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BIG DATA FOR WOMEN'S HEALTH ISSUE

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Cover Image: adapted from the United Nations, https://www.unescap.org/news/asia-and-pacific-marks-international-womens-day-2024.

This week's issue was organized by Guest Editor Linhong Wang.

Foreword

Using Healthcare Big Data Analytics to Improve Women's Health: Benefits, Challenges, and Perspectives

Heling Bao[1]; Hui Liu[1,#]; Linhong Wang[2,3,#]

Women's health is of paramount importance for the attainment of the Sustainable Development Goals (SDGs) and Healthy China 2030, encompassing reproductive health and physical and mental well-being. This multifaceted concept of health is integral to the health of maternal, newborn, child, adolescent, and adult populations (*1–3*). Despite China's substantial achievements in diminishing maternal and child mortality rates over the last thirty years, there remain several under-addressed aspects of women's health, including preconception and menopause care, adolescent health, reproductive cancers, sexually transmitted infections, and mental health (*4–5*). Additionally, sociocultural determinants such as societal norms, income disparities, power dynamics, and prejudiced attitudes from family and society can disproportionately impact women's health outcomes. The scarcity of healthcare resources has led to a dearth of research on women's health, resulting in limited evidence-based insights. This gap in knowledge hinders the formulation and execution of effective health policies and interventions.

This special issue comprises a collection of articles emphasizing the application of big data analytics in two primary domains: disease monitoring and risk factor identification. These studies utilized data drawn from population-wide screening and surveillance initiatives in actual clinical environments. Each piece of research incorporated, to varying degrees, the principles and techniques of healthcare big data analytics, specifically within the sphere of women's health. Liu et al. explored fluctuations in anemia prevalence across various levels of severity among women aged 18 years and above in 2021, utilizing a vast screening database. This database comprises data on over six million women from approximately 70% of the prefecture-level cities within all 31 provincal-level administrative divisions (PLADs) of Chinese mainland (*6*). Sun et al. scrutinized the incidence and mortality rates associated with five types of female genital cancers in 2022, examining their evolutionary trends (*7*). Due to the exponential expansion of China's cancer registry data across volume, diversity, and speed, there's a burgeoning necessity for advanced big data analytics. Yang et al. uncovered a correlation between preterm births and preconception alanine aminotransferase concentrations in a cohort of over five million women of childbearing age, drawn from the National Free Preconception Checkups Project — a database that stands as China's most extensive in terms of pregnancy-related data (*8*). Zhang et al. investigated the occurrence of multiple reproductive tract infections and their links to HPV infection, integrating data from various clinical databases across six hospitals (*9*). This special issue aims to underscore the transformative power of healthcare big data and its associated technologies in enhancing women's health outcomes.

While the use of big data in women's health is on the rise in China, it remains in a nascent stage, and evidence to substantiate the impact of big data analytics on enhancing women's health outcomes is scarce (*10*). At the time of preparing this issue, a search in PubMed yielded 11,598 articles with "big data" in the title over the past five years, of which merely 10% pertained directly to women's health. It is crucial to acknowledge and address the principal challenges hindering the application of big data in this field. Common obstacles mirror those encountered in other sectors, such as inconsistency in medical terminology, biased sampling and selection, confounding factors, and the tendency to overfit predictive models. Additionally, health professionals grapple with the surge of data in clinical settings and struggle to determine the optimal utilization of this information for guiding patient care. Furthermore, the sensitivity of women's status in social culture mandates careful consideration of privacy, consent, data security, and associated ethical and legal issues in the application of big data. Notably, current evidence, derived from studies employing risk models or observational approaches, indicates only a slight, if any, improvement in accuracy over traditional methods (*11*). Looking ahead, research predicated on big data should not only encompass women's health but also extend across the entire lifespan through more comprehensive data integration. Prioritizing the synthesis of evidence from big data analytics with clinical and population health practices is essential to truly advance women's health.

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[#] Corresponding authors: Hui Liu, liuhui@pumc.edu.cn; Linhong Wang, linhong@chinawch.org.cn.

[1] Institute of Medical Information, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China; [2] National Center for Chronic and Non-communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China; [3] Women's Health Care Branch, Chinese Preventive Medicine Association, Beijing, China.

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Hui Liu
Professor and Director of the Institute of Medical Information, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

Linhong Wang
Professor and Chief Expert of the National Center for Chronic and Noncommunicable Disease Control and Prevention, China CDC
Women's Health Care Branch, Chinese Preventive Medicine Association, Beijing, China.

Preplanned Studies

Variations in the Prevalence of Anemia of Varying Severity Among Urban Non-Pregnant Women — China, 2021

Xiaoxi Liu[1,&]; Bo Wang[2,3,4,&]; Sailimai Man[2,3,5,6,&]; Heling Bao[1]; Yuanyuan Huang[1]; Canqing Yu[2,4,5,6]; Jun Lyu[2,4,5,6]; Linhong Wang[7,#]; Liming Li[2,4,5,6,#]; Hui Liu[1,#]

Summary

What is already known about this topic?

Anemia is a significant public health issue affecting women globally. Prior studies in China predominantly concentrated on anemia in pregnant or reproductive-age women, leaving a gap in available data concerning anemia in non-pregnant women of all age groups in China.

What is added by this report?

In 2021, the prevalence of anemia and moderate to severe anemia among women aged 18 years and older in urban China was 14.8% and 5.7%, respectively. Anemia prevalence exhibited significant variations based on factors such as age, body mass index (BMI), geographic location, and socioeconomic status.

What are the implications for public health practice?

The strategy for addressing anemia should account for non-pregnant women aged 30–49 years and those aged 70 years and older, taking into consideration differences related to socioeconomic development and geography.

Anemia represents a significant global public health concern, being identified as the third most prevalent cause of disability worldwide according to the Global Burden of Disease Study (*1*). Women are disproportionately affected by anemia compared to men. In China, the emphasis of governmental and research efforts on anemia has predominantly centered on pregnant women and those of reproductive age, with insufficient attention given to anemia in other groups, such as elderly women. Previous studies have primarily focused on anemia prevalence among Chinese women, with a lack of comprehensive data for non-pregnant women across all age groups (*2*–*4*). This study aimed to assess the prevalence of anemia by severity among non-pregnant women in urban areas of China at both national and provincial levels, while also evaluating the socioeconomic disparities in anemia prevalence. The research included a total of 6,034,533 non-pregnant women aged 18 years and above from all 31 provincial-level administrative divisions (PLADs) in China's urban regions between January 1, 2021, and December 31, 2021. Findings revealed that 14.8% of non-pregnant women aged 18 years and above in urban China experienced anemia, with 5.7% classified as having moderate to severe anemia. Anemia prevalence exhibited significant variations correlated with factors such as age, body mass index (BMI), geographic location, and economic status. It is imperative for comprehensive anemia intervention strategies to specifically target non-pregnant women aged 30–49 years and those aged 70 years and above, adapting to the varying levels of socioeconomic development and geographical disparities.

The data for this study were obtained from the Meinian Healthcare Group system, which, as China's largest health exam chain, offers extensive services with facilities in 231 prefecture-level cities across 31 PLADs (*5*). The population investigated was comprised primarily of employees (70%) and non-working urban residents. Standardized procedures were employed to collect socio-demographic data, physical measurements, and biochemical indices from venous blood samples. Within the period from January 1, 2021, to December 31, 2021, a total of 6,034,533 non-pregnant women aged 18 years and above were eligible for and included in the analysis. The World Health Organization (WHO) defines anemia in non-pregnant women aged 15 years and over as a hemoglobin concentration below 120.0 g/L. Levels ranging from 110.0 to 119.0 g/L are classified as mild anemia, 80.0–109.0 g/L as moderate, and below 80.0 g/L as severe (*6*). Hemoglobin levels were adjusted for the mean altitude of the prefecture-level cities. Socioeconomic factors were represented by the city-level Engel coefficient and gross domestic product (GDP), which were categorized into quartiles and merged with individual participant data. For analytical purposes, China's geographic regions were segmented

into six areas: the northern, eastern, central, southwestern, northwestern, and northeastern.

Using the sample structure as a reference and adjusting for population distribution by PLAD and age, we calculated standardized prevalence rates and their 95% confidence intervals (*CI*s). We employed the χ^2 test with the Rao-Scott correction to assess differences across groups. To explore the relationship between anemia and various socioeconomic factors, we adjusted for age, BMI, history of cesarean delivery, GDP, systolic blood pressure, total cholesterol, hyperuricemia, glomerular filtration rate, and geographic region using multivariable logistic regression that accounted for clustering effects. SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses. We conducted two-sided statistical tests, with a *P*-value of less than 0.05 considered to indicate statistical significance. The Peking University Institutional Review Board (IRB-0000152-19077) provided ethical approval for this study.

The average age of eligible women was 48.4 years [standard deviation (SD)=14.5], with 2,834,987 aged 50 years and older. Among them, 43.1% were overweight or obese, 3.9% had a history of cesarean delivery, and 59.8% lived in eastern or central China.

In 2021, an estimated 14.8% (95% *CI*: 13.9%, 15.5%) of non-pregnant women were found to have anemia, with 5.7% (95% *CI*: 5.4%, 6.0%) experiencing moderate to severe anemia (Table 1). The prevalence of anemia varied based on factors such as age and region. Urban non-pregnant women aged 40–49 years showed the highest prevalence of moderate to severe anemia at 10.6% (95% *CI*: 10.1%, 11.1%), followed by those who had a prior cesarean delivery (8.4%, 95% *CI*: 7.7%, 9.1%), were underweight (6.6%, 95% *CI*: 6.1%, 7.0%), and resided in the northwest region (6.3%, 95% *CI*: 5.5%, 7.1%).

The prevalence of anemia varied among PLADs, ranging from 5.6% to 38.0% (Figure 1), with the highest rates observed in Xizang, Guangxi, and Hubei PLADs. Moderate to severe anemia prevalence ranged from 3.5% to 15.6%. Anemia prevalence by PLAD exhibited distinct patterns across various age groups of women.

Multivariable logistic regression analysis revealed that individuals aged 30–49 and those 70 years and older, along with those who are underweight, were significantly more likely to have anemia when compared to their respective reference groups. Additionally, residents in the central, eastern, northern, and northwestern regions of China displayed a higher prevalence of anemia (Table 2). Women residing in regions with the lowest GDP had an increased likelihood of moderate to severe anemia, with odds ratios (*OR*) of 1.18 (95% *CI*: 1.04, 1.34) for both the age groups of 18–49 years and those above 49 years. In separate analyses, urban non-pregnant women aged 18–49 living in the lowest GDP areas (*OR*=1.16, 95% *CI*: 1.03, 1.31), with a history of cesarean delivery (*OR*=1.06, 95% *CI*: 1.01, 1.12), and those who are obese (*OR*=1.03, 95% *CI*: 1.01, 1.06) were found to have a greater risk of moderate to severe anemia. For non-pregnant women aged 50 years and above, a lower Engel coefficient (*OR*=1.24, 95% *CI*: 1.05, 1.47) and being underweight (*OR*=1.71, 95% *CI*: 1.63, 1.79) were associated with an increased risk of anemia.

DISCUSSION

In 2021, the prevalence of anemia among non-pregnant, urban women in China was 14.8%. This rate aligns with the WHO's classifications as a mild public health concern (*6*). However, in certain demographics, such as non-pregnant women between the ages of 18 and 49, 9 PLADs exhibit anemia prevalence rates over 20%, indicating a moderate public health issue. Moreover, the incidence of moderate to severe anemia — which has substantial health and economic repercussions — stood at 5.7% among non-pregnant women. Prior research indicates that anemia prevalence is lower in urban women compared to their rural counterparts (*4*,*7*), suggesting that the anemia burden may be more pronounced across the broader population of non-pregnant women nationwide.

This study found that the prevalence of anemia in non-pregnant women varied by age, with the highest risk observed in the 40–49 year age group, followed by those aged ≥70 years, and then the 30–39 year age group. These findings suggest that women of reproductive age remain particularly vulnerable to anemia. The increased risk in women aged 40–49 may be attributed to menorrhagia common during the perimenopausal period, while the elevated risk in women aged ≥70 years could be related to the higher incidence of chronic diseases and inflammation accompanying aging (*6*,*8*–*10*). Consistent with other research, our study confirmed regional variations in anemia prevalence. Non-pregnant women in the central, eastern, northern, and northwestern regions of China were found to have a higher likelihood of

TABLE 1. Prevalence of anemia by severity among non-pregnant women in urban China, 2021.

Variable	Number (%)	Anemia (%, 95% *CI*)	*P* value	Moderate-severe anemia (%, 95% *CI*)	*P* value
Overall	6,034,533 (100.0)	14.8 (13.9, 15.5)		5.7 (5.4, 6.0)	
Age group (years)			<0.001		<0.001
18–29	554,856 (9.2)	13.4 (12.4, 14.3)		4.6 (4.3, 5.0)	
30–39	1,371,860 (22.7)	18.4 (17.5, 19.4)		7.7 (7.2, 8.1)	
40–49	1,272,830 (21.1)	21.3 (20.4, 22.3)		10.6 (10.1, 11.1)	
50–59	1,382,241 (22.9)	10.1 (9.4, 10.9)		3.4 (3.1, 3.6)	
60–69	930,278 (15.4)	8.5 (7.7, 9.3)		1.6 (1.4, 1.8)	
70+	522,468 (8.7)	13.8 (12.8, 14.8)		3.6 (3.2, 4.0)	
BMI			<0.001		<0.001
Underweight	253,928 (4.2)	16.7 (15.8, 17.6)		6.6 (6.1, 7.0)	
Normal	3,176,775 (52.6)	18.5 (17.3, 19.6)		6.4 (6.0, 6.7)	
Overweight	1,926,434 (31.9)	12.5 (11.9, 13.2)		5.0 (4.8, 5.3)	
Obesity	677,392 (11.2)	10.7 (10.1, 11.3)		4.5 (4.2, 4.7)	
History of cesarean delivery			<0.001		<0.001
Yes	232,645 (3.9)	18.5 (17.2, 19.9)		8.4 (7.7, 9.1)	
No	5,801,888 (96.1)	14.6 (13.8, 15.4)		5.6 (5.3, 5.9)	
GDP			0.016		0.108
Lowest	1,714,069 (28.4)	15.6 (13.9, 17.3)		6.2 (5.6, 6.9)	
Up to median	1,714,528 (28.4)	13.5 (12.3, 14.6)		5.5 (4.9, 6.0)	
Above median	1,165,930 (19.3)	13.9 (12.7, 14.9)		5.4 (4.8, 5.9)	
Highest	1,440,005 (23.9)	15.9 (14.4, 17.6)		5.8 (5.3, 6.3)	
Engel coefficient			0.950		0.420
Highest	2,020,415 (33.5)	15.1 (13.6, 16.6)		5.6 (5.0, 6.2)	
Above median	1,496,599 (24.8)	14.6 (12.6, 16.6)		5.4 (4.8, 6.1)	
Up to median	1,471,689 (24.4)	14.7 (13.4, 16.0)		5.9 (5.4, 6.4)	
Lowest	1,045,831 (17.3)	14.5 (13.4, 15.6)		6.1 (5.6, 6.7)	
Geographic region			<0.001		0.001
Northern	768,980 (12.7)	13.8 (12.4, 15.2)		6.1 (5.5, 6.7)	
Eastern	1,914,120 (31.7)	15.1 (13.9, 16.4)		5.8 (5.4, 6.2)	
Central	1,697,789 (28.1)	16.5 (15.3, 17.8)		6.2 (5.8, 6.6)	
Southwestern	785,872 (13.0)	13.5 (10.6, 16.5)		4.7 (3.4, 6.0)	
Northwestern	407,411 (6.8)	14.4 (11.9, 16.8)		6.3 (5.5, 7.1)	
Northeastern	460,362 (7.6)	10.5 (9.6, 11.5)		4.4 (4.2, 4.6)	

Note: hemoglobin concentration between 110.0 and 119.0 g/L was considered mild, 80–109 g/L as moderate, and lower than 80 g/L as severe.
Abbreviation: *CI*=confidential interval; BMI=body mass index; GDP=gross domestic product.

