (unadjusted), Model 2 (adjusted for high-risk factors), and Model 3 (fully adjusted) using conventional logistic regression; Model 4 (fully adjusted) using multilevel logistic regression as an extended analytical approach. All covariates are listed in Supplementary Table S2. Results are presented as odds ratios (95% *CI*). Associations are considered statistically significant at *P*<0.05, corresponding to 95% *CI*s that exclude 1.
Abbreviation: *CI*=confidence interval; SA=spontaneous abortion.

Conflicts of interest: No conflicts of interest.

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Ethical statements: Approved by the Institutional Review Board of the National Research Institute for Family Planning (IRB-201001). Written informed consent was obtained from all National Free Preconception Care Project (NFPCP) participants. The study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki (2000), and its reporting adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

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Subgroup	Maternal characteristic	*N*	*OR* (95% *CI*)
Age at last menstrual, years			
20–34	Both normal	3,468,043	1.00 (1.00–1.00)
	Irregular cycle only	63,568	1.10 (1.02–1.19)
	Irregular period only	52,218	1.21 (1.12–1.31)
	Both abnormal	4,354	1.15 (0.90–1.48)
35–49	Both normal	189,904	1.00 (1.00–1.00)
	Irregular cycle only	3,475	1.00 (0.78–1.26)
	Irregular period only	4,773	1.39 (1.16–1.66)
	Both abnormal	372	0.97 (0.48–1.98)
BMI (kg/m^2)			
Underweight	Both normal	366,536	1.00 (1.00–1.00)
	Irregular cycle only	6,804	1.10 (0.87–1.39)
	Irregular period only	6,649	1.24 (1.00–1.54)
	Both abnormal	515	1.64 (0.89–3.00)
Normal weight	Both normal	2,613,507	1.00 (1.00–1.00)
	Irregular cycle only	42,022	1.06 (0.97–1.17)
	Irregular period only	38,644	1.23 (1.12–1.34)
	Both abnormal	2,832	1.04 (0.76–1.43)
Overweight or obesity	Both normal	673,340	1.00 (1.00–1.00)
	Irregular cycle only	18,124	1.15 (1.01–1.31)
	Irregular period only	11,621	1.26 (1.08–1.46)
	Both abnormal	1,463	1.12 (0.73–1.72)
Adverse pregnancy history (%)			
No	Both normal	3,120,572	1.00 (1.00–1.00)
	Irregular cycle only	49,757	1.06 (0.97–1.16)
	Irregular period only	41,520	1.19 (1.09–1.30)
	Both abnormal	3,051	1.18 (0.88–1.59)
Yes	Both normal	537,375	1.00 (1.00–1.00)
	Irregular cycle only	17,286	1.17 (1.03–1.33)
	Irregular period only	15,471	1.31 (1.16–1.48)
	Both abnormal	1,675	1.05 (0.72–1.54)

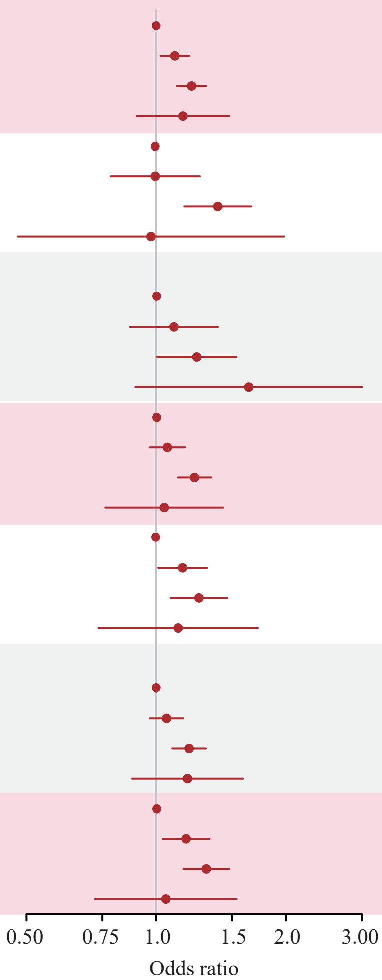

FIGURE 3. Forest plot of the association between menstrual characteristics and spontaneous abortion (SA) risk, stratified by age, BMI, and adverse pregnancy history.

Note: This forest plot presents subgroup analysis results examining the association between combined menstrual characteristic categories and SA risk. *OR*s and 95% *CI*s were derived from fully adjusted multivariable logistic regression models. Exposure categories were defined based on combinations of menstrual cycle length and menstrual period duration, with women having both normal cycle length and normal period length serving as the reference group. Both Normal: normal menstrual cycle length (24–38 days) and normal period length (3–7 days). Irregular Cycle Only: irregular menstrual cycle (<24 or >38 days) with normal period length. Irregular Period Only: normal menstrual cycle with irregular period length (<3 or >7 days). Both Abnormal: irregular menstrual cycle and irregular period length. Analyses were stratified by three key maternal characteristics: age at last menstrual period (20–34 *vs*. 35–49 years); body mass index (BMI) category (underweight, normal weight, or overweight/obesity); and a history of adverse pregnancy (no vs. yes). Within each stratum, four mutually exclusive exposure categories were compared, with the "Both Normal" group serving as the common reference (*OR*=1.00). Each estimate is represented by a solid square (point estimate, *OR*) with a horizontal line denoting the 95% *CI*. The area of each square is proportional to the precision of the estimate. The vertical dashed line at *OR*=1.0 indicates no association; statistical significance is indicated when the *95% CI* does not cross this line (i.e., excludes 1.0).

Abbreviation: *OR*=odds ratio; *CI*=confidence interval; SA=spontaneous abortion; BMI=body mass index (kg/m^2).

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE S1. Geographic distribution of the study population by economic region and PLAD.

