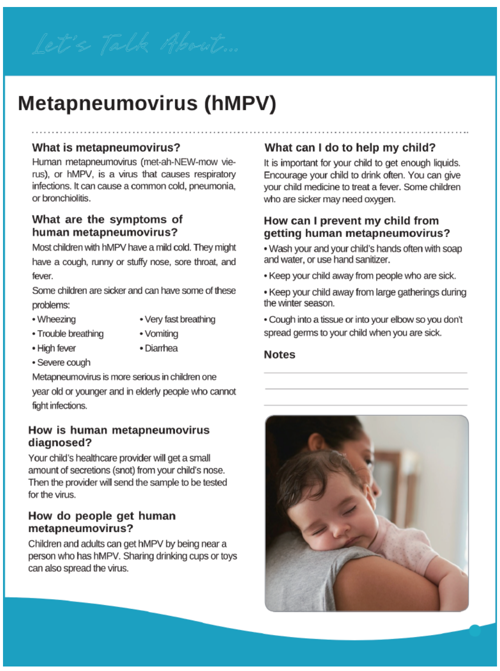
ISSN 2096-7071
CN 10-1629/R1

CHINA CDC WEEKLY

CCDC weekly

Vol. 5 No. 23 Jun. 9, 2023

中国疾病预防控制中心周报



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Preplanned Studies

Periconceptional Folic Acid Only Versus Multiple Micronutrients Containing Folic Acid and Association with Gestational Diabetes Mellitus — Beijing Municipality, China, 2017–2021

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Summary

What is already known about this topic?

Inconsistent results have been reported on the association between periconceptional folic acid only (FAO) or multiple micronutrients containing folic acid (MMFA) supplementation and the risk of gestational diabetes mellitus (GDM) in previous research.

What is added by this report?

In a prospective cohort study conducted among pregnant women in Haidian District, Beijing Municipality, it was observed that those who took MMFA demonstrated a higher likelihood of developing GDM in comparison to those who consumed FAO periconceptionally. Interestingly, the increased risk for GDM in pregnant women supplemented with MMFA compared to FAO was primarily due to changes in fasting plasma glucose.

What are the implications for public health practice?

It is highly recommended that women prioritize the use of FAO in order to yield potential benefits in the prevention of GDM.

Gestational diabetes mellitus (GDM) is defined as diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation, posing a serious risk to maternal and infant health (*1*). The prevalence of GDM in China has been increasing, with a recent meta-analysis revealing that the prevalence of GDM in China is 14.8% (*2*). Folic acid (FA) supplementation is widely promoted among pregnant women in China to reduce the risk of fetal neural tube defects. However, concerns have arisen about the potential effects of FA supplementation on maternal health. Recent studies investigating the association between FA supplementation and GDM have yielded inconclusive results, particularly in regards to maternal supplementation with FA only (FAO) or with multiple micronutrients containing FA (MMFA) (*3*). This study analyzed data from a prospective cohort of pregnant women at the Haidian Maternal and Child Health Hospital in Beijing, China, during the period from 2017 to 2021, where the prevalence of GDM was 18.8%. The results revealed that women taking MMFA were more likely to develop GDM than women taking FAO.

This ongoing prospective cohort study focuses on pregnant women and has been previously described in detail (*4*). From October 2017 to October 2021, 4,239 pregnant women at or before 20 weeks of gestation were recruited at the Haidian Maternal and Child Health Hospital in Beijing, China. A structured questionnaire, which included demographic characteristics and detailed FA supplementation information, was administered during recruitment. Information on periconceptional FA supplementation among pregnant women included whether they took supplements (no or yes), type of supplements (FAO or MMFA), timing (before or after conception), and frequency (>24 or ≤24 capsules/month). Frequency of FA supplementation was divided into two groups based on 80% of the recommended standard (30 capsules/month).

After recruitment, the pregnant women underwent the oral glucose tolerance test (OGTT) for blood glucose at 24–28 weeks of pregnancy. GDM diagnosis followed the International Association of Diabetes and Pregnancy Study Group criteria, which required that a pregnant woman met one or more of the following criteria: fasting plasma glucose (FPG) ≥5.1 mmol/L, 1-hour plasma glucose (1 h PG) ≥10.0 mmol/L during OGTT, or 2-hour plasma glucose (2 h PG) ≥8.5 mmol/L during OGTT (*1*). A total of 818 women were excluded due to unclear information on FA intake, missing OGTT results at 24–28 weeks of pregnancy, and a history of pre-pregnancy diabetes or first-degree family history of diabetes. Consequently, the final analysis included data from 3,421 women.

This study was approved by the Biomedical Institutional Review Board of Peking University (IRB00001052-17028), and written consent was obtained from all participants.