anemia compared to their counterparts in the northeastern region. Additionally, in the population aged 50 and above, the prevalence of anemia was notably higher in the southwestern than in the northeastern region, underscoring the significant impact of anemia in these regions. These regional disparities may be influenced by local characteristics, dietary practices, prevalence of chronic illnesses, and existing health interventions (*11*–*12*). In terms of body weight, being underweight was associated with an increased risk of anemia, while being overweight or obese appeared to be protective. This trend aligns with previous research, possibly because overweight and obese women may consume a high-energy diet that adequately supplies iron (*12*–*13*). Previous studies have reported inconsistent findings concerning the

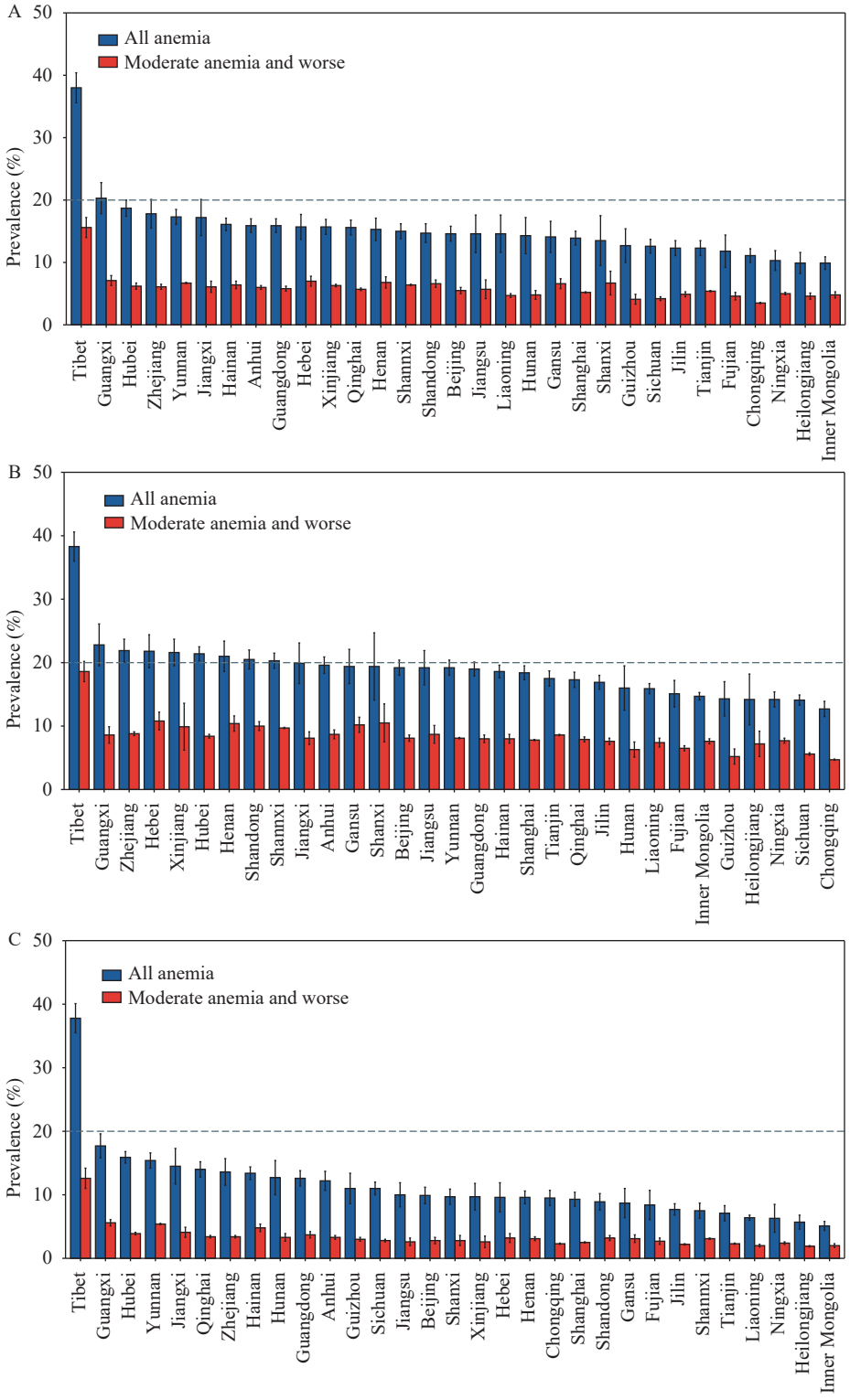

FIGURE 1. Regional disparities in the prevalence of anemia among non-pregnant women in urban China, standardized by age, 2021. (A) Anemia among all women; (B) Anemia among women aged 18–49; (C) Anemia among women aged 50 and over.

association between economic status and anemia in women (*2*,*11*). Our study revealed that residing in areas with the lowest GDP correlates with a heightened risk of moderate to severe anemia across various age groups among non-pregnant women.

This study is subject to some limitations. Its

TABLE 2. Multilevel logistic regression analysis for the factors associated with anemia prevalence among non-pregnant women in urban China, 2021.

Variable	Overall		18–49 years		50 years and above	
	Anemia	Moderate-severe anemia	Anemia	Moderate-severe anemia	Anemia	Moderate-severe anemia
	OR (95% *CI*)	*OR* (95% *CI*)	*OR* (95% *CI*)	*OR* (95% *CI*)	*OR* (95% *CI*)	*OR* (95% *CI*)
Age group (years)						
18–29	Reference	Reference				
30–39	1.54 (1.49, 1.59)**	1.74 (1.68, 1.81)**				
40–49	2.12 (2.03, 2.21)**	2.81 (2.68, 2.94)**				
50–59	1.05 (0.99, 1.11)	0.99 (0.94, 1.05)				
60–69	0.95 (0.87, 1.04)	0.50 (0.44, 0.56)**				
70+	1.60 (1.48, 1.73)**	1.07 (0.94, 1.21)				
BMI						
Underweight	1.12 (1.09, 1.16)**	1.04 (1.01, 1.08)*	1.02 (1.00, 1.04)*	0.96 (0.93, 0.98)*	1.71 (1.63, 1.79)**	1.72 (1.58, 1.87)**
Normal	Reference	Reference	Reference	Reference	Reference	Reference
Overweight	0.83 (0.81, 0.85)**	0.95 (0.93, 0.97)**	0.92 (0.90, 0.93)**	1.01 (0.99, 1.03)	0.73 (0.72, 0.75)**	0.83 (0.80, 0.86)**
Obese	0.76(0.73, 0.79)**	0.93 (0.90, 0.96)**	0.89 (0.86, 0.92)**	1.03 (1.01, 1.06)*	0.64 (0.61, 0.67)**	0.78 (0.74, 0.82)**
History of cesarean delivery						
Yes	1.04 (0.99, 1.09)	1.06 (1.01, 1.08)*	1.04 (1.00, 1.09)*	1.06 (1.01, 1.12)*	1.03 (0.96, 1.10)	1.07 (0.98, 1.17)
No	Reference	Reference	Reference	Reference	Reference	Reference
GDP						
Lowest	1.10 (0.94, 1.27)	1.18 (1.04, 1.34)*	1.10 (0.96, 1.2t6)	1.16 (1.03, 1.31)*	1.07 (0.89, 1.29)	1.22 (1.03, 1.45)*
Up to median	0.92 (0.79, 1.06)	1.01 (0.90, 1.15)	0.94 (0.93, 1.07)	1.01 (0.89, 1.15)	0.86 (0.71, 1.04)	1.03 (0.87, 1.22)
Above median	0.95 (0.82, 1.10)	1.04 (0.92, 1.18)	0.96 (0.84, 1.09)	1.02 (0.91, 1.15)	0.94 (0.78, 1.13)	1.08 (0.91, 1.28)
Highest	Reference	Reference	Reference	Reference	Reference	Reference
Engel coefficient						
Highest	1.03 (0.91, 1.17)	0.94 (0.84, 1.05)	0.94 (0.83, 1.06)	0.87 (0.78, 0.99)*	1.24 (1.05, 1.47)*	1.16 (0.98, 1.37)
Above median	1.06 (0.91, 1.24)	0.95 (0.84, 1.07)	0.98 (0.84, 1.14)	0.91 (0.80, 1.03)	1.23 (1.03, 1.47)*	1.10 (0.94, 1.28)
Up to median	1.06 (0.93, 1.20)	0.98 (0.87, 1.10)	1.02 (0.91, 1.14)	0.97 (0.86, 1.10)	1.15 (0.98, 1.36)	1.02 (0.87, 1.20)
Lowest	Reference	Reference	Reference	Reference	Reference	Reference
Geographic region						
Northern	1.34 (1.12, 1.60)*	1.30 (1.14, 1.47)**	1.25 (1.07, 1.46)*	1.23 (1.07, 1.41)*	1.44 (1.11, 1.87)**	1.45 (1.17, 1.79)*
Eastern	1.47 (1.27, 1.70)**	1.31 (1.20, 1.43)**	1.30 (1.15, 1.46)**	1.19 (1.10, 1.29)**	1.79 (1.46, 2.20)**	1.66 (1.42, 1.94)**
Central	1.58 (1.36, 1.84)**	1.36 (1.23, 1.49)**	1.32 (1.16, 1.51)**	1.18 (1.08, 1.29)**	2.11 (1.72, 2.59)**	1.96 (1.65, 2.31)**
Southwestern	1.29 (0.97, 1.71)	1.03 (0.77, 1.39)	1.01 (0.77, 1.33)	0.85 (0.65, 1.11)	1.82 (1.33, 2.49)**	1.57 (1.08, 2.28)*
Northwestern	1.32 (1.02, 1.72)*	1.30 (1.08, 1.57)**	1.24 (0.97, 1.60)	1.25 (1.04, 1.50)*	1.40 (1.02, 1.91)*	1.41 (1.11, 1.78)*
Northeastern	Reference	Reference	Reference	Reference	Reference	Reference

Note: hemoglobin concentration between 110.0 and 119.0 g/L was considered mild, 80–109 g/L as moderate, and lower than 80 g/L as severe.
Abbreviation: *OR*=odds ratio; *CI*=confidential interval; BMI=body mass index; GDP=gross domestic product.
* $P<0.05$; ** $P<0.01$.

predominantly urban participant base may lead to underestimating anemia prevalence among non-pregnant Chinese women, limiting a comprehensive understanding of their anemia status. Additionally, the cross-sectional design impedes establishing causal relationships between anemia risk and influencing factors. Furthermore, the absence of etiological data restricts the study's capability to offer specific intervention recommendations.

This research is the first to utilize extensive data to determine anemia prevalence among non-pregnant women in urban China, enhancing the estimate's reliability and representativeness. In conclusion, anemia is a significant public health concern among non-pregnant women of all ages in urban China. Intervention strategies should focus on high-risk groups. Particularly, priority should be given to the 9 PLADs where anemia prevalence exceeds 20%. A nationwide survey is essential to design customized interventions aimed at reducing anemia effectively.

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[#] Corresponding authors: Hui Liu, liuhui@pumc.edu.cn; Linhong Wang, linhong@chinawch.org.cn; Liming Li, lmlee@bjmu.edu.cn.

[1] Institute of Medical Information, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China; [2] Peking University Health Science Center Meinian Public Health Institute, Beijing, China; [3] Meinian Institute of Health, Beijing, China; [4] Peking University Center for Public Health and Epidemic Preparedness & Response, Beijing, China; [5] Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing, China; [6] Key Laboratory of Epidemiology of Major Diseases (Peking University), Ministry of Education, Beijing, China; [7] National Center for Chronic and Non-communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China.
[&] Joint first authors.

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Preplanned Studies

Maternal Preconception Serum Alanine Aminotransferase Levels and Risk of Preterm Birth among Reproductive-Aged Women — China, 2013–2017

Chuanyu Zhao[1,2,3,&]; Jiajing Jia[4,&]; Hanbin Wu[1,2]; Qin Xu[1,2]; Xinyi Lyu[1,2,3]; Meiya Liu[1,2]; Xuan Hu[1,2]; Jueming Lei[1,2]; Yuzhi Deng[1,2]; Yuan He[1,2,3]; Yuanyuan Wang[1,2,3]; Zuoqi Peng[1,2]; Ya Zhang[1,2]; Hongguang Zhang[1,2]; Qiaomei Wang[1,2]; Haiping Shen[1,2]; Yiping Zhang[1,2]; Donghai Yan[1,2]; Ying Yang[1,2,3,#]; Xu Ma[1,2,3,#]

Summary

What is already known about this topic?

The significance of maternal liver health concerning preterm birth (PTB) is well recognized; however, there is a gap in understanding the precise influence of preconception serum alanine aminotransferase (ALT) levels on the risk of PTB.

What is added by this report?

In this retrospective cohort study, a J-shaped relationship between preconception serum ALT levels and risk of PTB was observed, indicating that both significantly elevated and decreased ALT levels may contribute to the risk.

What are the implications for public health practice?

Maintaining optimal preconception serum ALT levels may reduce the risk of PTB, thereby informing specific preventive measures for women of reproductive age.

Preterm birth (PTB), defined as the delivery of an infant prior to 37 complete weeks of gestation, accounted for approximately 10.9% of all live births worldwide in 2019 and has emerged as the leading cause of neonatal and under-five mortality (*1*–*3*). Recently, maternal liver health has become a focus of interest, given its potential influence on PTB (*4*–*6*). Serum alanine aminotransferase (ALT), a critical biomarker for evaluating hepatocellular injury and liver dysfunction (*7*), suggests that regular monitoring and maintaining ALT levels within an appropriate range before and during pregnancy may enhance maternal health and decrease the likelihood of PTB. Current clinical references for ALT, however, are derived from a generalized population pool consisting of both sexes, raising the question of their validity for preconception women, a concern that lacks empirical support. In this study, we examined the link between preconception maternal serum ALT concentrations and PTB risk within a cohort of reproductive-aged Chinese women. The findings revealed that abnormal increases, as well as somewhat diminished levels, of preconception serum ALT are associated with PTB and its subcategories, presenting a non-linear, J-shaped correlation.

This retrospective cohort study was carried out by the National Free Preconception Checkups Project (NFPCP), a nationwide initiative offering complimentary preconception health services, including examinations, counseling, and post-conception outcome monitoring to couples of reproductive age aiming to start a family. Further specifics regarding the structure, management, and execution of the NFPCP have been documented in previous publications (*8*–*10*).

Between January 1, 2013, and December 31, 2016, a total of 5,817,003 Chinese women aged 20 to 49 who took part in the NFPCP successfully conceived within a year after their preconception examination. By December 31, 2017, all participants were followed up on their pregnancy outcomes. Exclusions were made for those with a history of multiparous pregnancies (n=433,212), non-viable births (such as fetal death, ectopic pregnancy, spontaneous abortion, included therapeutic or medical abortions) (n=21,720), or self-reported medication use (n=174,835). Individuals with missing preconception serum ALT values (n=17,414) or insufficient information on gestational weeks (n=10) were also removed from the study.

Experienced doctors conducted physical examinations and routine clinical laboratory measurements following standard guidelines. Venous blood samples, collected after an 8-hour fasting period, were stored at −30 °C and analyzed within 24 hours for ALT, blood glucose, and hepatitis B surface antigen (HBsAg). Serum ALT levels were analyzed using an automatic biochemical analyzer by measuring the

absorbance change at 340 nm following a substrate reaction with the serum.

The gestational age was determined by the interval in weeks between the date of the last menstrual period (LMP) adjusted by ultrasound examination and the delivery date. PTB was defined as live birth before completion of 37 weeks of gestation, with further classification into moderate to late preterm birth (MPTB, 32 to less than 37 weeks), very preterm birth (VPTB, 28 to less than 32 weeks), and extremely preterm birth (EPTB, less than 28 weeks) based on gestational age (*1*).

Baseline characteristics were presented as counts and percentages, means with standard deviations (SDs), or medians with interquartile ranges (IQRs). Group differences in ALT levels were analyzed using the χ^2 test, Fisher's exact test, or Kruskal-Wallis H test. The relationship between maternal preconception serum ALT levels and PTB was examined through restricted cubic spline (RCS) curves, with nonlinearities assessed using Wald statistics. ALT levels were categorized based on general thresholds (normal: ≤40 U/L; elevated: >40 U/L) and population-specific threshold ranges derived from RCS curves: <20 U/L, 20–40 U/L (reference range), and >40 U/L.