Economic region	PLADs	Participants *N*	Region Subtotal *N* (%)	SA cases *N*	SA rate *N* (%)
Eastern Region		876,531	22.68	1,801	0.21
	Tianjin	51,651	1.34	233	0.45
	Shandong	793,426	20.53	1,387	0.17
	Liaoning	31,454	0.81	181	0.58
Central Region		2,359,289	61.04	5,373	0.23
	Henan	1,716,248	44.40	3,142	0.18
	Jilin	52,736	1.36	234	0.44
	Anhui	590,305	15.27	1997	0.34
Western Region		629,528	16.29	5163	0.82
	Sichuan	302,767	7.83	3,940	1.30
	Gansu	285,458	7.39	682	0.24
	Qinghai	41,303	1.07	541	1.31

Note: Data were derived from the National Free Preconception Care Project (NFPCP) database.
Abbreviation: SA=spontaneous abortion; PLAD=provincial-level administrative division.

SUPPLEMENTARY TABLE S2. Definitions of covariates.

Covariates	Definition
Demographic Factors	
Education level	The highest level of educational attainment of the participant (junior high school and below, senior high school or above).
Ethnicity	The ethnic group to which the participant belongs (Han or other).
Residence type	The type of area where the participant lives (rural or urban).
Individual Physiological Factors	
Age	Maternal age at the last menstrual period of the participant (20–24, 25–29, 30–34, 35–39, and ≥40 years).
Reproductive system status	Whether the participant has a history of infertility or adnexal inflammation (yes or no).
Endocrine system abnormalities	
BMI level	Calculated as weight in kilograms divided by height in meters squared [underweight (less than 18.5 kg/m^2), normal (18.5–23.9 kg/m^2), overweight (24.0–27.9 kg/m^2), or obese (28.0 kg/m^2 or more)].
Blood sugar status	Self-reported hyperglycemia or fasting blood glucose ≥6.1 mmol/L (yes or no).
Blood pressure status	Self-reported hypertension or systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg (yes or no).
Thyroid function status	Self-reported thyroid disease or abnormal thyroid function (yes or no).
Immune system status	Whether the participant's white blood cell count was $\geq 4.0 \times 10^9$/L and $\leq 10.0 \times 10^9$/L (yes or no).
Obstetric History Covariates	
Adverse pregnancy history	Participants had any adverse pregnancy outcomes (yes or no).
Parity	Whether the participant had previous deliveries (nulliparous or parous).
Menstruation-related Covariates	
Dysmenorrhea status	Participants self-reported whether they experienced dysmenorrhea during their menstrual period (none, mild, or severe).
Menstrual flow	Participants self-reported menstrual blood volume (slight, moderate, or large).
Age of menarche status	Whether the menarche age reported by participants is normal (between 10–15 years old) (normal or abnormal).
Lifestyle and Behavior-Related Factors	
Smoking status	Whether the participant actively smokes (yes or no).
Secondhand smoking status	Whether the participant smokes passively (yes or no).
Alcohol consumption	Whether the participant has consumed alcohol (yes or no).
Pressure status	Whether the participant experiences work and life pressure, social pressure, or economic pressure (yes or no).
Medication status	Whether the participant is currently on medication (yes or no).

Note: Four logistic regression models were constructed. Model 1 was unadjusted. Model 2 was adjusted for high-risk factors, including age, BMI, fasting plasma glucose, blood pressure, adverse pregnancy history, and menstruation-related covariates. Model 3 was fully adjusted, incorporating demographic factors (education, ethnicity, and residence), physiological factors (age, BMI, blood glucose, blood pressure, thyroid function, and immune status), reproductive factors (reproductive system status, adverse pregnancy history, parity, dysmenorrhea, menstrual flow, and age at menarche), and lifestyle factors (smoking, secondhand smoke exposure, alcohol consumption, psychological stress, and medication use). Model 4 applied the same full covariate adjustment as Model 3 within a multilevel logistic regression framework to account for clustering by economic region.
Abbreviation: BMI=body mass index.

SUPPLEMENTARY TABLE S3. Complete baseline characteristics of the study population by menstrual cycle regularity and menstrual period regularity.