Logistic regression models were utilized to calculate odds ratios (*OR*s) and 95% confidence intervals (*CI*s), with and without adjusting for pre-selected covariates, to assess the relationship between maternal preconception serum ALT levels and the risk of PTB and its subtypes. The covariates used for adjustment are described in Supplementary Table S1 (available at https://weekly.chinacdc.cn/). Subgroup analyses were conducted to confirm the consistency of the association across different populations after controlling for multiple covariates. Statistical analyses were carried out using R software (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided, and a *P*-value <0.05 was considered statistically significant.

A total of 5,169,812 women were included in this cohort study, with an average age of 26.52 years (SD: 4.21) and a PTB incidence rate of 6.65% (343,992 events) (Figure 1). PTB rates across different serum ALT level groups — <20 U/L, 20–40 U/L, and >40 U/L — were 6.78% (218,403 events), 6.31% (106,062 events), and 7.38% (19,527 events), respectively, with the lowest rate observed in the 20–40 U/L group. Women with preconception ALT levels <20 U/L had a higher likelihood of being underweight [body mass index (BMI) <18.5 kg/m^2, *n* (%): 481,090 (14.92%) *vs.* 189,707 (11.28%)], whereas those with ALT levels >40 U/L were more inclined to be overweight or obese [BMI of 24.0–27.9 kg/m^2: 46,612 (17.61%) *vs.* 232,028 (13.80%); BMI ≥28 kg/m^2: 16,438 (6.21%) *vs.* 57,561 (3.42%)] (*P*<0.001) (Table 1).

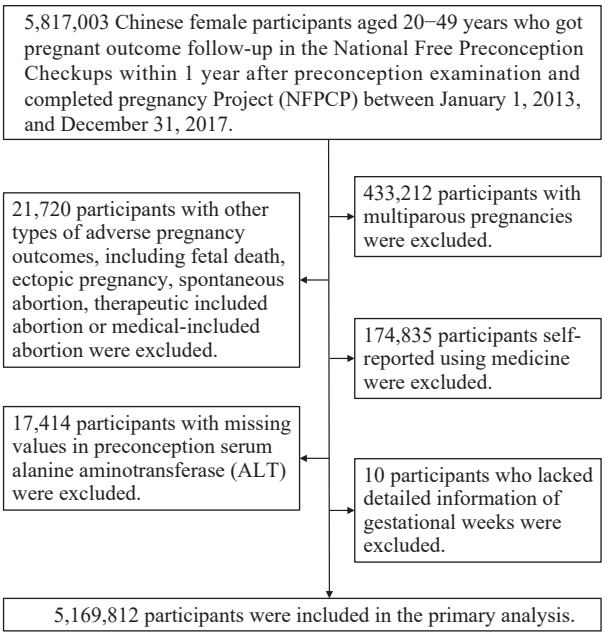

FIGURE 1. Flowchart illustrating the study population of reproductive-aged women in China from 2013 to 2017.

The dose-response relationship between preconception serum ALT levels in mothers and various categories of PTB is delineated in Figure 2, which suggests a J-shaped association. Statistically significant nonlinear effects were observed for all categories of PTB, including MPTB, VPTB, and EPTB, with chi-square values and *P*-values indicating nonlinearity as follows: for PTB (χ^2=613.12, *P*<0.001), MPTB (χ^2=476.43, *P*<0.001), VPTB (χ^2=128.03, *P*<0.001), and EPTB (χ^2=138.01, *P*<0.001). Notably, critical serum ALT threshold ranges were identified: 17 to 40 U/L for PTB and MPTB, 17 to 37 U/L for VPTB, and 15 to 31 U/L for EPTB. Compared to the reference group with preconception ALT levels between 20–40 U/L, women with ALT levels below 20 U/L had a 7% increased risk of PTB (*OR*: 1.07, 95% *CI*: 1.06, 1.07), while those with levels above 40 U/L had a 15% higher risk (*OR*: 1.15, 95% *CI*: 1.13, 1.17), as outlined in Table 2. Similar patterns were evident across different PTB subtypes (Table 3). Subgroup analyses revealed that the observed associations were consistent across most subgroups and were not markedly affected by modifying factors. Compared to women with

TABLE 1. Baseline characteristics of 5,169,812 reproductive-aged women in China, 2013–2017.

Maternal characteristic	Total (*n*=5,169,812)	ALT level (U/L)			*P* value*
		<20 (*n*=3,223,504)	20–40 (*n*=1,681,607)	>40 (*n*=264,701)	
Age at LMP (years), mean (SD)	26.52 (4.21)	26.52 (4.16)	26.52 (4.30)	26.46 (4.27)	<0.001†
Age at LMP (years), *n* (%)					<0.001†
20–24	1,811,519 (35.04)	1,112,313 (34.51)	601,897 (35.79)	97,309 (36.76)	
25–29	2,327,309 (45.02)	1,477,004 (45.82)	736,831 (43.82)	113,474 (42.87)	
30–34	741,964 (14.35)	459,234 (14.25)	243,827 (14.50)	38,903 (14.70)	
35–39	241,702 (4.68)	147,047 (4.56)	81,958 (4.87)	12,697 (4.80)	
≥40	47,318 (0.92)	27,906 (0.87)	17,094 (1.02)	2,318 (0.88)	
Preconception BMI (kg/m^2), *n* (%)					<0.001†
<18.5	698,452 (13.51)	481,090 (14.92)	189,707 (11.28)	27,655 (10.45)	
18.5–23.9	3,665,734 (70.91)	2,295,998 (71.23)	1,196,830 (71.17)	172,906 (65.32)	
24.0–27.9	635,294 (12.29)	356,654 (11.06)	232,028 (13.80)	46,612 (17.61)	
≥28	145,745 (2.82)	71,746 (2.23)	57,561 (3.42)	16,438 (6.21)	
Missing	24,587 (0.48)	18,016 (0.56)	5,481 (0.33)	1,090 (0.41)	
Education, *n* (%)					<0.001
Junior high school and below	3,135,739 (60.65)	1,892,092 (58.70)	1,079,663 (64.20)	163,984 (61.95)	
Senior high school or above	1,879,334 (36.35)	1,226,039 (38.03)	561,238 (33.38)	92,057 (34.78)	
Missing	154,739 (2.99)	105,373 (3.27)	40,706 (2.42)	8,660 (3.27)	
Nationality, *n* (%)					<0.001
Han	4,754,322 (91.96)	2,973,137 (92.23)	1,541,688 (91.68)	239,497 (90.48)	
Other	354,381 (6.85)	208,609 (6.47)	124,208 (7.39)	21,564 (8.15)	
Missing	61,109 (1.18)	41,758 (1.30)	15,711 (0.93)	3,640 (1.38)	
Occupation, *n* (%)					<0.001
Farmer	3,670,941 (71.01)	2,215,353 (68.72)	1,268,826 (75.45)	186,762 (70.56)	
Non-farmer	1,329,778 (25.72)	893,104 (27.71)	368,175 (21.89)	68,499 (25.88)	
Missing	169,093 (3.27)	115,047 (3.57)	44,606 (2.65)	9,440 (3.57)	
Residence, *n* (%)					<0.001
Rural	4,719,410 (91.29)	2,915,213 (90.44)	1,561,686 (92.87)	242,511 (91.62)	
Urban	449,991 (8.70)	307,948 (9.55)	119,867 (7.13)	22,176 (8.38)	
Missing	411 (0.01)	343 (0.01)	54 (0.00)	14 (0.01)	
Region, *n* (%)					<0.001
Eastern	1,800,946 (34.84)	1,539,760 (47.77)	889,719 (52.91)	89,548 (33.83)	
Central	2,552,013 (49.36)	1,236,843 (38.37)	474,555 (28.22)	122,534 (46.29)	
Western	816,853 (15.80)	446,901 (13.86)	317,333 (18.87)	52,619 (19.88)	
Parity, *n* (%)					<0.001
Primipara	3,158,062 (61.09)	1,960,188 (60.81)	1,030,173 (61.26)	167,701 (63.35)	
Multipara	2,011,750 (38.91)	1,263,316 (39.19)	651,434 (38.74)	97,000 (36.65)	
Hypertension, *n* (%)					<0.001
No	5,055,184 (97.78)	3,154,849 (97.87)	1,644,195 (97.78)	256,140 (96.77)	
Yes	81,071 (1.57)	47,032 (1.46)	27,382 (1.63)	6,657 (2.51)	
Missing	33,557 (0.65)	21,623 (0.67)	10,030 (0.60)	1,904 (0.72)	

TABLE 1. (Continued)

Maternal characteristic	Total (*n*=5,169,812)	ALT level (U/L)			*P* value*
		<20 (*n*=3,223,504)	20–40 (*n*=1,681,607)	>40 (*n*=264,701)	
Hyperglycemia, *n* (%)					<0.001
No	4,937,590 (95.51)	3,079,691 (95.54)	1,612,949 (95.92)	244,950 (92.54)	
Yes	201,358 (3.89)	123,428 (3.83)	59,698 (3.55)	18,232 (6.89)	
Missing	30,864 (0.60)	20,385 (0.63)	8,960 (0.53)	1,519 (0.57)	
Smoking, *n* (%)					<0.001
No	5,132,139 (99.27)	3,198,243 (99.22)	1,671,189 (99.38)	262,707 (99.25)	
Yes	10,608 (0.21)	6,761 (0.21)	3,156 (0.19)	691 (0.26)	
Missing	27,065 (0.52)	18,500 (0.57)	7,262 (0.43)	1,303 (0.49)	
Drinking, *n* (%)					<0.001
No	4,997,403 (96.67)	3,104,545 (96.31)	1,636,845 (97.34)	256,013 (96.72)	
Yes	140,600 (2.72)	97,448 (3.02)	36,014 (2.14)	7,138 (2.70)	
Missing	31,809 (0.62)	21,511 (0.67)	8,748 (0.52)	1,550 (0.59)	
Periconception folic acid intake, *n* (%)					<0.001
No	1,059,359 (20.49)	650,583 (20.18)	354,576 (21.09)	54,200 (20.48)	
Yes	4,055,168 (78.44)	2,536,091 (78.67)	1,311,328 (77.98)	207,749 (78.48)	
Missing	55,285 (1.07)	36,830 (1.14)	15,703 (0.93)	2,752 (1.04)	
Preconception harmful exposure, *n* (%)					<0.001
No	4,555,857 (88.12)	2,815,462 (87.34)	1,508,161 (89.69)	232,234 (87.73)	
Yes	586,854 (11.35)	389,622 (12.09)	166,073 (9.88)	31,159 (11.77)	
Missing	27,101 (0.52)	18,420 (0.57)	7,373 (0.44)	1,308 (0.49)	
History of adverse pregnancy outcomes, *n* (%)					<0.001
No	4,337,030 (83.89)	2,684,307 (83.27)	1,436,552 (85.43)	216,171 (81.67)	
Yes	832,782 (16.11)	539,197 (16.73)	245,055 (14.57)	48,530 (18.33)	
Serum HBsAg status, *n* (%)					<0.001
Negative	4,920,895 (95.19)	3,109,439 (96.46)	1,579,261 (93.91)	232,195 (87.72)	
Positive	244,832 (4.74)	111,470 (3.46)	101,070 (6.01)	32,292 (12.20)	
Missing	4,085 (0.08)	2,595 (0.08)	1,276 (0.08)	214 (0.08)	

Abbreviation: ALT=alanine aminotransferase; IQR=interquartile range; SD=standard deviation; LMP=last menstrual period; BMI=body mass index; HBsAg=hepatitis B surface antigen.

* Multiple comparison with Bonferroni-adjusted $P<0.05$ compared with the ALT 20–40 U/L group (<20 U/L group *vs*. 20–40 U/L group; >40 U/L group *vs*. 20–40 U/L group).

† The Kruskal-Wallis H test was used to examine the differences of baseline characteristics among ALT groups; otherwise, the χ^2 test was used.

preconception ALT levels within the reference range, both lower and higher ALT concentrations were linked to increased PTB risk in the majority of subgroups, as illustrated in Figure 3.

DISCUSSION

In this large population-based retrospective cohort study involving more than 5.1 million Chinese women, we found that individuals with preconception serum ALT levels below 20 U/L had a 7% higher risk of PTB, while those with levels above 40 U/L had a 15% higher risk, compared to participants with ALT levels between 20–40 U/L.

Elevated ALT is often a sign of hepatocellular injury or liver dysfunction and acts as an indicator for conditions such as viral hepatitis, non-alcoholic fatty liver disease, or metabolic syndrome (*11*–*13*). These conditions are associated with systemic inflammation and metabolic disturbances, including insulin

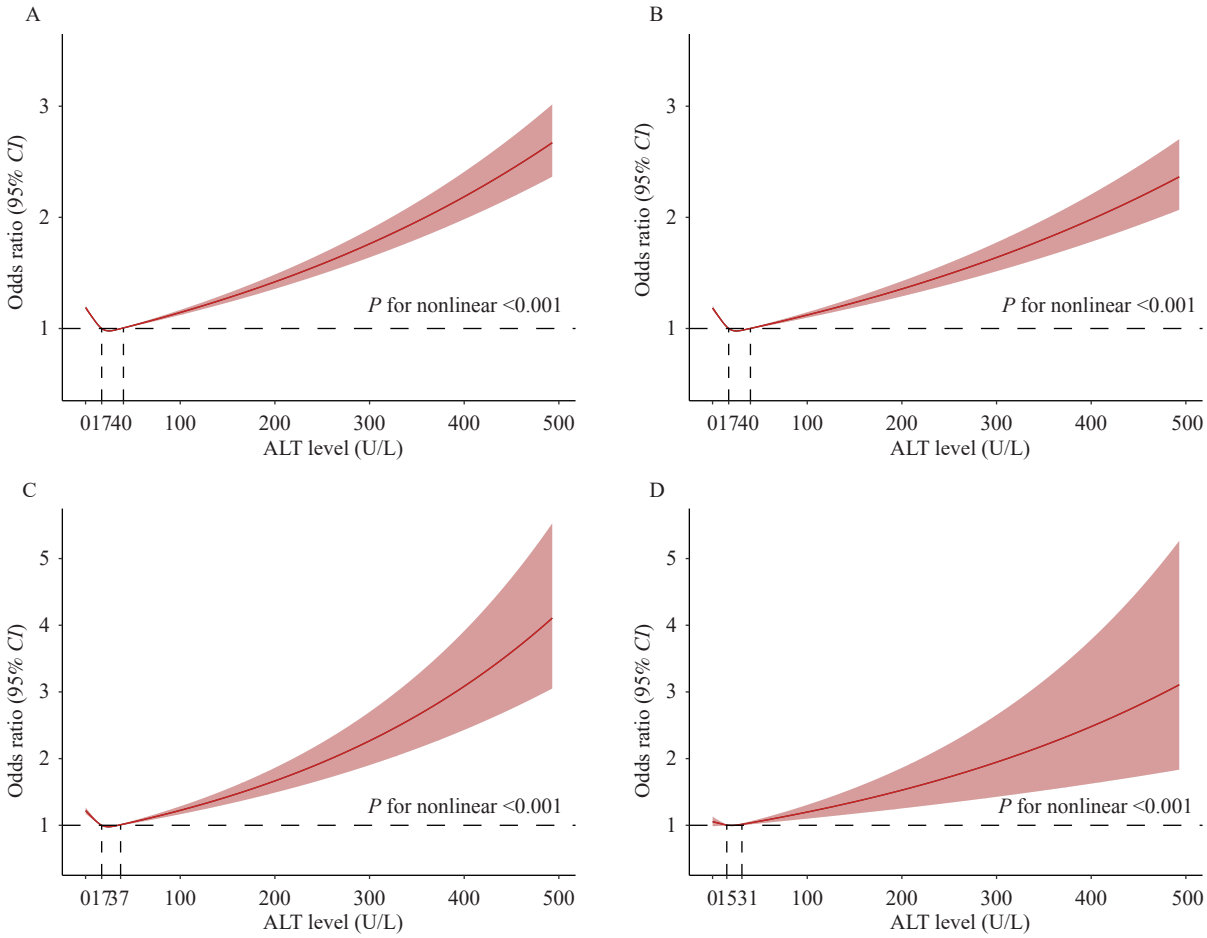

FIGURE 2. Restricted cubic spline curves with logistic regression between maternal preconception serum ALT concentrations and risk of (A) PTB (<37 weeks), (B) MPTB (32 to <37 weeks), (C) VPTB (28 to <32 weeks), and (D) EPTB (<28 weeks) among 5,169,812 reproductive-aged women in China, 2013–2017.
Note: Red dashed horizontal lines depict an odds ratio of 1.0. Red lines represent the estimated *OR*, while shaded ribbons depict a 95% *CI*. The dashed line denotes the reference level. The models were adjusted for maternal age at the last menstrual period, preconception BMI, education, nationality, occupation, residence, region, parity, hypertension, hyperglycemia, smoking, drinking, periconception folic acid intake, exposure to harmful substances, history of adverse pregnancy outcomes, and serum HBsAg status.
Abbreviation: PTB=preterm birth; MPTB=moderate-to-late preterm birth; VPTB=very preterm birth; EPTB=extremely preterm birth; ALT=alanine aminotransferase; *OR*=odds ratio; *CI*=confidence interval; BMI=body mass index.

resistance, heightened pro-inflammatory cytokine production, oxidative stress, and mitochondrial dysfunction, which can lead to hepatocyte damage or demise (*14*). These are recognized pathophysiological mechanisms implicated in the development of PTB (*15*). Conversely, preconception serum ALT levels that are low but within the normal range may signal malnutrition, frailty, disability, and sarcopenia (*16*–*18*), reflecting a compromised health status. Such a condition could interrupt vital metabolic processes necessary for fetal development and pregnancy, thereby representing an alternative, yet significant, pathway that may increase the risk of PTB.