Maternal characteristic	Menstruation: Menstrual cycle regularity		*P*	Menstruation: Menstrual period regularity		*P*
	Regularity (*N*=3,743,087)	Irregularity (*N*=117,828)		Regularity (*N*=3,729,300)	Irregularity (*N*=61,810)	
Age at last menstrual period, years (*n*, %)			<0.001			<0.001
20–24	1,478,896 (39.51)	42,220 (35.83)		1,476,231 (39.58)	18,311 (29.62)	
25–29	1,561,268 (41.71)	51,791 (43.95)		1,556,429 (41.73)	26,447 (42.79)	
30–34	506,842 (13.54)	18,032 (15.30)		503,009 (13.49)	11,900 (19.25)	
35–49	196,081 (5.24)	5,785 (4.91)		193,661 (5.19)	5,152 (8.34)	
BMI (kg/m^2)			<0.001			<0.001
Underweight	375,595 (10.03)	11,720 (9.95)		373,815 (10.02)	7,173 (11.60)	
Normal weight	2,672,162 (71.39)	74,583 (63.30)		2,658,515 (71.29)	41,536 (67.20)	
Overweight	551,434 (14.73)	22,657 (19.23)		551,471 (14.79)	10,120 (16.37)	
Obesity	139,047 (3.71)	8,590 (7.29)		140,861 (3.78)	2,896 (4.69)	
Unknown	4,849 (0.13)	278 (0.24)		4,668 (0.13)	85 (0.14)	
Blood sugar status (*n*, %)			<0.001			<0.001
Normal glucose level	3,216,942 (85.94)	100,104 (84.96)		3,204,832 (85.94)	52,510 (84.95)	
Prediabetes	479,579 (12.81)	15,870 (13.47)		477,901 (12.81)	8,490 (13.74)	
Diabetes	29,522 (0.79)	1,204 (1.02)		29,639 (0.79)	504 (0.82)	
Unknown	17,044 (0.46)	650 (0.55)		16,958 (0.45)	306 (0.50)	
Blood pressure status (*n*, %)			<0.001			<0.001
Normal	3,332,227 (89.02)	100,573 (85.36)		3,319,996 (89.02)	53,053 (85.83)	
Hypertension	39,778 (1.06)	2,118 (1.80)		39,659 (1.06)	1,035 (1.67)	
Unknown	371,082 (9.91)	15,137 (12.85)		369,675 (9.91)	7,722 (12.49)	
Thyroid function status (*n*, %)			<0.001			<0.001
Normal	3,735,987 (99.81)	117,312 (99.56)		3,722,199 (99.81)	61,526 (99.54)	
Abnormal	7,100 (0.19)	516 (0.44)		7,131 (0.19)	284 (0.46)	
Reproductive system status (*n*, %)			<0.001			<0.001
Normal	1,890,043 (50.49)	74,883 (63.55)		1,885,006 (50.55)	37,559 (60.77)	
Abnormal	9,605 (0.26)	1,023 (0.87)		9,680 (0.26)	536 (0.87)	
Unknown	1,843,439 (49.25)	41,922 (35.58)		1,834,644 (49.20)	23,715 (38.37)	
Immune system status (*n*, %)			<0.001			<0.001
Normal	1,746,894 (46.67)	69,752 (59.20)		1,742,750 (46.73)	34,598 (55.97)	
Abnormal	147,217 (3.93)	5,886 (5.00)		146,451 (3.93)	3,382 (5.47)	
Unknown	1,848,976 (49.40)	42,190 (35.81)		1,840,129 (49.34)	23,830 (38.55)	
Dysmenorrhea status (*n*, %)			<0.001			<0.001
None	2,902,978 (77.56)	76,971 (65.32)		2,886,189 (77.39)	44,034 (71.24)	
Mild	801,085 (21.40)	36,225 (30.74)		803,670 (21.55)	16,268 (26.32)	
Severe	29,654 (0.79)	2,903 (2.46)		30,188 (0.81)	1,347 (2.18)	
Unknown	9,370 (0.25)	1,729 (1.47)		9,283 (0.25)	161 (0.26)	
Menstrual flow (*n*, %)			<0.001			<0.001
Slight	72,082 (1.93)	6,726 (5.79)		69,712 (1.87)	6,110 (9.90)	
Moderate	3,594,677 (96.22)	104,608 (90.03)		3,584,151 (96.30)	52,417 (84.93)	
Large	69,000 (1.85)	4,857 (4.18)		68,144 (1.83)	3,188 (5.17)	
Age of menarche status (*n*, %)			<0.001			<0.001
Normal	3,461,387 (92.47)	102,707 (87.17)		3,458,062 (92.73)	53,889 (87.18)	

Continued

Maternal characteristic	Menstruation: Menstrual cycle regularity: Regularity (*N*=3,743,087)	Menstruation: Menstrual cycle regularity: Irregularity (*N*=117,828)	*P*	Menstruation: Menstrual period regularity: Regularity (*N*=3,729,300)	Menstruation: Menstrual period regularity: Irregularity (*N*=61,810)	*P*
Abnormal	263,662 (7.04)	14,345 (12.17)		263,396 (7.06)	7,784 (12.59)	
Unknown	18,038 (0.48)	776 (0.66)		7,872 (0.21)	137 (0.22)	
Education level (*n*, %)			<0.001			<0.001
Junior high school or below	2,426,323 (64.82)	66,952 (56.82)		2,408,328 (64.58)	39,942 (64.62)	
Senior high school or above	1,181,982 (31.58)	46,838 (39.75)		1,188,935 (31.88)	20,604 (33.33)	
Unknown	134,782 (3.60)	4,038 (3.43)		132,067 (3.54)	1,264 (2.04)	
Ethnicity (*n*, %)			<0.001			<0.001
Han	3,610,322 (96.45)	114,083 (96.82)		3,599,376 (96.52)	58,988 (95.43)	
Non-Han	78,800 (2.11)	2,118 (1.80)		77,690 (2.08)	2,384 (3.86)	
Unknown	53,965 (1.44)	1,627 (1.38)		52,264 (1.40)	438 (0.71)	
Residence type (*n*, %)			<0.001			<0.001
Urban	233,895 (6.25)	12,246 (10.39)		234,371 (6.28)	6,240 (10.10)	
Rural	3,509,192 (93.75)	105,582 (89.61)		3,494,959 (93.72)	55,570 (89.90)	
Smoking status (*n*, %)			<0.001			<0.001
Never smoker	3,729,951 (99.65)	117,070 (99.36)		3,716,073 (99.64)	61,465 (99.44)	
Ever smoker	6,728 (0.18)	490 (0.42)		6,814 (0.18)	235 (0.38)	
Unknown	6,408 (0.17)	268 (0.23)		6,443 (0.17)	110 (0.18)	
Secondhand smoking status (*n*, %)			<0.001			<0.001
No	3,418,224 (91.32)	98,151 (83.30)		3,403,108 (91.25)	52,603 (85.10)	
Yes	318,264 (8.50)	19,415 (16.48)		319,601 (8.57)	9,100 (14.72)	
Unknown	6,599 (0.18)	262 (0.22)		6,621 (0.18)	107 (0.17)	
Alcohol consumption (*n*, %)			<0.001			<0.001
Never drinker	3,683,329 (98.40)	114,217 (96.94)		3,669,155 (98.39)	60,026 (97.11)	
Ever drinker	51,065 (1.36)	3,240 (2.75)		51,459 (1.38)	1,618 (2.62)	
Unknown	8,693 (0.23)	371 (0.31)		8,716 (0.23)	166 (0.27)	
Pressure status (*n*, %)			<0.001			<0.001
No	3,720,428 (99.39)	116,281 (98.69)		3,706,452 (99.39)	61,149 (98.93)	
Yes	9,324 (0.25)	1,024 (0.87)		9,511 (0.26)	445 (0.72)	
Unknown	13,335 (0.36)	523 (0.44)		13,367 (0.36)	216 (0.35)	
Medication status (n, %)			<0.001			<0.001
No use	3,637,488 (97.18)	111,814 (94.90)		3,622,825 (97.14)	58,513 (94.67)	
Use	95,995 (2.56)	5,674 (4.82)		96,858 (2.60)	3,161 (5.11)	
Unknown	9,604 (0.26)	340 (0.29)		9,647 (0.26)	136 (0.22)	
Adverse pregnancy history (*n*, %)			<0.001			<0.001
No	3,186,350 (85.13)	90,078 (76.45)		3,173,876 (85.11)	44,634 (72.21)	
Yes	556,737 (14.87)	27,750 (23.55)		555,454 (14.89)	17,176 (27.79)	
Parity (*n*, %)			<0.001			<0.001
Nulliparous	2,085,449 (55.71)	61,670 (52.34)		2,081,289 (55.81)	25,327 (40.98)	
Parous	1,657,638 (44.29)	56,158 (47.66)		1,648,041 (44.19)	36,483 (59.02)	

Note: All variables are presented as *N* (%). All *P*<0.001. Baseline characteristics were stratified by menstrual cycle regularity — regular (24–38 days) versus irregular (<24 days, 38–53 days, or >53 days) — and by menstrual bleeding duration (menstrual period) — normal (3–7 days) versus abnormal (<3 or >7 days). All variables were classified into appropriate categories, and chi-square (χ^2) tests were used to calculate *P*.

Abbreviation: BMI=body mass index.

Preplanned Studies

Association Between Longitudinal Serum Ferritin and Gestational Diabetes Mellitus — Beijing, Shanxi, and Shandong PLADs, China, 2021–2024

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Summary

What is already known about this topic?

Elevated ferritin levels have been associated with increased insulin resistance, impaired insulin secretion, and heightened risk of type 2 diabetes in non-pregnant populations. However, the relationship between ferritin concentrations and the development of gestational diabetes mellitus (GDM) remains poorly understood.

What is added by this report?

This study identified a U-shaped association between serum ferritin measured at 11–13 weeks of gestation and GDM risk, demonstrating that both low and high ferritin levels predict increased GDM incidence. Additionally, elevated ferritin concentrations at 16–19 weeks and 24–27 weeks of gestation were independently associated with greater GDM risk.

What are the implications for public health practice?

These findings underscore the critical importance of monitoring serum ferritin throughout the first and second trimesters for early identification and prevention of GDM. Enhanced strategies are needed to improve clinical understanding and optimize the utility of ferritin assessment in prenatal care.

ABSTRACT

Introduction: The influence of serum ferritin on gestational diabetes mellitus (GDM) development remains unclear. This study evaluated associations between longitudinal serum ferritin measurements in the first and second trimesters and GDM risk.

Methods: This multicenter, prospective cohort study enrolled participants from four hospitals across Beijing Municipality, and Shanxi and Shandong provinces in China between July 2021 and June 2024. Participants were stratified into tertiles based on serum ferritin concentrations measured at 11–13, 16–19, and 24–27 weeks' gestation. Poisson regression and restricted cubic spline models were employed to examine associations between serum ferritin and GDM.

Results: Among 6,614 participants, 1,427 (21.6%) developed GDM. At 11–13 weeks' gestation, a U-shaped relationship between serum ferritin and GDM was identified ($P_{non\text{-}linear}$=0.008), demonstrating that both the lowest [risk ratio (*RR*): 1.31; 95% confidence interval (*CI*): 1.05, 1.63] and highest tertiles (*RR*: 1.33; 95% *CI*: 1.07, 1.66) were associated with elevated GDM risk after adjusting for demographic, socioeconomic, and clinical confounders. Women in the highest tertile of serum ferritin at 16–19 weeks' (*RR*: 1.28; 95% *CI*: 1.03, 1.58) and 24–27 weeks' gestation (*RR*: 1.18; 95% *CI*: 1.03, 1.35) had significantly greater GDM risk compared with the medium tertile.

Conclusion: Serum ferritin concentrations in the first and second trimesters were independently associated with GDM risk. Enhanced strategies are needed to improve understanding and clinical utility of serum ferritin measurements for early identification and prevention of GDM.

Gestational diabetes mellitus (GDM) has emerged as a major health concern during pregnancy worldwide. The prevalence of GDM has increased steadily over recent decades; by 2024, its global prevalence was estimated at 15.6%, with China reporting 15.7% (*1*). In the short term, GDM contributes to numerous adverse pregnancy complications and outcomes, including preeclampsia, cesarean delivery, shoulder dystocia, macrosomia, and neonatal hypoglycemia. Long-term consequences extend to both mothers and offspring, who face elevated risks of obesity, type 2 diabetes, and cardiovascular disease later in life (*2*).

Iron serves as an essential trace element for various life-sustaining processes, including hematopoiesis, oxygen transport, cell proliferation, and iron deficiency

(*3*). Iron deficiency affects an estimated 45% of pregnant women in well-resourced countries and 80% in low- and middle-income countries, increasing the risk of adverse maternal and neonatal outcomes such as anemia, gestational hypertension, preterm birth, and low birth weight (*3*–*4*). Conversely, accumulating evidence indicates that elevated iron storage is associated with enhanced insulin resistance, reduced insulin secretion, and higher risk of type 2 diabetes in non-pregnant populations (*3*). However, the influence of iron storage across different trimesters on GDM occurrence remains unclear. Ferritin is widely recognized as the primary indicator of iron status in epidemiological studies, as it represents the stable storage form of iron in humans. Therefore, this study aimed to prospectively evaluate the magnitude and shape of associations between serum ferritin levels in the first and second trimesters and GDM risk.