Our study has several notable strengths. First, we conducted a detailed classification to assess the link between preconception serum ALT levels and the risk of PTB. This analysis was based on the largest Chinese population-based preconception cohort, comprising over 5.1 million participants. Second, all serum ALT tests were done within a year before pregnancy, offering a more accurate reflection of preconception liver function status. The NFPCP ensured data reliability by conducting quality checks and reviewing all testing procedures, including serum ALT measurements. Additionally, the inclusion of comprehensive individual covariate information provided ample statistical power for subgroup analysis.

This study was subject to some limitations. First,

TABLE 2. Associations between maternal preconception serum ALT concentrations and the risk of PTB among 5,169,812 reproductive-aged women in China, 2013–2017.

ALT level (U/L)	No. cases (%)	*OR* (95% *CI*)		
		Model Ⅰ*	Model Ⅱ†	Model Ⅲ§
Classification Ⅰ				
≤40	324,465 (6.61)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
>40	19,527 (7.38)	1.12 (1.11, 1.14)	1.11 (1.09, 1.13)	1.11 (1.09, 1.12)
Classification Ⅱ				
<20	218,403 (6.78)	1.08 (1.07, 1.09)	1.06 (1.06, 1.07)	1.07 (1.06, 1.07)
20–40	106,062 (6.31)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
>40	19,527 (7.38)	1.18 (1.16, 1.20)	1.16 (1.14, 1.17)	1.15 (1.13, 1.17)

Abbreviation: PTB=preterm birth; ALT=alanine aminotransferase; *OR*=odds ratio; *CI*=confidence interval.
* Model Ⅰ was an unadjusted model.
† Model Ⅱ was adjusted for maternal age at the last menstrual period, preconception body mass index (BMI), education, nationality, occupation, residence, region, parity, hypertension, hyperglycemia, smoking, drinking, periconception folic acid intake, harmful exposure, and history of adverse pregnancy outcomes.
§ Model Ⅲ was additionally adjusted for maternal serum hepatitis B surface antigen (HBsAg) status.

TABLE 3. Associations between maternal preconception serum ALT concentrations and the risk of MPTB, VPTB, and EPTB among 5,169,812 reproductive-aged women in China from 2013 to 2017.

ALT level (U/L)	MPTB		VPTB		EPTB	
	No. cases (%)	*OR* (95% *CI*)	No. cases (%)	*OR* (95% *CI*)	No. cases (%)	*OR* (95% *CI*)
Classification Ⅰ						
≤40	268,398 (5.47)	1.00 (Reference)	41,378 (0.84)	1.00 (Reference)	14,689 (0.30)	1.00 (Reference)
>40	16,099 (6.08)	1.10 (1.08, 1.12)	2,508 (0.95)	1.11 (1.07, 1.16)	920 (0.35)	1.15 (1.08, 1.23)
Classification Ⅱ						
<20	181,402 (5.63)	1.07 (1.06, 1.08)	27,504 (0.85)	1.05 (1.02, 1.07)	9,497 (0.29)	0.98 (0.95, 1.01)
20–40	86,996 (5.17)	1.00 (Reference)	13,874 (0.83)	1.00 (Reference)	5,192 (0.31)	1.00 (Reference)
>40	16,099 (6.08)	1.15 (1.13, 1.17)	2,508 (0.95)	1.14 (1.09, 1.19)	920 (0.35)	1.14 (1.06, 1.22)

Note: The models were adjusted for maternal age at the last menstrual period, preconception body mass index (BMI), education, nationality, occupation, residence, region, parity, hypertension, hyperglycemia, smoking, drinking, periconception folic acid intake, harmful exposure, history of adverse pregnancy outcomes, and serum hepatitis B surface antigen (HBsAg) status.
Abbreviation: MPTB=moderate-to-late preterm birth; VPTB=very preterm birth; EPTB=extremely preterm birth; ALT=alanine aminotransferase; *OR*=odds ratio; *CI*=confidence interval.

due to its observational design, causal relationships cannot be determined, and findings should be interpreted cautiously. Second, the absence of longitudinal liver function assessments during pregnancy may restrict the complete comprehension of the link between serum ALT levels and PTB. Third, similar to prior research, not all potential confounding variables were accounted for, and there is a chance of unmeasured or unidentified covariates.

Our results indicate that both abnormally high and relatively low levels of preconception serum ALT are linked to the risk of PTB and its subtypes in a J-shaped relationship. This underscores the importance of maintaining optimal preconception serum ALT levels to decrease the risk of PTB, highlighting the need for specific interventions in women of reproductive age.

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Corresponding authors: Ying Yang, angela-yy65@hotmail.com; Xu Ma, nfpcc_ma@163.com.

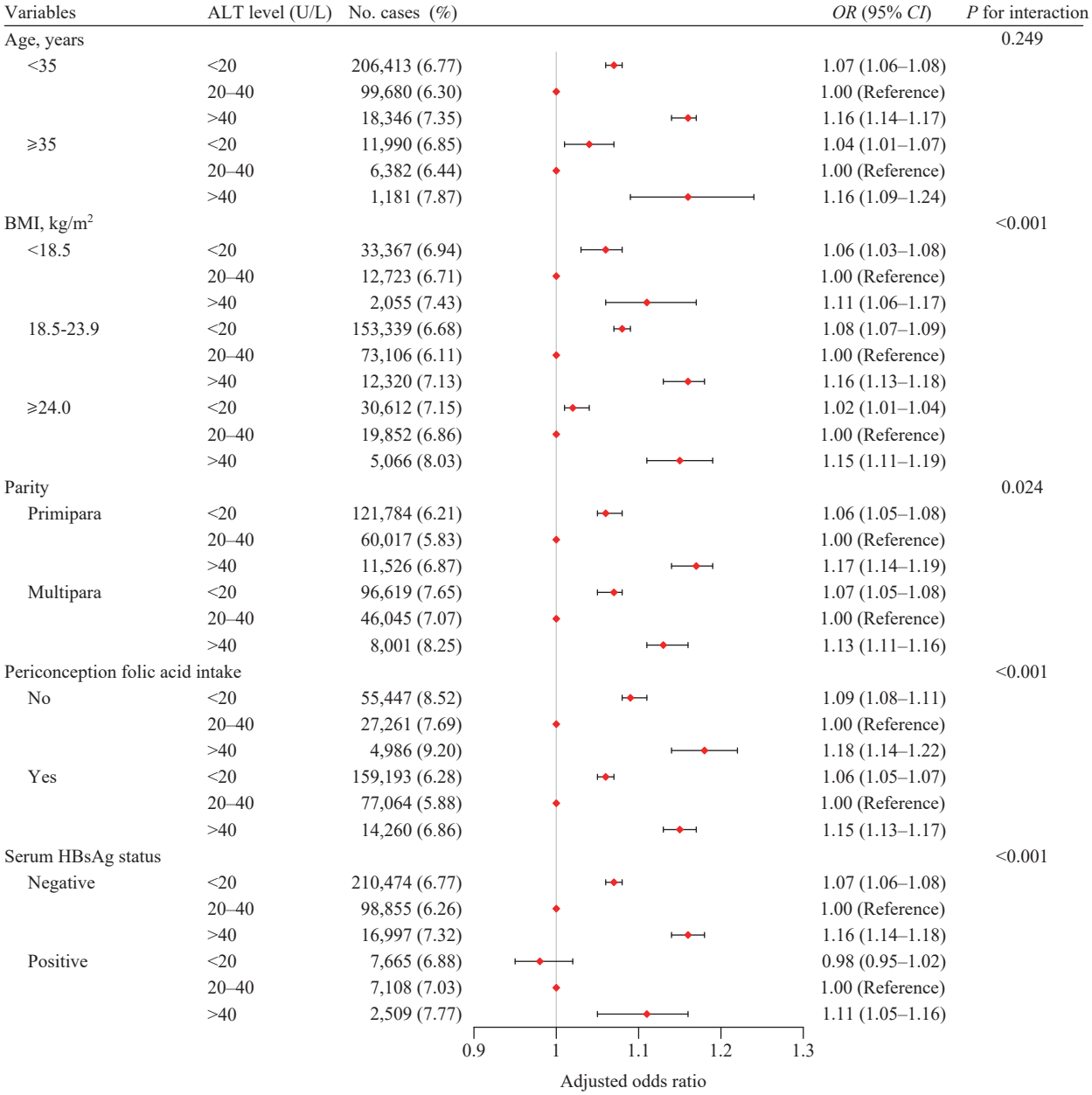

FIGURE 3. Subgroup analyses of the association between maternal preconception serum ALT concentrations and the risk of PTB among 5,169,812 reproductive-aged women in China from 2013 to 2017.
Note: Covariates in subgroup analyses were consistent with the variables adjusted in the multivariable logistic regression model for all participants, with the exception of the grouping variable.
Abbreviations: PTB=preterm birth; ALT=alanine aminotransferase; BMI=body mass index; HBsAg=hepatitis B surface antigen; *OR*=odds ratio; *CI*=confidence interval.

[1] National Research Institute for Family Planning, Beijing, China; [2] National Human Genetic Resources Center, Beijing, China; [3] Graduate School of Peking Union Medical College, Beijing, China; [4] Department of Epidemiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China.
[&] Joint first authors.

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE S1. Definition of the covariates.

Covariates	Definition
Demographic covariates	
Age	Maternal age at the last menstrual period of the participant (20–24, 25–29, 30–34, 35–39, and ≥ 40 years).
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).
Occupation	The type of work or profession engaged in by the participant (farmer or non-farmer).
Residence area	The type of area where the participant lives (rural or urban).
Region of geographical location	The geographical division of the provincial-level administrative division to which the participant resides based on the official China Statistics Bureau [eastern region (Beijing, Tianjin, Hebei, Liaoning, Shanghai, Jiangsu, Zhejiang, Fujian, Shandong, Guangdong, and Hainan), central region (Shanxi, Jilin, Heilongjiang, Hubei, Hunan, Anhui, Jiangxi, and Henan), or western region (Inner Mongolia, Guangxi, Chongqing, Sichuan, Guizhou, Yunnan, Xizang, Shaanxi, Gansu, Qinghai, Ningxia, and Xinjiang)].
Parity	Whether the participant has previous deliveries (primipara or multipara).
Smoking	Whether the participant actively smokes (yes or no).
Alcohol drinking	Whether the participant has consumed alcohol (yes or no).
Harmful exposure	Whether the participant has potential exposure to radial, high temperature, pesticide, new decoration, paint, other organic solvents, fever, common cold, or passive smoking (yes or no).
Periconception folic acid intake	Whether the participant has taken folic acid around the time of conception (yes or no).
History of adverse pregnancy outcomes	Whether the participant has a history of fatal death, ectopic pregnancy, spontaneous abortion, induced abortion, or preterm birth (yes or no).
Preconception clinical covariates	
Body mass index (BMI)	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)]
Hypertension	Self-reported hypertension or systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg (*1*) (yes or no).
Hyperglycemia	Self-reported hyperglycemia or fasting blood glucose ≥ 6.1 mmol/L (*2*) (yes or no).
Serum hepatitis B surface antigen (HBsAg) status	The testing for the presence or absence of the hepatitis B virus surface antigen in the participant's bloodstream (positive or negative).

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Preplanned Studies

Prevalence of Reproductive Tract Infections and Association with Human Papillomavirus Infection Among Reproductive-Age Women — Six Tertiary Hospitals, China, June 2021–December 2022

Di Gao[1]; Jiayue Li[2]; Gengli Zhao[1]; Zhaohui Liu[3]; Hui Bi[1]; Dai Zhang[1]; Fengxia Xue[4]; Chen Liu[5]; Hongtao Ma[6]; Bei Lin[7]; Xu Wang[1]; Xiaosong Zhang[1,#]; Linhong Wang[8,#]

Summary

What is already known about this topic?

Previous studies have indicated a possible association between reproductive tract infections (RTIs) and high-risk human papillomavirus (HPV) infection, but the evidence is still inconclusive.

What is added by this report?

This multicenter study found significantly higher positive rates of HPV, including general HPV, high-risk HPV, and HPV 16/18 infections, among women who tested positive for single or multiple RTIs compared to women who tested negative for RTIs in gynecological outpatient clinics.

What are the implications for public health practice?

Infection with HPV, especially high-risk types, is linked to RTIs and imbalances in the vaginal microbiota. Implementing standardized protocols for identifying and treating RTIs could support the establishment of a healthy vaginal microenvironment. This, in turn, may offer a novel approach to preventing cervical cancer.

Human papillomavirus (HPV) infections and reproductive tract infections (RTIs) are significant public health concerns that primarily spread through sexual activity, affecting women's health. Co-infection of HPV and RTIs can increase the risk of female reproductive tract infections and cervical cancer. This cross-sectional study, conducted in six tertiary hospitals in China from June 2021 to December 2022, aims to investigate the associations between various RTIs pathogens and HPV infections among women aged 18–49 years. The analysis included 3,133 women attending gynecology outpatient clinics. The overall rate of co-infection with HPV and RTIs was 13.2%. After adjusting for demographic factors, both the single-RTI-positive group [odds ratio (*OR*)=1.97, 95% confidence interval (*CI*): 1.59, 2.45] and the multiple-RTI-positive group (*OR*=4.85, 95% *CI*: 3.59, 6.56) showed significantly higher infection rates of HPV in general, as well as high-risk HPV (HR-HPV) and HPV 16/18. The study also found significant associations between RTI pathogens, including *Neisseria gonorrhoeae* (NG), *Chlamydia trachomatis* (CT), *Ureaplasma* species (UU), *Mycoplasma genitalium* (MG), *Mycoplasma hominis* (MH), and Herpes Simplex Virus Type II (HSV-2) infections, and HPV infections (general HPV, HR-HPV, and HPV 16/18). This research highlights the importance of understanding the relationship between RTIs and HPV infection, especially HR-HPV infection, in order to raise awareness of RTIs and HPV co-infection and facilitate early detection of disease-free latent infections.

RTIs can cause a range of symptoms and complications in the female reproductive tract, with potential long-term effects (*1*). Main pathogens include NG, CT, MG, and HSV-2, which are associated with conditions such as gonorrhea, chlamydial infections, and genital herpes. MH and UU, including *Ureaplasma urealyticum* (Uu) and *Ureaplasma parvum* (Up), are the most common *Mycoplasma* species in the reproductive tract and are also classified as RTIs in this study. In 2016, the World Health Organization (WHO) estimated 376.4 million new cases of chlamydia, gonorrhea, syphilis, and trichomoniasis globally (*2*). HPV is a significant sexually transmitted infectious pathogen, and persistent HR-HPV infection is a leading cause of cervical cancer. HPV types 16 and 18 are responsible for approximately 70% of all cervical cancer cases (*3*). The increasing prevalence of co-infections between HPV and other RTIs, coupled with changing modern lifestyles and sexual attitudes, highlights the need for

heightened attention in public health and medicine. RTI pathogens, such as NG, CT, and *Mycoplasma* species, have been found to potentially enhance HPV replication and persistence, leading to accelerated cervical neoplasia development (*4*). Therefore, it is crucial to detect and treat HPV and RTIs co-infections to develop targeted testing and screening programs, facilitate treatment and management strategies, and ultimately improve disease outcomes. Nevertheless, research on the association between RTI pathogens and HPV, as well as the prevalence of HPV-RTIs co-infections, is limited. Hence, this study aims to investigate the prevalence and association between various RTI pathogens and HPV to provide evidence and recommendations for the clinical diagnosis and management of vaginal and cervical infections.

This multicenter, cross-sectional study was conducted from June 2021 to December 2022 at six tertiary hospitals in China: Peking University First Hospital, Beijing Obstetrics and Gynecology Hospital, Shengjing Hospital of China Medical University, Tianjin Medical University General Hospital, Northwest Women's and Children's Hospital, and the Third Affiliated Hospital of Zhengzhou University. We recruited women of reproductive age (18–49 years) who attended the gynecology outpatient clinics at each hospital for either reproductive tract infection treatment or opportunistic screening for cervical cancer. Inclusion criteria included previous sexual history, pre-menopausal status, absence of menstruation at the time of sampling, and no sexual activity, vaginal medication, or douching within 3 days prior to sample collection. Exclusion criteria included pregnancy or within 8 weeks postpartum, vaginal bleeding, history of genital tract tumors, recent treatment for HPV infection or sexually transmitted diseases associated with pathogens, history of hysterectomy, cervical surgery, or pelvic radiotherapy, cervical ablation or excision treatment within the past 12 months, and antibiotic or probiotic use within the past month.

Based on previous studies, the estimated prevalence of co-infection between HPV and other RTIs in gynecology outpatients was approximately 15%. Therefore, we aimed to recruit a sample size of 2,242 participants for this cross-sectional study. Ultimately, cervical samples were collected from a total of 3,281 participants for HPV and RTI pathogens detection. After excluding samples that did not meet the qualification criteria or had missing results, 3,133 samples were included in the final analysis. HPV genotyping was performed using the 21 HPV GenoArray Diagnostic Kit (HBGA-21PKG; HybriBio Ltd., Chaozhou, China), which detects 14 HR-HPV types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), 1 suspected HR-HPV type (HPV 53), and 6 low-risk HPV (LR-HPV) types (HPV 6, 11, 42, 43, 44, and CP8304). The STD6 GenoArray Diagnostic Kit (HBGA-STD6; HybriBio Ltd.) was used to detect 6 common RTI pathogens, including NG, CT, UU (Uu, Up1, Up3, Up6, Up14), MG, MH, and HSV-2.

Categorical variables were presented as numbers (*n*) and percentages (%), and the chi-square test was used to compare the co-infection of HPV and other RTI pathogens. Univariate and multivariate logistic regression models were used to analyze the association between common RTI pathogens and HPV infection, with calculation of *OR*s and 95% confidence intervals *CI*s. Statistical analyses were performed using STATA (version 14.0; Stata Corporation, College Station, TX, USA) and R (version 4.2.3; R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was determined using two-tailed tests with a significance level of 0.05. The study design underwent review and approval by the Biomedical Research Ethics Committee of Peking University First Hospital (2021KY069), and sample collection received authorization from the Human Genetics Resources Administration of China ([2022]CJ0124).

A total of 3,133 subjects were included in the study, with 13.2% having co-infections of both HPV and RTI pathogens. The co-infection rates varied across different demographic characteristics (Supplementary Table S1, available at https://weekly.chinacdc.cn/). The overall RTIs positive rate was 46.0%, with UU (42.1%), CT (4.9%), and MH (4.7%) being the most prevalent RTI pathogens. Of the 109 women (3.5%) with multiple RTIs co-infections, the most common combinations were MH+UU (43.1%), CT+UU (36.7%), and CT+MH (4.6%) (Figure 1C). The co-infection rates were 13.2% for HPV-positive, 11.4% for HR-HPV-positive, and 3.0% for HPV 16/18-positive (Table 1). HPV and RTI pathogens co-infections were found in 413 women (13.2%), with the most common combinations being HPV+UU (65.9%), HPV+MH+UU (9.9%), and HPV+CT+UU (9.2%) (Figure 1D). After adjusting for age group, ethnicity, education level, family monthly income, marital status, and parity, both the single-RTI-positive group (*OR*=1.97, 95% *CI*: 1.59, 2.45) and multiple-RTI-positive group (*OR*=4.85, 95% *CI*: 3.59, 6.56) had higher rates of HPV infection compared to the RTI-negative group. Furthermore, individuals infected

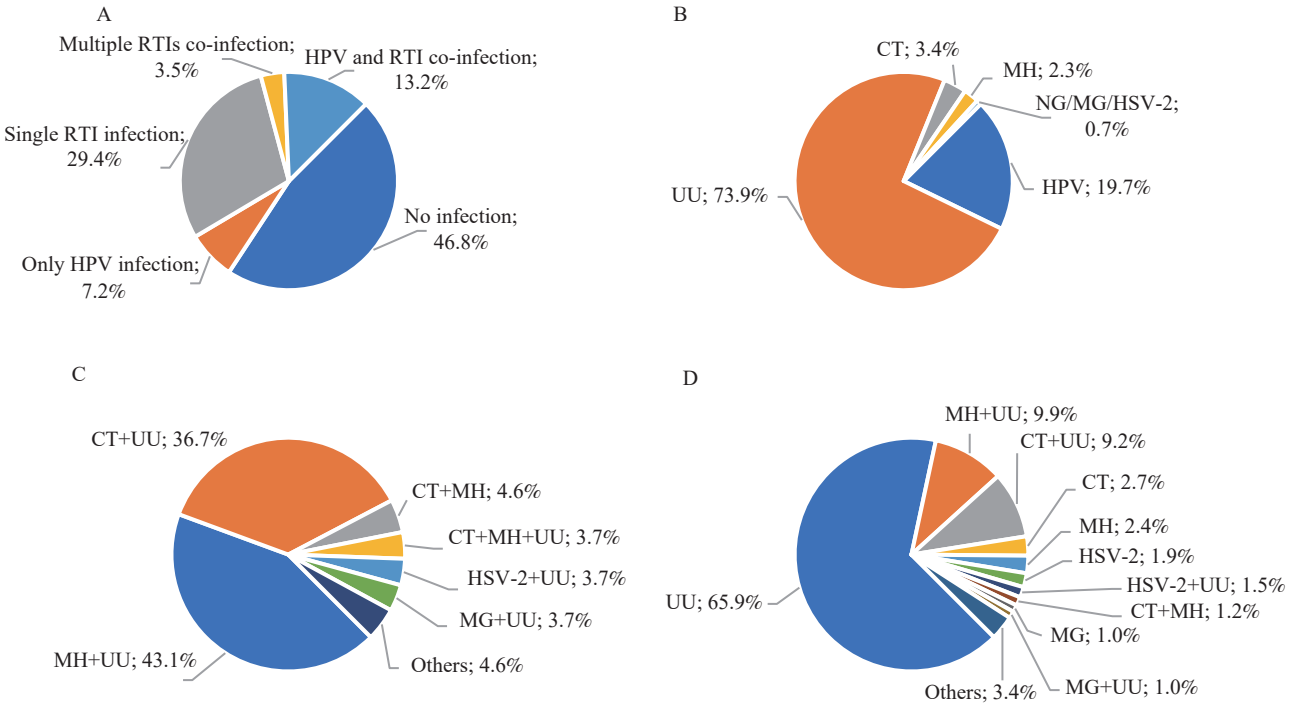

FIGURE 1. Patterns of RTI pathogens and HPV infection among reproductive-age women in six tertiary hospitals in China from June 2021 to December 2022. (A) Pattern of infection (*n*=3,133) (B) Pattern of single infection (*n*=1,146) (C) Multiple RTI co-infections (*n*=109); (D) HPV and RTI co-infection (*n*=413).
Note: RTI pathogens in our study included NG, CT, UU, MG, MH, and HSV-2.
Abbreviation: HPV=human papillomavirus; RTI=reproductive tract infection; NG=*Neisseria gonorrhoeae*; CT=*Chlamydia trachomatis*; UU=*Ureaplasma* species; MG=*Mycoplasma genitalium*; MH=*Mycoplasma hominis*; HSV-2=Herpes Simplex Virus Type II.

with NG, CT, Uu, Up1, Up3, Up6, any UU, MG, MH, or HSV-2 also had a significantly higher risk of HPV infection. Similar results were observed for HR-HPV and HPV 16/18 infections (Table 2). Significant correlations were also found between different HPV genotypes and RTI pathogens (Supplementary Figure S1, available at https://weekly.chinacdc.cn/).

DISCUSSION

The co-infection rate of HPV and RTI pathogens in this study was found to be 13.2%, emphasizing the importance of recognizing clinical co-infection of HPV and RTIs. Notably, the rates of general HPV infection, HR-HPV infection, and HPV 16/18 infection were significantly higher among women who tested positive for either single or multiple RTIs, compared to those who tested negative for RTIs. These findings indicate a positive association between HPV and RTIs, underscoring the need for prevention, detection, and proper management of RTIs. Preventing and treating reproductive tract infections may help reduce the prevalence of HPV infection, particularly HR-HPV infection.

The findings of this study provide support for the potential link between RTIs and HPV infection, which is consistent with recent research. However, previous studies have primarily focused on the presence of a single RTI pathogen. CT, a primary pathogen associated with HPV, has been extensively investigated. CT promotes HPV penetration into epithelial cells by inducing inflammation and altering the cervical microenvironment. In turn, HPV can facilitate the spread and multiplication of CT (*4*). This study also found a positive association between these two infections. Our current understanding of the relationships between NG, MG, HSV-2, and HPV remains limited. A meta-analysis revealed that MG was significantly associated with an increased risk of HR-HPV infection (*OR*=1.50, 95% *CI*: 1.11, 2.02) (*5*). Another cross-sectional study reported that individuals positive for HR-HPV had higher rates of HSV-2 seroprevalence and active infection compared to those who were negative. This may be attributed to co-infection of HSV-2 and HR-HPV, which disrupts local immune responses and promotes HPV-related

TABLE 1. Detection rate of different RTI pathogens and HPV co-infection among reproductive-age women in six tertiary hospitals in China from June 2021 to December 2022 [*n* (%)].

RTI pathogens	Total (*n*=3,133)	Co-infection with HPV	Co-infection with HR-HPV	Co-infection with HPV 16/18
NG-positive	10 (0.3)	6 (0.2)	5 (0.2)	2 (0.1)
CT-positive	152 (4.9)	61 (1.9)	49 (1.6)	12 (0.4)
UU-positive	1,320 (42.1)	371 (11.8)	322 (10.3)	79 (2.5)
Uu-positive	319 (10.2)	100 (3.2)	84 (2.7)	23 (0.7)
Up1-positive	169 (5.4)	48 (1.5)	44 (1.4)	9 (0.3)
Up3-positive	556 (17.7)	142 (4.5)	121 (3.9)	31 (1.0)
Up6-positive	424 (13.5)	137 (4.4)	122 (3.9)	30 (1.0)
Up14-positive	11 (0.4)	4 (0.1)	3 (0.1)	0 (0)
MG-positive	21 (0.7)	12 (0.4)	11 (0.4)	4 (0.1)
MH-positive	147 (4.7)	62 (2.0)	54 (1.7)	13 (0.4)
HSV-2-positive	27 (0.9)	18 (0.6)	18 (0.6)	3 (0.1)
Any RTIs-positive	1,442 (46.0)	413 (13.2)	357 (11.4)	93 (3.0)

Abbreviation: HPV=human papillomavirus; HR-HPV=high risk HPV; RTI=reproductive tract infection; NG=*Neisseria gonorrhoeae*; CT=*Chlamydia trachomatis*; UU=*Ureaplasma* species; Uu=*Ureaplasma urealyticum*; Up=*Ureaplasma parvum*; MG=*Mycoplasma genitalium*; MH=*Mycoplasma hominis*; HSV-2=Herpes Simplex Virus Type II.

disease progression (*6*). The findings of this study are consistent with the aforementioned positive associations.

Additionally, this study identified associations between UU and MH infections with both HPV and HR-HPV infections. UU, a common pathogen causing urinary tract infections, had controversial impact due to a lack of differentiation between Uu and Up subtypes. Previous studies have reported significant associations between UU and HPV, including HR-HPV (*5*,*7*), although Zhong et al. found no significant association (*8*). Despite these significant findings, the high rate of UU positivity in clinical practice limits its clinical diagnostic and treatment significance. Research has also shown a significant association between persistent MH infection and persistent HR-HPV infection ($P<0.05$), but no significant correlation between prevalent MH and prevalent HR-HPV infection (*9*). Overall, the associations between MH, UU, and HPV infections remain understudied. Further research is needed to investigate the impacts of UU and MH infection, specifically high-risk UU subtypes, on vaginal microecological balance, persistence and recurrence of HPV infection, and their contribution to cervical cancer development.

There are several limitations worth noting in this study. First, the cross-sectional design prevents us from establishing causal relationships between RTI pathogens and HPV infection, as well as determining their impact on persistent HPV infection. Second, the data collected for this study was limited to 6 hospitals in China, which may not be representative of the overall prevalence of HPV-RTI co-infection. However, this limitation does not affect the results pertaining to the relationship between HPV infection and RTIs. To gain a better understanding of the impact of specific subtypes of MH and UU on health, while excluding other traditional RTIs, further well-designed studies are needed. These studies will provide valuable information to guide routine testing and treatment recommendations.

In conclusion, this study found that the rates of general HPV, HR-HPV, and HPV 16/18 infections were significantly higher in both single-RTI-positive and multiple-RTI-positive groups. Additionally, specific RTI pathogens (NG, CT, UU, MG, MH, and HSV-2) were also associated with higher infection rates. These findings highlight the importance of standardizing the detection and treatment of RTI. By doing so, it may be possible to reduce the risk of high-risk and persistent HPV infection, providing a new approach to preventing cervical cancer and contributing to the goal of eliminating cervical cancer (*10*).

Conflicts of interest: No conflicts of interest.

Acknowledgments: All the participants and investigators from six tertiary hospitals: Peking University First Hospital, Beijing Obstetrics and Gynecology Hospital, Shengjing Hospital of China Medical University, Tianjin Medical University General Hospital, Northwest Women's and Children's Hospital, and the Third Affiliated Hospital of Zhengzhou University.

TABLE 2. Association between HPV infection and other RTI pathogens infection among reproductive-age women in six tertiary hospitals in China from June 2021 to December 2022.