This multicenter, prospective cohort study was conducted at four hospitals across Beijing Municipality, Shanxi Province, and Shandong Province in China between July 2021 and June 2024. Women at 11–13 weeks of gestation receiving antenatal care at these four hospitals were enrolled. Inclusion criteria required participants to be aged ≥18 years and to intend to receive routine antenatal care and delivery at the study hospitals. Exclusion criteria included severe chronic diseases and/or serious mental illnesses before pregnancy. The study was approved by the institutional review board of Peking University First Hospital, and all participants provided written informed consent. At enrollment, a well-trained investigator conducted a face-to-face interview with each participant using a structured questionnaire to collect demographic characteristics, lifestyle behaviors, and medical and obstetric history. Participants were followed up at 16–19, 24–27, 32–35, and 36–40 weeks of gestation. A total of 8,091 pregnant women were recruited. After excluding women diagnosed with anemia (*n*=319), diabetes (*n*=49), or hypertension before pregnancy (*n*=38); those with twin or multiple pregnancies (*n*=36); those lost to follow-up (*n*=212); those with spontaneous/induced abortions or stillbirths (*n*=124); and those missing all three serum ferritin measurements at 11–13, 16–19, and 24–27 weeks of gestation (*n*=1,012), the current analysis included 6,614 pregnant women (Supplementary Figure S1, available at https://weekly.chinacdc.cn/). Serum ferritin levels at 11–13, 16–19, and 24–27 weeks of gestation were extracted from medical records and divided into three groups according to corresponding tertiles. Serum ferritin was measured using chemiluminescent microparticle immunoassay. All laboratory tests were performed according to standardized protocols and underwent regular quality control oversight by the National Center for Clinical Laboratories. GDM was diagnosed based on the International Association of Diabetes and Pregnancy Study Groups criteria (*5*), which recommend diagnosis when any one of the following plasma glucose values is met or exceeded during the 75g oral glucose tolerance test at 24–28 weeks of gestation: 5.1 mmol/L for fasting, 10.0 mmol/L at 1 hour, and 8.5 mmol/L at 2 hours. Pre-pregnancy body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters, measured at the first antenatal visit.

Baseline characteristics are presented as numbers and frequencies for categorical variables and as medians with interquartile ranges (IQRs) for continuous variables. Mann-Whitney U tests and chi-square tests were used to compare skewed continuous variables and categorical variables, respectively. We conducted Poisson regression models to estimate risk ratios (*RR*s) and 95% confidence intervals (*CI*s) for GDM across tertiles of serum ferritin measured at 11–13, 16–19, and 24–27 weeks of gestation. The middle tertile of serum ferritin served as the reference group in all analyses. Models were adjusted for demographic and socioeconomic characteristics, including maternal age, education level, employment status, average monthly household income, and ethnicity. Subsequent models incorporated additional adjustments for pre-pregnancy BMI, alcohol consumption during pregnancy, smoking status before pregnancy, passive smoking exposure during pregnancy, parity, and iron supplementation. We further employed restricted cubic spline (RCS) models to examine the dose-response relationship between serum ferritin at 11–13, 16–19, and 24–27 weeks of gestation and GDM risk, with the median serum ferritin value as the reference point and 4 knots positioned at the 5th, 35th, 65th, and 95th percentiles of the distribution. Statistical significance was defined as $P<0.05$, and all P values were two-sided. All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

Among the 6,614 pregnant women enrolled, 1,427 (21.6%) developed GDM. The median (IQR) serum ferritin concentrations were 48.6 (27.5, 77.0), 40.2

(23.1, 66.1), and 21.4 (13.7, 33.1) μg/L at 11–13, 16–19, and 24–27 weeks of gestation, respectively (Supplementary Table S1, available at https://weekly.chinacdc.cn/). Women with GDM demonstrated significantly higher serum ferritin levels at both 16–19 weeks [43.1 (23.7, 73.4) *vs*. 39.4 (23.0, 64.8) μg/L, *P*=0.008] and 24-27 weeks of gestation [22.7 (14.5, 36.7) *vs*. 21.1 (13.5, 32.3) μg/L, *P*<0.001] compared to non-GDM counterparts (Supplementary Table S1). At 11-13 weeks of gestation, GDM rates exhibited a U-shaped pattern across ferritin tertiles, with elevated rates in both the lowest and highest tertiles compared to the medium tertile (Tertile 1 *vs*. Tertile 2 *vs*. Tertile 3: 21.1% *vs*. 16.5% *vs*. 21.7%, *P*=0.012). In contrast, at 16-19 weeks (18.9% *vs*. 18.7% *vs*. 23.7%, *P*=0.018) and 24-27 weeks of gestation (20.7% *vs*. 21.4% *vs*. 25.6%, *P*<0.001), the highest ferritin tertile demonstrated the greatest GDM rates (Supplementary Table S2, available at https://weekly.chinacdc.cn/). Compared to women without GDM, participants with GDM were significantly older, had higher pre-pregnancy BMI and average household income, exhibited higher rates of Han ethnicity and iron supplementation, and were less likely to be employed or nulliparous (all *P*<0.05; Table 1).

At 11–13 weeks of gestation, women in both the lowest (crude *RR*: 1.28; 95% *CI*: 1.03, 1.60; adjusted *RR*: 1.31; 95% *CI*: 1.05, 1.63) and highest tertiles (crude *RR*: 1.32; 95% *CI*: 1.06, 1.64; adjusted *RR*: 1.33; 95% *CI*: 1.07, 1.66) demonstrated significantly increased GDM risk in both unadjusted and adjusted models compared with the medium tertile. At 16–19 weeks of gestation, women in the highest serum ferritin tertile exhibited a 1.28-fold elevated risk of GDM (*RR*: 1.28; 95% *CI*: 1.03, 1.58) after full adjustment. Similarly, at 24–27 weeks of gestation, the highest tertile showed an adjusted *RR* of 1.18 (95% *CI*: 1.03, 1.35) for GDM compared with the medium tertile (Table 2). RCS analysis revealed a U-shaped association between serum ferritin at 11–13 weeks of gestation and GDM risk after adjusting for potential confounders ($P_{overall}$<0.001, $P_{non\text{-}linear}$=0.008), demonstrating that both lower and higher serum ferritin levels were associated with elevated GDM risk relative to the median value of 48.6 μg/L (Figure 1A). Furthermore, continuous positive associations were observed between serum ferritin at 16–19 weeks ($P_{overall}$<0.001, $P_{non\text{-}linear}$=0.265; Figure 1B) and 24–27 weeks of gestation ($P_{overall}$=0.001, $P_{non\text{-}linear}$=0.331; Figure 1C) and GDM risk.