RTI pathogens	Total	HPV-positive			HR-HPV- positive			HPV 16/18-positive		
		n (%)	Crude *OR* (95% *CI*)	Adjusted *OR* (95% *CI*)*	*n* (%)	Crude *OR* (95% *CI*)	Adjusted *OR* (95% *CI*)*	*n* (%)	Crude *OR* (95% *CI*)	Adjusted *OR* (95% *CI*)*
Neisseria gonorrhoeae										
Negative	3,123	633 (20.3)	Ref.	Ref.	558 (17.9)	Ref.	Ref.	137 (4.4)	Ref.	Ref.
Positive	10	6 (60.0)	5.90 (1.66, 20.97)	10.82 (2.04, 57.4)	5 (50.0)	4.60 (1.33, 15.93)	6.86 (1.49, 31.72)	2 (20.0)	5.45 (1.15, 25.9)	9.31 (1.70, 51.08)
Chlamydia trachomatis										
Negative	2,981	578 (19.4)	Ref.	Ref.	514 (17.2)	Ref.	Ref.	127 (4.3)	Ref.	Ref.
Positive	152	61 (40.1)	2.79 (1.99, 3.90)	2.64 (1.80, 3.86)	49 (32.2)	2.28 (1.60, 3.25)	2.18 (1.47, 3.24)	12 (7.9)	1.93 (1.04, 3.57)	2.14 (1.13, 4.05)
Ureaplasma species										
Negative	1,813	268 (14.8)	Ref.	Ref.	241 (13.3)	Ref.	Ref.	60 (3.3)	Ref.	Ref.
Positive	1,320	371 (28.1)	2.25 (1.89, 2.69)	2.13 (1.75, 2.59)	322 (24.4)	2.10 (1.75, 2.53)	1.96 (1.60, 2.41)	79 (6.0)	1.86 (1.32, 2.62)	1.73 (1.18, 2.54)
Ureaplasma urealyticum										
Negative	2,814	539 (19.2)	Ref.	Ref.	479 (17.0)	Ref.	Ref.	116 (4.1)	Ref.	Ref.
Positive	319	100 (31.3)	1.93 (1.49, 2.49)	1.97 (1.46, 2.65)	84 (26.3)	1.74 (1.33, 2.28)	1.67 (1.22, 2.29)	23 (7.2)	1.81 (1.14, 2.87)	1.59 (0.92, 2.72)
Ureaplasma parvum 1										
Negative	2,964	591 (19.9)	Ref.	Ref.	519 (17.5)	Ref.	Ref.	130 (4.4)	Ref.	Ref.
Positive	169	48 (28.4)	1.59 (1.13, 2.25)	1.45 (1.00, 2.12)	44 (26.0)	1.66 (1.16, 2.37)	1.58 (1.07, 2.32)	9 (5.3)	1.23 (0.61, 2.45)	1.01 (0.46, 2.24)
Ureaplasma parvum 3										
Negative	2,577	497 (19.3)	Ref.	Ref.	442 (17.2)	Ref.	Ref.	108 (4.2)	Ref.	Ref.
Positive	556	142 (25.5)	1.44 (1.16, 1.78)	1.36 (1.07, 1.73)	121 (21.8)	1.34 (1.07, 1.68)	1.23 (0.95, 1.58)	31 (5.6)	1.35 (0.90, 2.03)	1.16 (0.73, 1.85)
Ureaplasma parvum 6										
Negative	2,709	502 (18.5)	Ref.	Ref.	441 (16.3)	Ref.	Ref.	109 (4.0)	Ref.	Ref.
Positive	424	137 (32.3)	2.10 (1.68, 2.63)	1.93 (1.51, 2.48)	122 (28.8)	2.08 (1.64, 2.62)	1.97 (1.52, 2.54)	30 (7.1)	1.82 (1.20, 2.76)	1.76 (1.12, 2.78)
Ureaplasma parvum 14										
Negative	3,122	635 (20.3)	Ref.	Ref.	560 (17.9)	Ref.	Ref.	139 (4.5)		
Positive	11	4 (36.4)	2.24 (0.65, 7.67)	2.86 (0.80, 10.3)	3 (27.3)	1.72 (0.45, 6.49)	2.22 (0.57, 8.69)	0 (0)	–†	–†
Mycoplasma genitalium										
Negative	3,112	627 (20.1)	Ref.	Ref.	552 (17.7)	Ref.	Ref.	135 (4.3)	Ref.	Ref.
Positive	21	12 (57.1)	5.28 (2.22, 12.6)	3.17 (1.22, 8.22)	11 (52.4)	5.1 (2.16, 12.07)	3.06 (1.17, 7.99)	4 (19.0)	5.19 (1.72, 15.63)	6.09 (1.91, 19.49)

Continued

RTI pathogens	Total	HPV-positive			HR-HPV- positive			HPV 16/18-positive		
		n (%)	Crude *OR* (95% *CI*)	Adjusted *OR* (95% *CI*)*	*n* (%)	Crude *OR* (95% *CI*)	Adjusted *OR* (95% *CI*)*	*n* (%)	Crude *OR* (95% *CI*)	Adjusted *OR* (95% *CI*)*
Mycoplasma hominis										
Negative	2,986	577 (19.3)	Ref.	Ref.	509 (17.0)	Ref.	Ref.	126 (4.2)	Ref.	Ref.
Positive	147	62 (42.2)	3.05 (2.17, 4.28)	2.76 (1.87, 4.08)	54 (36.7)	2.83 (1.99, 4.00)	2.48 (1.66, 3.71)	13 (8.8)	2.20 (1.21, 4.00)	2.23 (1.15, 4.30)
Herpes simple virus type Ⅱ										
Negative	3,106	621 (20.0)	Ref.	Ref.	545 (17.5)	Ref.	Ref.	136 (4.4)	Ref.	Ref.
Positive	27	18 (66.7)	8.00 (3.58, 17.90)	6.67 (2.89, 15.36)	18 (66.7)	9.40 (4.20, 21.03)	7.94 (3.44, 18.29)	3 (11.1)	2.73 (0.81, 9.18)	2.38 (0.69, 8.25)
Any RTIs										
Negative	1,691	226 (13.4)	Ref.	Ref.	206 (12.2)	Ref.	Ref.	46 (2.7)	Ref.	Ref.
Single-RTI-positive	1,125	273 (24.3)	2.08 (1.71, 2.53)	1.97 (1.59, 2.45)	235 (20.9)	1.90 (1.55, 2.34)	1.82 (1.45, 2.28)	63 (5.6)	2.12 (1.44, 3.13)	2.17 (1.41, 3.34)
Multiple-RTI-positive	317	140 (44.2)	5.13 (3.94, 6.66)	4.85 (3.59, 6.56)	122 (38.5)	4.51 (3.45, 5.90)	4.17 (3.06, 5.68)	30 (9.5)	3.74 (2.32, 6.02)	3.47 (2.01, 6.00)

Abbreviation: HPV=human papillomavirus; HR-HPV=high risk HPV; RTI=reproductive tract infection; *OR*=odds ratio; *CI*=confidence interval.

* Adjusted for age group, ethnic group, education level, family monthly income, marital status, and parity.

† Regression was not possible because the sample size of the positive group was 0.

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Corresponding authors: Xiaosong Zhang, zhangxiaosong@bjmu.edu.cn; Linhong Wang, linhong@chinawch.org.cn.

[1] Department of Obstetrics and Gynecology, Peking University First Hospital, Beijing, China; [2] School of Medicine, University College Dublin, Ireland; [3] Beijing Obstetrics and Gynecology Hospital, Beijing, China; [4] Tianjin Medical University General Hospital, Tianjin, China; [5] Northwest Women's and Children's Hospital, Xi'an City, Shaanxi Province, China; [6] Third Affiliated Hospital of Zhengzhou University, Zhengzhou City, Henan Province, China; [7] Shengjing Hospital of China Medical University, Shenyang City, Liaoning Province, China; [8] National Center for Chronic and Non-Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China.

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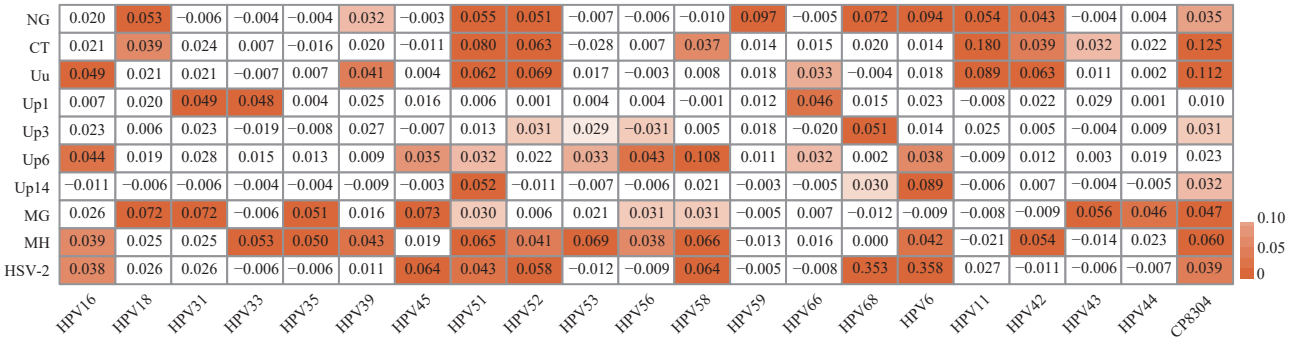
SUPPLEMENTARY MATERIALS

SUPPLEMENTARY TABLE S1. Demographic characteristics and co-infection of RTI pathogens with HPV among reproductive-age women in six tertiary hospitals in China from June 2021 to December 2022 [*n* (%)].

Characteristics	Total	HPV-positive & RTI-positive	HPV-positive & RTI-negative	HPV-negative & RTI-positive	HPV-negative & RTI-negative	χ^2	*P*
Overall	3,133	413 (13.2)	226 (7.2)	1029 (32.8)	1465 (46.8)		
Age group (years)						6.864	0.334
18–29	744	110 (14.8)	51 (6.9)	260 (34.9)	323 (43.4)		
30–39	1,628	202 (12.4)	124 (7.6)	519 (31.9)	783 (48.1)		
40–49	761	101 (13.3)	51 (6.7)	250 (32.9)	359 (47.2)		
Ethnic group*						9.504	0.023
Han	2,936	381 (13.0)	209 (7.1)	960 (32.7)	1,386 (47.2)		
Others	147	29 (19.7)	15 (10.2)	48 (32.7)	55 (37.4)		
Education level*						16.319	0.012
High school or below	533	84 (15.8)	31 (5.8)	172 (32.3)	246 (46.2)		
College	2,086	279 (13.4)	163 (7.8)	694 (33.3)	950 (45.5)		
Graduate or above	458	46 (10.0)	25 (5.5)	142 (31.0)	245 (53.5)		
Family monthly income (CNY)*						8.897	0.447
<5,000	572	75 (13.1)	37 (6.5)	190 (33.2)	270 (47.2)		
5,000–10,000	1,257	158 (12.6)	94 (7.5)	409 (32.5)	596 (47.4)		
10,001–20,000	836	115 (13.8)	65 (7.8)	256 (30.6)	400 (47.8)		
>20,000	322	43 (13.4)	21 (6.5)	125 (38.8)	133 (41.3)		
Marital status*						56.397	<0.001
Unmarried	621	125 (20.1)	50 (8.1)	210 (33.8)	236 (38.0)		
Married	2,407	264 (11.0)	169 (7.0)	781 (32.4)	1,193 (49.6)		
Divorce/others	80	19 (23.8)	5 (6.3)	28 (35.0)	28 (35.0)		
Parity*						65.536	<0.001
Nulliparous	800	154 (19.3)	74 (9.3)	290 (36.3)	282 (35.3)		
Multiparous	1,945	220 (11.3)	130 (6.7)	606 (31.2)	989 (50.8)		

Abbreviation: HPV=human papillomavirus; RTI=reproductive tract infection.
* There are missing values in the data.



SUPPLEMENTARY FIGURE S1. Heatmap of phi coefficients between different HPV genotypes and various RTI pathogens among reproductive-age women in six tertiary hospitals in China from June 2021 to December 2022.
Note: The number within each box indicates the phi correlation coefficient, while the color intensity of the boxes represents the magnitude of correlation. A white box indicates a correlation coefficient with a *P*-value greater than 0.01.
Abbreviation: HPV=human papillomavirus; RTI=reproductive tract infection; NG=*Neisseria gonorrhoeae*; CT=*Chlamydia trachomatis*;Uu=*Ureaplasma urealyticum*; Up=*Ureaplasma parvum*; MG=*Mycoplasma genitalium*; MH=*Mycoplasma hominis*; HSV-2=Herpes Simplex Virus Type II.

Vital Surveillances

Incidence and Mortality of Cancers in Female Genital Organs — China, 2022

Kexin Sun[1]; Bingfeng Han[1]; Hongmei Zeng[1]; Shaoming Wang[1]; Li Li[1]; Ru Chen[1]; Rongshou Zheng[1,#]; Wenqiang Wei[1,#]

ABSTRACT

Introduction: This study presented the incidence and mortality rates of cancers affecting the female genital organs in China, along with their trends spanning from 2010 to 2018.

Methods: 700 population-based cancer registries provided relevant cancer incidence and mortality data for the year 2018. Among these, 106 registries had continuous monitoring data suitable for trend analysis from 2010 to 2018. We focused specifically on cancers affecting female genital organs (ICD10=C51–C54, C56) and projected their incidences and mortalities in China for 2022 based on data from 2018 and the trends observed from 2010 to 2018. Age-standardized incidence rate (ASIR) and mortality rate (ASMR) were calculated using Segi's world standard population.

Results: In 2022, there were an estimated 296,300 new cases and 104,900 deaths from female cancers in China. ASIRs for vulva (C51), vagina (C52), cervix uteri (C53), corpus uteri (C54), and ovary (C56) were 0.32, 0.23, 13.83, 6.84, and 5.68 per 100,000 population. ASIRs for corpus uteri and ovary cancers were higher in urban areas. ASMRs for vulva, vagina, cervix, corpus uteri, and ovary cancers were 0.14, 0.08, 4.54, 1.05, and 2.64 per 100,000 population, respectively. ASMR for ovarian cancer was higher in urban areas. ASIRs and ASMRs for most female genital organ cancers increased from 2010 to 2018, although the rate of increase for vulvar and cervical cancers in rural areas has slowed recently.

Conclusions: Tailored cancer prevention and control programs specific to each region are necessary to address the growing disease burden.

Globally, female genital organ cancers (vulva, vagina, cervix, corpus uteri, ovary) accounted for approximately 15% of all female cancer cases and fatalities (*1*–*2*). In February 2024, the International Agency for Research on Cancer (IARC) published the most recent data on cancer incidence globally across 185 countries. It was estimated that there were 1,472,801 new cases and 680,041 deaths attributed to female genital organ cancers worldwide in 2022 (*3*).

The World Health Organization (WHO) Global Cervical Cancer Elimination Initiative, launched in 2020, underscored the importance of ongoing surveillance and monitoring of female-specific cancers as a critical component of effective intervention strategies against these diseases. Yet, in China, there is a notable scarcity of recent surveillance data regarding cancers of the female genital tract, particularly those affecting less common sites such as the vulva and vagina. Addressing this deficiency, our study aimed to present the latest incidence and mortality figures for cancers of the female genital organs in 2022, as well as their epidemiological trends spanning from 2010 to 2018 within China. These findings were consistent with the data published in GLOBOCAN 2022. The insights garnered from this research are intended to assess the impact of existing cancer prevention and control measures for women and to guide future health policy decisions in China.

METHODS

Data Sources

A total of 700 population-based cancer registries in China provided high-quality cancer surveillance data in 2018, which were aggregated to estimate cancer incidence and mortality rates based on sex (male/female), age groups (0–84 in 5-year increments, and ≥85 years), and geographical regions (urban/rural). Out of these registries, 106 provided consistent high-quality data from 2010 to 2018, which were combined to analyze rate trends over this period using an age-period-cohort model. Detailed information on quality control and calculations can be found in a previous publication (*4*). Projections for cancer incidence and

mortality rates in 2022 were made using baseline data from 2018 and the rate trends estimated from 2010 to 2018. For this study, we specifically focused on datasets related to female genital cancers (C51–54 and C56, ICD-10).

The National Bureau of Statistics of China supplied the total population numbers of China for 2022 categorized by region and sex. Based on the demographic distribution from the Seventh National Census of China in 2020, we calculated the population estimates by age group for 2022. Subsequently, the incidences and mortalities of cancer were determined by applying rates to the respective population groups.

Statistical Analysis

The age-standardized incidence rate (ASIR) and age-standardized mortality rate (ASMR) were calculated using Segi's world standard population. The proportion of cases or deaths from specific cancer sites among total cancer cases or deaths was determined. Trend analysis was conducted through Joinpoint regression analysis, and results included annual percent changes (APC) and average annual percent change (AAPC). Statistical analyses were performed using Stata (version 13.0, Stata Corporation, College Station, Texas, USA) and Joinpoint software (version 4.6.0.0, Applications Branch, National Cancer Institute, Bethesda, USA).

RESULTS

Incidence in 2022

In 2022, there were approximately 296,300 new cases of female genital cancer in China, representing 12.93% of all new cancer cases in females. The ASIR was 26.90 per 100,000, with a higher rate in rural areas compared to urban areas.

Cervical cancer showed the highest incidence with 150,700 cases and an ASIR of 13.83 per 100,000, followed by corpus uteri cancer, ovarian cancer, vulvar cancer and vaginal cancer. The ASIRs for corpus uteri and ovarian cancers were higher in urban areas than in rural areas, while the ASIRs for vulvar, vaginal, and cervical cancers were higher in rural areas compared to urban areas (Table 1).

The incidence rate of vulvar cancer increased with age, reaching its peak in the 80–84 age group. Vaginal cancer peaked at ages 70–74 in urban areas and 75–80 in rural areas. Both cervical and corpus uteri cancers peaked in the 50–54 age group. Ovarian cancer had high incidence rates in the 60–74 age groups (Figure 1).

Mortality in 2022

In 2022, there were an estimated 104,900 deaths from female genital cancers in China, representing 11.10% of all cancer-related deaths in females. The ASMR was 8.44 per 100,000, with higher rates observed in rural areas compared to urban areas.

Cervical cancer had the highest mortality with 55,700 cases and an ASMR of 4.54 per 100,000. This was followed by ovarian corpus uteri, vulvar and vaginal cancer. Ovarian cancer had a higher ASMR in urban areas, whereas other cancers in female genital organs showed higher ASMRs in rural areas compared to urban areas (Table 1).

Mortality rates for cancer generally rise with age, except for ovarian cancer in rural areas, where the rates peak among individuals aged 70–74. Minor increases were noted in the 50–54 age group for cervical cancer across all regions, as well as for cancers affecting the vagina and ovary in rural areas. (Figure 2).

Trends in Incidence Rates from 2010 to 2018

The ASIR for female genital cancers showed a notable increase from 2010 to 2016 [APC=2.6%, 95% confidence interval (*CI*): 2.1%, 3.1%, $P<0.001$], followed by a stabilization between 2016 and 2018. Analyzing by region, urban areas displayed a significant and consistent increase in ASIR throughout 2010 to 2018. In contrast, rural areas witnessed a steep rise from 2010 to 2014, then leveling off from 2014 to 2018.

The ASIRs for vulvar, vaginal, and ovarian cancers remained stable in urban areas from 2010 to 2018. However, there was a significant increase in the ASIRs of cervical cancer and corpus uteri cancer over the same period.

In rural areas, from 2010 to 2018, there was a significant increase in the ASIRs for vaginal cancer, corpus uteri cancer, and ovarian cancer. The ASIRs for vulvar cancer and cervical cancer initially increased significantly, stabilizing around 2014–2016 (Figure 3, Supplementary Table S1, available at http://weekly.chinacdc.cn/).

Trends in Mortality Rates from 2010 to 2018

The ASMRs for female genital cancers showed a

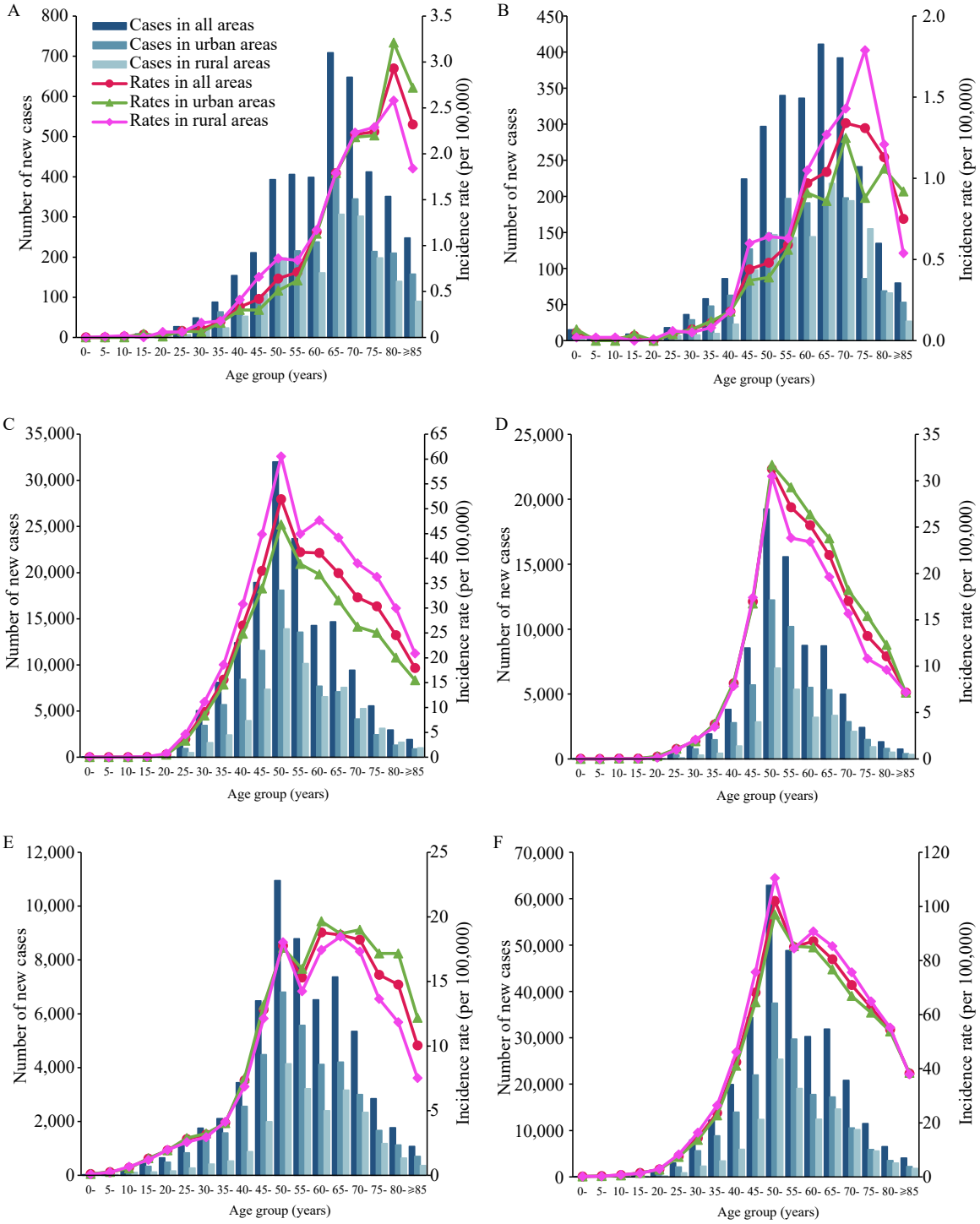


FIGURE 1. The incidence cases and rates of female genital cancers in China by cancer site, age group and area, 2022. (A) Vulva (C5l); (B) Vagina (C52); (C) Cervix (C53); (D) Corpus uteri (C54); (E) Ovary (C56); (F) All (C51–54, 56).

significant increase from 2010 to 2018, with an APC of 3.4% (95% *CI*: 2.3%, 4.5%, *P*<0.001). This increase was observed in both urban areas and rural areas.

When examining specific cancer sites, there were no notable changes in the ASMRs for vulva, corpus uteri and ovary cancers (*P*>0.05) in urban areas. Conversely, there was a significant increase in ASMRs for vaginal cancer and cervix cancer over the period 2010 to 2018 in urban areas. In rural regions, most female genital cancers saw notable increases in ASMRs over the same period, except for corpus uteri cancer, which did not

TABLE 1. The incidence and mortality of female genital cancers in China by cancer site and area, 2022.

Area	Site	ICD-10	Incidence				Mortality			
			Cases (×10,000)	Ratio	Crude rate (1/10^5)	ASIR (1/10^5)	Deaths (×10,000)	Ratio	Crude rate (1/10^5)	ASMR (1/10^5)
All	All	C51–54, C56	29.63	12.94	42.89	26.90	10.49	11.10	15.18	8.44
	Vulva	C51	0.41	0.18	0.60	0.32	0.20	0.21	0.28	0.14
	Vagina	C52	0.27	0.12	0.39	0.23	0.11	0.11	0.15	0.08
	Cervix	C53	15.07	6.58	21.81	13.83	5.57	5.89	8.06	4.54
	Corpus uteri	C54	7.77	3.39	11.25	6.84	1.35	1.43	1.96	1.05
	Ovary	C56	6.11	2.67	8.84	5.68	3.26	3.46	4.73	2.64
Urban	All	C51–54, C56	17.84	12.43	39.38	25.94	5.98	11.54	13.20	8.05
	Vulva	C51	0.23	0.16	0.51	0.30	0.11	0.21	0.24	0.13
	Vagina	C52	0.14	0.10	0.32	0.21	0.06	0.13	0.14	0.08
	Cervix	C53	8.55	5.96	18.87	12.49	3.02	5.82	6.66	4.11
	Corpus uteri	C54	5.01	3.49	11.06	7.10	0.79	1.52	1.74	1.03
	Ovary	C56	3.91	2.72	8.62	5.84	2.00	3.86	4.42	2.70
Rural	All	C51–54, C56	11.78	13.77	49.60	28.73	4.50	10.57	18.98	9.04
	Vulva	C51	0.18	0.21	0.76	0.36	0.09	0.21	0.37	0.15
	Vagina	C52	0.12	0.15	0.53	0.26	0.04	0.10	0.17	0.08
	Cervix	C53	6.52	7.61	27.42	16.23	2.55	5.98	10.74	5.16
	Corpus uteri	C54	2.76	3.23	11.63	6.45	0.56	1.32	2.38	1.07
	Ovary	C56	2.20	2.57	9.26	5.43	1.26	2.96	5.32	2.58

Note: Ratio means the proportion of the cases/deaths of the cancer site in the total cancer cases/deaths.
Abbreviation: ASIR=age-standardized incidence rate; ASMR=age-standardized mortality rate.

show a statistically significant trend in ASMR (Figure 3, Supplementary Table S2, available at http://weekly.chinacdc.cn/).

CONCLUSIONS

Cervical cancer was the most common malignancy and cause of death in female genital organs, accounting for 6.9% of all female cancer cases and 8.1% of all deaths worldwide (*3*). Globally, the rates of cervical cancer rates decline with higher Human Development Index (HDI) scores (*5*). China's figures from GLOBOCAN 2022 show that the country ranks 94th for age-standardized incidence rate and 126th for mortality rate out of 185 countries, both falling below global averages (ASIR of 14.1 per 100,000 and ASMR of 7.1 per 100,000) (*3*).

Although cervical cancer rates in China have historically been low, a concerning increase in both incidence and mortality was observed across urban and rural areas from 2010 to 2018. This trend poses a potential threat to the national goal of eradicating cervical cancer by 2030. Nonetheless, due to the long-term nature of cancer prevention strategies, it is premature to make definitive judgments at this stage (*6*). Despite the implementation of a cervical and breast cancer screening program for rural women in 2009, its coverage remained limited when considering the overall population of at-risk females (*7*). Singh et al. (*5*) conducted a comparison of age-specific incidence between countries with extensive screening programs and those with limited or no screening, revealing a post-35-year-age stabilization of cervical cancer rates in the former and a dramatic upsurge peaking around 55–64 years in the latter. Our current findings indicate that China's incidence pattern closely resembles that of countries with insufficient screening coverage, underscoring the need to enhance our national screening efforts. On a more positive note, earlier analyses have shown early signs of the impact of comprehensive cervical cancer prevention and control measures on younger Chinese women (*8*). The China Women's Development Guidelines (2021–2030) has set forth clear directives aiming to eradicate cervical cancer (*9*). Projections suggest that if vaccination and screening outreach are maximized, this goal could be attainable as early as the 2050s (*10*). Patience is necessary, as the full benefits of these interventions will

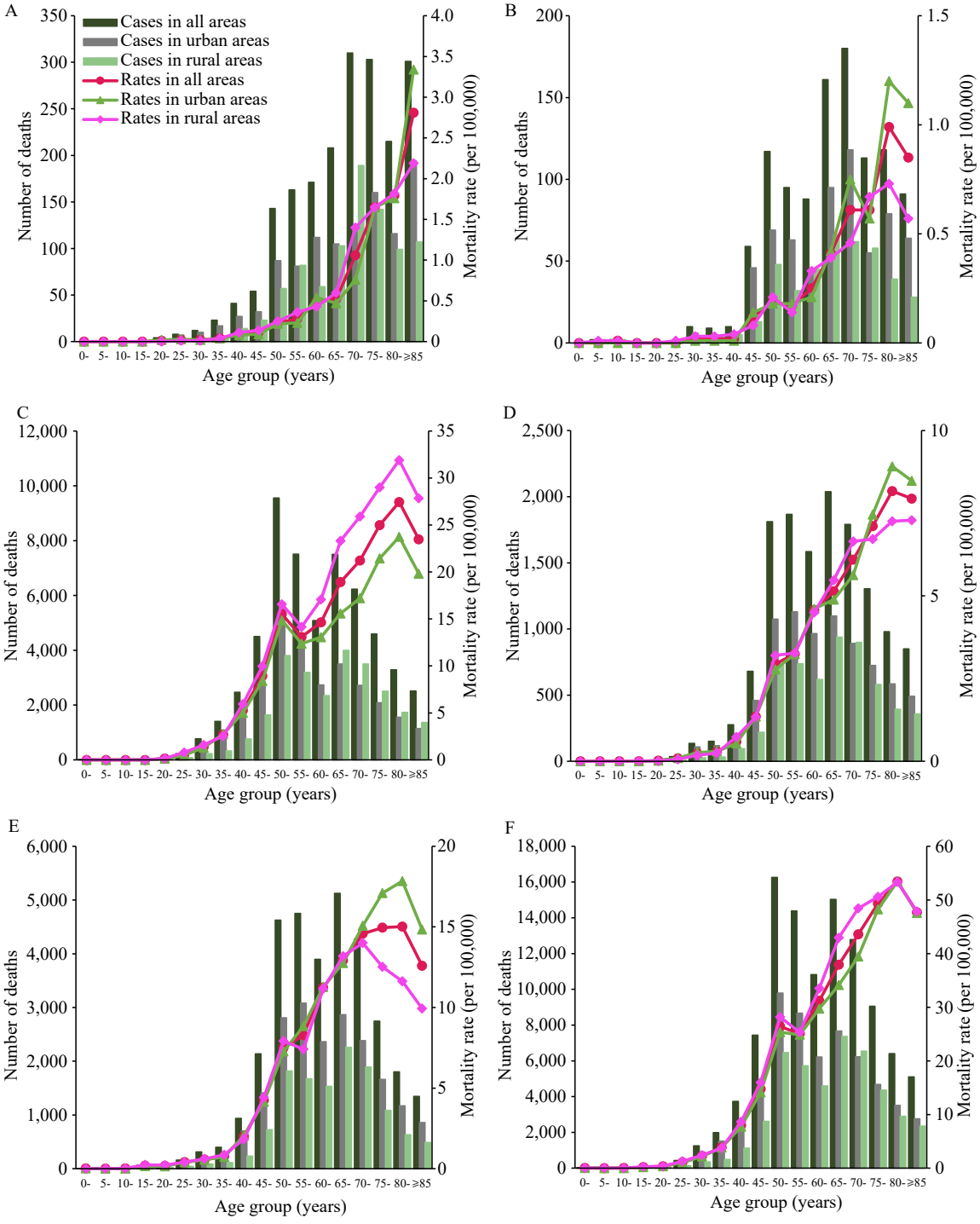


FIGURE 2. The deaths and mortality rates of female genital cancers in China by cancer site, age group and area, 2022. (A) Vulva (C5l); (B) Vagina (C52); (C) Cervix (C53); (D) Corpus uteri (C54); (E) Ovary (C56); (E) All (C51–54, 56).

unfold over time.