DISCUSSION

This multicenter, prospective cohort study provides longitudinal evidence on serum ferritin levels measured at multiple time points during the first and second trimesters. Most notably, this study identified a U-shaped association between serum ferritin at 11–13 weeks of gestation and GDM risk — the first study to demonstrate this relationship in a Chinese population. Additionally, we found that elevated ferritin levels at both 16–19 and 24–27 weeks of gestation were independently associated with increased GDM risk.

A key finding of this study was the U-shaped relationship between serum ferritin at 11–13 weeks of gestation and GDM, indicating that both lower and higher ferritin concentrations were associated with elevated GDM risk. Supporting our findings, a previous prospective study in Anhui province, China, reported a similar U-shaped relationship between first-trimester serum iron — another important indicator of iron status — and GDM risk (*6*). Earlier case-control studies in U.S., Danish, and Chinese populations with relatively small sample sizes revealed that excessive first-trimester ferritin levels were significantly associated with higher GDM risk, while several larger prospective and retrospective cohort studies demonstrated positive associations between first-trimester ferritin and GDM (*3*,*7*–*8*). However, the relationship between lower ferritin levels and GDM has received insufficient attention. To our knowledge, this represents the first prospective cohort study to demonstrate a U-shaped association between first-trimester serum ferritin and GDM risk in a Chinese population, contributing to a more comprehensive understanding of the ferritin-GDM relationship.

Our findings also demonstrated that higher ferritin levels at 16–19 and 24–27 weeks of gestation were independently associated with increased GDM risk, consistent with a prior meta-analysis showing that the highest ferritin category in the second trimester was associated with a 79% increase in GDM risk compared with the lowest category (*9*). Supporting our results, a prospective cohort study of central Chinese women reported that elevated ferritin concentrations around 16 weeks of gestation were independently associated with higher GDM risk (*10*). Similarly, a recent retrospective study of western Chinese women indicated that GDM patients exhibited higher ferritin levels than controls in the second trimester (*11*). Iron overload may explain the relationship between elevated serum ferritin during pregnancy and GDM through

TABLE 1. Baseline characteristics of participants with and without gestational diabetes mellitus.

Characteristics	Total (*n*=6,614)	GDM (*n*=1,427)	Non-GDM (*n*=5,187)	*P*
Maternal age, year, median (IQR)	31 (28,34)	32 (29,35)	31 (28,34)	<0.001
Prepregnancy body mass index, kg/m^2, median (IQR)	21.97 (20.03, 24.35)	22.95 (20.75, 25.29)	21.67 (19.84, 24.03)	<0.001
Education, *n* (%)				0.817
Junior school and below	246 (3.7)	50 (3.5)	196 (3.8)	
Senior high school	493 (7.5)	103 (7.2)	390 (7.5)	
College or graduate school	5,875 (88.8)	1,274 (89.3)	4,601 (88.7)	
Employment, *n* (%)				0.013
Employed	5,782 (87.4)	1,220 (85.5)	4,562 (88.0)	
Unemployed	832 (12.6)	207 (14.5)	625 (12.0)	
Average household income per month, CNY, *n* (%)				<0.001
<3,000	226 (3.4)	39 (2.7)	187 (3.6)	
3,000 to <5,000	701 (10.6)	121 (8.5)	580 (11.2)	
5,000 to <10,000	2,099 (31.7)	419 (29.4)	1,680 (32.4)	
≥10,000	3,588 (54.3)	848 (59.4)	2,740 (52.8)	
Ethnicity				0.023
Han	6,377 (96.4)	1,390 (97.4)	4,987 (96.1)	
Others	237 (3.6)	37 (2.6)	200 (3.9)	
Drinking during pregnancy, *n* (%)				0.167
No	6,127 (92.6)	1,334 (93.5)	4,793 (92.4)	
Yes	487 (7.4)	93 (6.5)	394 (7.6)	
Smoking before pregnancy, *n* (%)				0.730
No	6,510 (98.4)	1,406 (98.5)	5,104 (98.4)	
Yes	104 (1.6)	21 (1.5)	83 (1.6)	
Passive smoking during pregnancy, *n* (%)				0.481
No	6,119 (92.5)	1,314 (92.1)	4,805 (92.6)	
Yes	495 (7.5)	113 (7.9)	382 (7.4)	
Parity, *n* (%)				0.018
0	4,833 (73.1)	1,003 (70.3)	3,830 (73.8)	
1	1,623 (24.5)	391 (27.4)	1,232 (23.8)	
≥2	158 (2.4)	33 (2.3)	125 (2.4)	
Iron supplementation, *n* (%)				0.007
No	4,223 (63.8)	868 (60.8)	3,355 (64.7)	
Yes	2,391 (36.2)	559 (39.2)	1,832 (35.3)	

Note: Data are presented as median (interquartile range) or *n* (%).
Abbreviation: GDM=gestational diabetes mellitus; IQR=interquartile range; CNY=Chinese Yuan.

multiple pathways: inducing hepatic and peripheral insulin resistance, causing β-cell injury and apoptosis, heightening oxidative stress and inflammatory responses, and impairing insulin signaling pathways and hepatocyte insulin uptake (*3*). Conversely, iron deficiency may contribute to GDM by increasing lipogenic gene expression and altering lipid profiles, which could partially promote hyperglycemia (*12*). Additionally, serum ferritin during pregnancy is influenced by dietary patterns, particularly heme iron intake, which has been significantly associated with increased GDM risk (*13*). Future mechanistic research is needed to elucidate the precise pathways through which serum ferritin in the first and second trimesters affects GDM development.