Ovarian cancer is a significant type of female genital cancer, representing 3.4% of all female cancer cases and 4.8% of all female cancer-related deaths (*3*). Research shows a positive association between the incidence of ovarian cancer and the HDI (*2*). According to GLOBOCAN 2022 data, China's ASIR and ASMR of ovarian cancer were relatively low, ranking 103rd and 155th out of 185 countries, indicating a lower disease burden compared to other nations (*3*).

Recent decades have shown a decline in ovarian cancer incidence in Europe and North America (*11*), partially due to the widespread use of oral

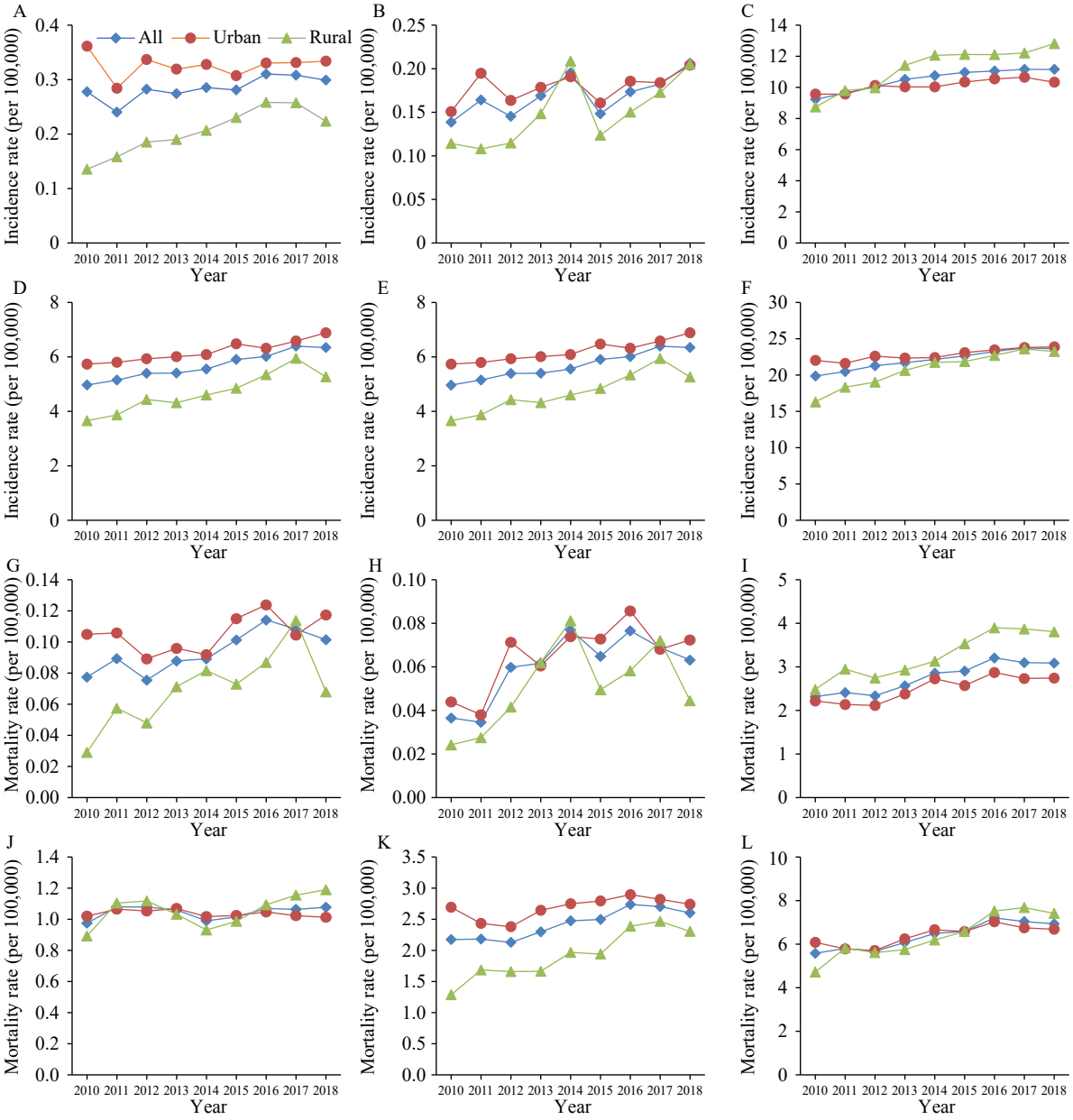


FIGURE 3. Trends in incidence and mortality rates of female genital cancers in China by cancer siteand area, 2010−2018, (A) Incidence rates for vulva (C5l); (B) Incidence rates for vagina (C52); (C) Incidence rates for cervix (C53); (D) Incidence rates for Corpus uteri (C54); (E) Incidence rates for ovary (C56); (F) Incidence rates for all (C51–54, 56); (G) Mortality rates for vulva (C5l); (H) Mortality rates for vagina (C52); (I) Mortality rates for cervix (C53); (J) Mortality rates for Corpus uteri (C54); (K) Mortality rates for ovary (C56); (L) Mortality rates for all (C51–54, 56).

contraceptive pills (*12*) and decreased use of menopausal hormone therapy (*13*). In contrast, upward trends have been observed in Japan, India, Belarus, and China, potentially linked to obesity and the adoption of a Western lifestyle (*14*). Notably, China's rural areas have experienced the most significant increases in both incidence and mortality rates of ovarian cancer, further research is imperative to elucidate the causes of these trends and to inform evidence-based policymaking.

Uterine corpus cancers represented 4.4% of all female cancer cases and 2.3% of global female cancer-related deaths. In the GLOBOCAN 2022 report, the ASIRs and ASMRs of uterine corpus cancer in China were lower than the global averages, ranking 98th and 128th out of 185 countries (*3*). Endometrial cancer was the primary type of uterine corpus cancer (ICD-10 C54). While the global incidence of endometrial

cancer has been rising, particularly in rapidly developing nations (*15*), we noted a significant increase in incidence rates in both urban and rural areas. However, mortality rates have remained relatively steady over time, suggesting improvements in disease detection, management, and treatment efficiency.

Vulvar and vaginal cancers represented 0.7% and 0.6% of all female cancer cases and deaths globally. According to GLOBOCAN 2022, China's age-standardized incidence and mortality rates for vulvar/vaginal cancer were ranked 139th/127th and 130th/121st, respectively, among 185 countries, which are below the global average (ASIR of 0.8/0.4 per 100,000 and ASMR of 0.3/0.2 per 100,000) (*3*). While a global increase in vulvar cancer incidences has been noted, particularly among younger women, the incidence of vaginal cancer has remained fairly stable (*16*). Despite the relatively low absolute numbers of vulvar and vaginal cancer cases and deaths in China, the country has experienced the fastest rates of increase and significant fluctuations, predominantly in rural areas. The majority of vaginal cancers and a proportion of vulvar cancers are associated with human papillomavirus (HPV), suggesting that HPV-related cancer risks remain high and may continue to escalate. Conversely, the sharp increases in these cancers may also be attributed to their rarity, which renders them more sensitive to changes in diagnostic specificity over time (*17*).

There were still some limitations. First, the projections of the incidence and mortality from 2018 to 2022 considered the demographic changes, but didn't take the impact of changes in disease diagnose ability or screening strategies into consideration. However, since the forecast year span was short, the impact of these factors was expected to be negligible. Second, since China is still undergoing a rapid socio-economic transformation, there may be noticeable changes in the population in rural areas, which may lead to possible estimation bias.

In conclusion, this study provides an overview of the current status and trends of female genital organ cancers in China, in alignment with GLOBOCAN 2022. Variations in the epidemiological patterns based on cancer site and geographic location highlight the necessity for tailored cancer prevention and control programs to address the growing disease burden.

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[#] Corresponding authors: Rongshou Zheng, zhengrongshou@cicams.ac.cn; Wenqiang Wei, weiwq@cicams.ac.cn.

[1] National Central Cancer Registry, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China.

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE S1. Trends for age-standardized incidence rates of female genital cancers for any time segments identified in Joinpoint analysis by cancer site and area, 2010 to 2018.

Site	ICD-10	Area	Trend1			Trend2			2010–2018		2014–2018	
			Years	APC (95% *CI*)	*P*	Years	APC (95% *CI*)	*P*	AAPC	*P*	AAPC	*P*
All	C51–54, 56	All	2010–2016	2.6 (2.1, 3.1)	<0.001*	2016–2018	0.8 (−1.9, 3.7)	0.455	2.2 (1.6, 2.7)	<0.001*	1.7 (0.7, 2.7)	<0.001*
		Urban	2010–2018	1.2 (0.8, 1.6)	<0.001*	–	–	–	1.2 (0.8, 1.6)	<0.001*	1.2 (0.8, 1.6)	<0.001*
		Rural	2010–2014	7.0 (4.2, 9.9)	0.002*	2014–2018	1.9 (−0.9, 4.6)	0.131	4.4 (3.0, 5.8)	0.001*	1.9 (−0.9, 4.6)	0.100
Vulva	C51	All	2010–2018	2.1 (0.4, 3.8)	0.020*	–	–	–	2.1 (0.4, 3.8)	0.020*	2.1 (0.4, 3.8)	0.020*
		Urban	2010–2018	0.1 (−2.0, 2.3)	0.904	–	–	–	0.1 (−2.0, 2.3)	0.904	0.1 (−2.0, 2.3)	0.904
		Rural	2010–2016	10.8 (7.6, 14.0)	<0.001*	2016–2018	-6.3 (−21.0, 11.2)	0.351	6.3 (2.7, 9.9)	0.001*	1.9 (−4.1, 8.3)	0.500
Vagina	C52	All	2010–2018	3.6 (0.5, 6.9)	0.029*	–	–	–	3.6 (0.5, 6.9)	0.029*	3.6 (0.5, 6.9)	0.029*
		Urban	2010–2018	2.0 (−0.7, 4.8)	0.130	–	–	–	2.0 (−0.7, 4.8)	0.130	2.0 (−0.7, 4.8)	0.130
		Rural	2010–2018	7.1 (1.3, 13.2)	0.022*	–	–	–	7.1 (1.3, 13.2)	0.022*	7.1 (1.3, 13.2)	0.022*
Cervix	C53	All	2010–2014	4.1 (3.7, 4.4)	<0.001*	2014–2018	0.8 (0.5, 1.1)	0.001	2.4 (2.4, 2.4)	0.001*	1.0 (1.0, 1.0)	0.001*
		Urban	2010–2018	1.2 (0.7, 1.8)	0.001*	–	–	–	1.2 (0.7, 1.8)	0.001*	1.2 (0.7, 1.8)	0.001*
		Rural	2010–2014	8.0 (4.4, 11.8)	0.003*	2014–2018	1.1 (−2.3, 4.6)	0.430	4.5 (2.7, 6.3)	0.001*	1.1 (−2.3, 4.6)	0.400
Corpus uteri	C54	All	2010–2018	3.3 (2.8, 3.8)	<0.001*	–	–	–	3.3 (2.8, 3.8)	<0.001*	3.3 (2.8, 3.8)	<0.001*
		Urban	2010–2018	2.2 (1.7, 2.7)	<0.001*	–	–	–	2.2 (1.7, 2.7)	<0.001*	2.2 (1.7, 2.7)	<0.001*
		Rural	2010–2018	5.5 (3.8, 7.4)	<0.001*	–	–	–	5.5 (3.8, 7.4)	<0.001*	5.5 (3.8, 7.4)	<0.001*
Ovary	C56	All	2010–2018	1.0 (0.4, 1.6)	0.004*	–	–	–	1.0 (0.4, 1.6)	0.004*	1.0 (0.4, 1.6)	0.004*
		Urban	2010–2018	0.2 (−0.8, 1.1)	0.680	–	–	–	0.2 (−0.8, 1.1)	0.680	0.2 (−0.8, 1.1)	0.680
		Rural	2010–2018	2.8 (1.1, 4.5)	0.006*	–	–	–	2.8 (1.1, 4.5)	0.006*	2.8 (1.1, 4.5)	0.006*

Note: "−" means no estimations in this time period.
Abbreviation: APC=Annual percent change. AAPC=Average annual percent change. *CI*=confidence interval.
* *P*<0.05.

SUPPLEMENTARY TABLE S2. Trends for age-standardized mortality rates of female genital cancers for any time segments identified in Joinpoint analysis by cancer site and area, 2010 to 2018.

Site	ICD−10	Area	Trend1			Trend2			2010–2018		2014–2018	
			Years	APC (95% *CI*)	*P*	Years	APC (95% *CI*)	*P*	AAPC	*P*	AAPC	*P*
All	C51–54,56	All	2010–2018	3.4 (2.3, 4.5)	<0.001*	–	–	–	3.4 (2.3, 4.5)	<0.001*	3.4 (2.3, 4.5)	<0.001*
		Urban	2010–2018	2.2 (0.8, 3.6)	0.006*	–	–	–	2.2 (0.8, 3.6)	0.006*	2.2 (0.8, 3.6)	0.006*
		Rural	2010–2018	5.8 (3.9, 7.6)	<0.001*	–	–	–	5.8 (3.9, 7.6)	<0.001*	5.8 (3.9, 7.6)	<0.001*
Vulva	C51	All	2010–2018	4.5 (1.9, 7.2)	0.005*	–	–	–	4.5 (1.9, 7.2)	0.005*	4.5 (1.9, 7.2)	0.005*
		Urban	2010–2018	2.1 (−1.1, 5.4)	0.161	–	–	–	2.1 (−1.1, 5.4)	0.161	2.1 (−1.1, 5.4)	0.161
		Rural	2010–2018	11.7(3.1, 21.1)	0.014*	–	–	–	11.7(3.1, 21.1)	0.014*	11.7 (3.1, 21.1)	0.014*
Vagina	C52	All	2010–2018	8.3 (1.6, 15.5)	0.021*	–	–	–	8.3 (1.6, 15.5)	0.021*	8.3 (1.6, 15.5)	0.021*
		Urban	2010–2018	7.4 (1.3, 13.9)	0.024*	–	–	–	7.4 (1.3, 13.9)	0.024*	7.4 (1.3, 13.9)	0.024*
		Rural	2010–2014	33.5(4.6, 70.4)	0.030*	2014–2018	−9.2 (−28.9, 15.9)	0.333	10.1(−2.6, 24.3)	0.100	−9.2(−28.9, 15.9)	0.300
Cervix	C53	All	2010–2018	4.5 (3.0, 6.1)	<0.001*	–	–	–	4.5 (3.0, 6.1)	<0.001*	4.5 (3.0, 6.1)	<0.001*
		Urban	2010–2018	3.9 (1.9, 5.9)	0.002*	–	–	–	3.9 (1.9, 5.9)	0.002*	3.9 (1.9, 5.9)	0.002*
		Rural	2010–2018	5.9 (4.0, 7.7)	<0.001*	–	–	–	5.9 (4.0, 7.7)	<0.001*	5.9 (4.0, 7.7)	<0.001*
Corpus uteri	C54	All	2010–2018	0.5 (−0.7, 1.7)	0.379	–	–	–	0.5 (−0.7, 1.7)	0.379	0.5 (−0.7, 1.7)	0.379
		Urban	2010–2018	−0.3 (−0.9, 0.3)	0.236	–	–	–	−0.3 (−0.9, 0.3)	0.236	−0.3 (−0.9, 0.3)	0.236
		Rural	2010–2018	2.0 (−0.7, 4.8)	0.119	–	–	–	2.0 (−0.7, 4.8)	0.119	2.0 (−0.7, 4.8)	0.119
Ovary	C56	All	2010–2018	3.3 (2.0, 4.5)	<0.001*	–	–	–	2.3 (−0.8, 5.5)	<0.001*	2.0 (−2.1, 6.1)	<0.001*
		Urban	2010–2018	1.6 (0.0, 3.3)	0.052	–	–	–	1.6 (0.0, 3.3)	0.052	1.6 (0.0, 3.3)	0.052
		Rural	2010–2018	7.5 (4.9, 10.2)	<0.001*	–	–	–	7.5 (4.9, 10.2)	<0.001*	7.5 (4.9, 10.2)	<0.001*

Note: "–" means no estimations in this time period.
Abbreviation: APC=Annual percent change; AAPC=Average annual percent change; *CI*=confidence interval.
* *P*<0.05.

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