These findings have important public health and clinical implications. The significant association between serum ferritin in the first and second trimesters and GDM risk supports the potential utility of ferritin monitoring for early identification and

TABLE 2. Risk ratios and 95% *CI*s of gestational diabetes mellitus according to tertiles of serum ferritin.

Serum ferritin	Case/non-case	Model 1		Model 2		Model 3	
		RR (95% *CI*)	*P*	*RR* (95% *CI*)	*P*	*RR* (95% *CI*)	*P*
11–13 weeks' gestation							
Tertile 1	179/669	**1.28 (1.03, 1.60)**	**0.028**	**1.28 (1.03, 1.60)**	**0.029**	**1.31 (1.05, 1.63)**	**0.018**
Tertile 2	140/710	Reference		Reference		Reference	
Tertile 3	184/664	**1.32 (1.06, 1.64)**	**0.014**	**1.34 (1.07, 1.66)**	**0.010**	**1.33 (1.07, 1.66)**	**0.010**
16–19 weeks' gestation							
Tertile 1	157/673	1.01 (0.81, 1.26)	0.918	1.02 (0.82, 1.27)	0.868	1.05 (0.84, 1.31)	0.677
Tertile 2	155/674	Reference		Reference		Reference	
Tertile 3	196/632	**1.27 (1.03, 1.56)**	**0.028**	**1.29 (1.04, 1.59)**	**0.019**	**1.28 (1.03, 1.58)**	**0.023**
24–27 weeks' gestation							
Tertile 1	389/1,490	0.97 (0.84, 1.11)	0.641	0.96 (0.83, 1.10)	0.531	0.97 (0.84, 1.11)	0.639
Tertile 2	400/1,469	Reference		Reference		Reference	
Tertile 3	479/1,390	**1.20 (1.05, 1.37)**	**0.008**	**1.21 (1.06, 1.38)**	**0.005**	**1.18 (1.03, 1.35)**	**0.014**

Abbreviation: *CI*=confidence interval; *RR*=risk ratio.

Note: Values in bold are statistically significant. Values represent risk ratios with 95% *CI*s. Model 1 presents unadjusted estimates. Model 2 were adjusted for demographic and socioeconomic characteristics, including maternal age, education level, employment status, average monthly household income, and ethnicity. Model 3 incorporates additional adjustments for pre-pregnancy body mass index, alcohol consumption during pregnancy, smoking status before pregnancy, passive smoking exposure during pregnancy, parity, and iron supplementation.

prevention of GDM. Our results suggest that serum ferritin measurement at 11–13 weeks of gestation should be incorporated into routine prenatal care, with pregnant women exhibiting either lower or higher levels undergoing enhanced glycemic screening before 24 weeks of gestation. Furthermore, iron supplementation during pregnancy should be individualized based on serum ferritin levels to prevent both deficiency and excess. Comprehensive screening strategies for serum ferritin during pregnancy are necessary to detect iron deficiency and overload, thereby optimizing the balance between the benefits and risks of iron supplementation.

This study has several limitations. First, we measured only serum ferritin as an indicator of iron stores and did not assess other markers such as serum iron and transferrin receptor, although serum ferritin is considered the preferred indicator of iron storage. Second, because serum ferritin levels can increase during acute inflammation and infections, the absence of inflammatory markers prevented us from examining how these factors might influence the association between serum ferritin and GDM. Third, we did not collect data on the dosage and duration of iron supplementation, limiting our ability to assess how these factors might modify GDM risk. Fourth, participants were recruited from four tertiary hospitals, which may not represent the general pregnant population in China. Therefore, multi-center, population-based studies are needed to validate these findings.

In conclusion, we identified a U-shaped association between first-trimester serum ferritin and GDM risk, and demonstrated that elevated second-trimester serum ferritin was independently associated with increased GDM risk. These findings underscore the need for strategies to enhance understanding and clinical application of serum ferritin measurements in the early identification and prevention of GDM.

Conflicts of interest: No conflicts of interest.

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Ethical statement: Approval by the institutional review board of Peking University First Hospital (2018[267]). All participants provided written informed consent prior to enrollment.

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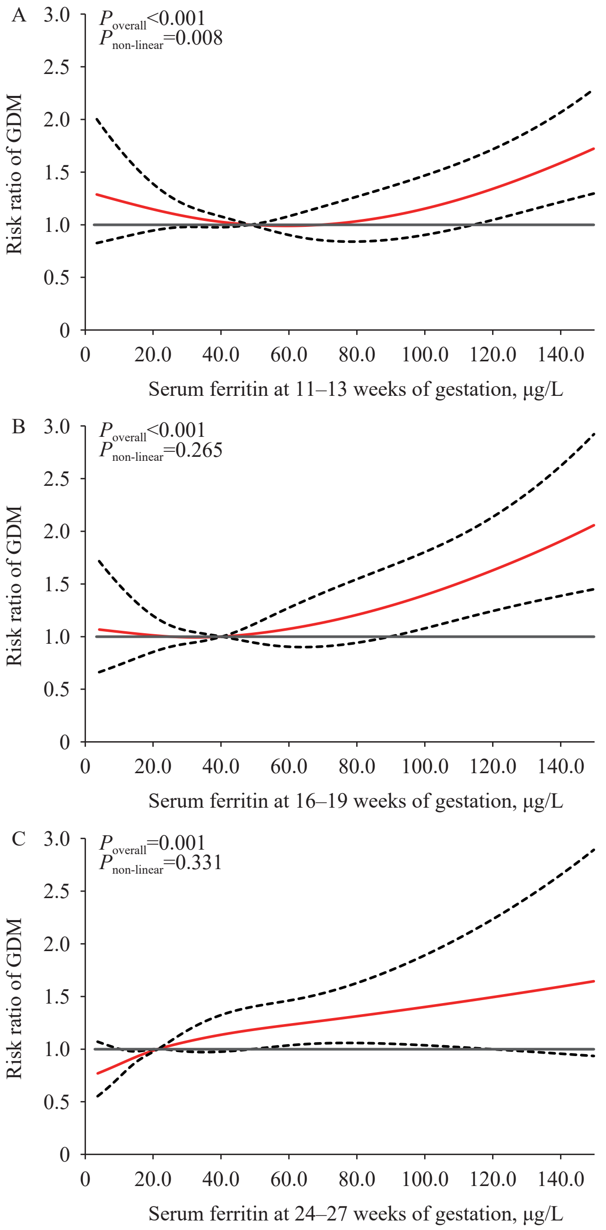

FIGURE 1. Risk ratios and 95% confidence intervals for the association between serum ferritin at 11–13 weeks; (A) 16–19 weeks, (B) and 24–27 weeks of gestation, (C) with GDM.

Abbreviation: GDM=gestational diabetes mellitus.

Note: Models were adjusted for maternal age, education level, employment status, average monthly household income, ethnicity, pre-pregnancy body mass index, alcohol consumption during pregnancy, smoking status before pregnancy, passive smoking exposure during pregnancy, parity, and iron supplementation.

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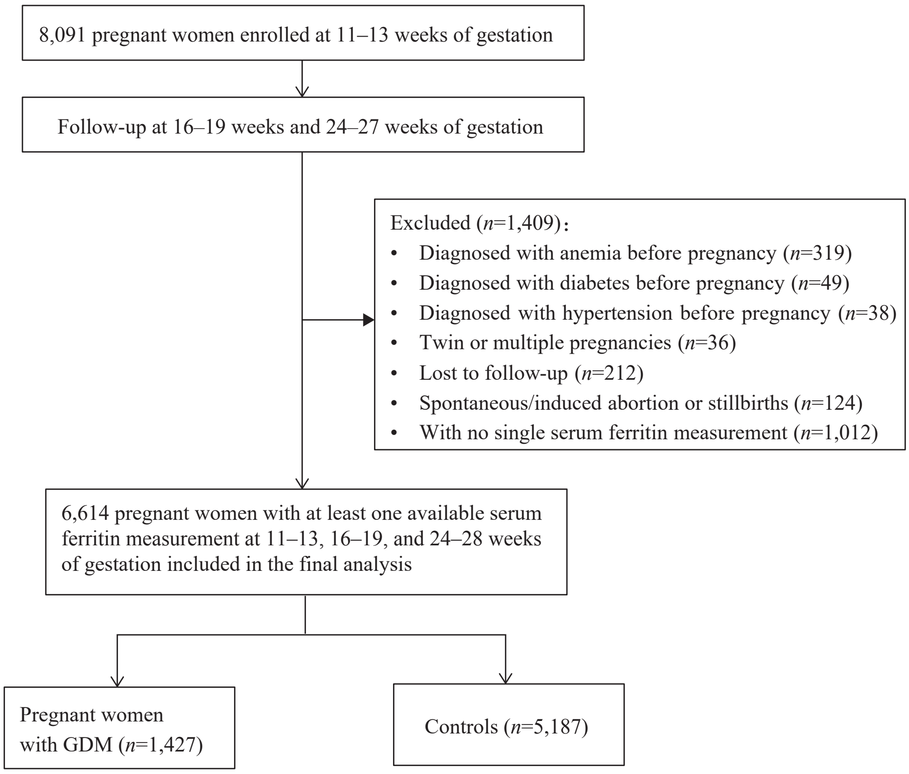
SUPPLEMENTARY MATERIALS



SUPPLEMENTARY FIGURE S1. Flowchart of the study.

SUPPLEMENTARY TABLE S1. Serum ferritin according to gestational diabetes mellitus.

Serum ferritin	Total	GDM	Non-GDM	*P*
11–13 weeks' gestation	48.6 (27.5, 77.0)	49.2 (26.8, 83.1)	48.5 (27.8, 75.1)	0.284
16–19 weeks' gestation	40.2 (23.1, 66.1)	43.1 (23.7, 73.4)	39.4 (23.0, 64.8)	0.008
24–27 weeks' gestation	21.4 (13.7, 33.1)	22.7 (14.5, 36.7)	21.1 (13.5, 32.3)	<0.001

Note: Data are presented as median (interquartile range).
Abbreviation: GDM=gestational diabetes mellitus.

SUPPLEMENTARY TABLE S2. Distribution of gestational diabetes mellitus according to tertiles of serum ferritin.

Serum ferritin	GDM	Non-GDM	*P*
11–13 weeks' gestation			0.012
Tertile 1 (≤33.9 μg/L)	179 (21.1)	669 (78.9)	
Tertile 2 (34.0–67.1 μg/L)	140 (16.5)	521 (83.5)	
Tertile 3 (>67.1 μg/L)	184 (21.7)	664 (78.3)	
16–19 weeks' gestation			0.018
Tertile 1 (≤28.7 μg/L)	157 (18.9)	673 (81.1)	
Tertile 2 (28.8–56.5 μg/L)	155 (18.7)	674 (81.3)	
Tertile 3 (>56.5 μg/L)	196 (23.7)	632 (76.3)	
24–27 weeks' gestation			<0.001
Tertile 1 (≤16.0 μg/L)	389 (20.7)	1490 (79.3)	
Tertile 2 (16.1–28.4 μg/L)	400 (21.4)	1469 (78.6)	
Tertile 3 (>28.4 μg/L)	479 (25.6)	1390 (74.4)	

Note: Data are presented as *n* (%).
Abbreviation: GDM=gestational diabetes mellitus.

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