In this study, binary logistic regression was employed to analyze the association between FA supplementation and GDM while adjusting for potential confounding variables. These variables, such as maternal age and pre-pregnancy body mass index (BMI), were chosen based on previously relevant studies (*5*). Additionally, certain food consumption characteristics were included since food can serve as a source of dietary folate. Outcome variables like FPG GDM, 1 h PG-GDM, and 2 h PG-GDM were defined based on distinct testing time points, which were utilized to further explore the association between FA supplementation and different GDM subtypes. The logistic analysis results are presented as odds ratios (*OR*s) and 95% confidence intervals (95% *CI*s). All analyses were conducted using R software (version 4.0.5; R Development Core Team, Vienna, Austria). A two-tailed $P \leq 0.05$ was considered statistically significant.

A total of 3,421 women were included in the final analysis, with ages ranging from 20 to 49 years old (mean=30.2, SD=3.7). Of these participants, 17.5% were classified as above normal weight before conception, with a pre-pregnancy BMI≥24 kg/m^2. Among the sample, 643 women (18.8%) were diagnosed with GDM. A higher prevalence of GDM was observed among older, more obese, multiparous, less educated women, and those exposed to smoking (all $P<0.05$). Additionally, GDM prevalence was higher among women who reported higher consumption of eggs and milk ($P<0.05$). However, no significant differences were observed in terms of occupation, ethnicity, education, or the frequency of meat, vegetable, fruit, and soybean consumption (all $P>0.05$) (Table 1).

Table 2 demonstrates that only 3.2% (109/3,421) of participants did not take FA periconceptionally, while 26.2% (880/3,421) took FAO, and the majority, 70.6% (2,432/3,421), took MMFA. Women who took MMFA were more likely to develop GDM compared

TABLE 1. Characteristics of pregnant women between groups of GDM and non-GDM in Beijing, China, 2017–2021, *n* (%).

Variable	Total*	Non-GDM*	GDM*	*P* value†
Total	3,421 (100.0)	2,778 (81.2)	643 (18.8)	
Age (years)				<0.001
<30	1,675 (49.0)	1,411 (84.2)	264 (15.8)	
≥30	1,746 (51.0)	1,367 (78.3)	379 (21.7)	
Pre-pregnancy BMI (kg/m^2)				<0.001
<24	2,654 (81.6)	2,219 (83.6)	435 (16.4)	
≥24	598 (18.4)	414 (69.2)	184 (30.8)	
Occupation				0.072
None	219 (6.5)	168 (76.7)	51 (23.3)	
Teacher/doctor/technician	1,109 (32.8)	927 (83.6)	182 (16.4)	
Business/service	791 (23.4)	642 (81.2)	149 (18.8)	
Public official	698 (20.7)	554 (79.4)	144 (20.6)	
Others	562 (16.6)	458 (81.5)	104 (18.5)	
Education				0.031
Master or above	957 (27.7)	795 (83.9)	152 (16.1)	
College or university	2,247 (65.1)	1,790 (80.4)	436 (19.6)	
High school or below	250 (7.2)	191 (78.3)	53 (21.7)	
Ethnicity				0.875
Han	3,208 (93.8)	2,629 (81.1)	613 (18.9)	
Others	211 (6.2)	175 (81.8)	39 (18.2)	
Smoking				0.003
No	2,574 (76.0)	2,120 (82.4)	454 (17.6)	
Yes§	813 (24.0)	631 (77.3)	182 (22.7)	
Parity				0.014
Nulliparous	2,464 (80.6)	2,020 (82.0)	444 (18.0)	
Multiparous	593 (19.4)	460 (77.6)	134 (22.4)	

TABLE 1. (Continued)

Variable	Total*	Non-GDM*	GDM*	*P* value†
Food consumption				
Meat (times/week)				0.198
≤3	1,965 (59.8)	1,610 (81.9)	365 (18.1)	
4–6	727 (22.1)	588 (80.9)	139 (19.1)	
>6	595 (18.1)	468 (78.7)	127 (21.3)	
Egg (times/week)				0.026
≤3	1,094 (32.2)	913 (83.5)	181 (16.5)	
4–6	1,116 (33.8)	903 (80.9)	213 (19.1)	
>6	1,087 (33.0)	858 (78.9)	229 (21.1)	
Milk (times/week)				0.015
≤3	1,253 (38.0)	1,048 (83.6)	205 (16.4)	
4–6	995 (30.2)	788 (79.2)	207 (20.8)	
>6	1,046 (31.8)	837 (80.0)	209 (20.0)	
Vegetable (times/week)				0.138
≤3	326 (9.9)	274 (84.0)	52 (16.0)	
4–6	809 (24.6)	668 (82.6)	141 (17.4)	
>6	2,159 (65.5)	1,733 (80.3)	426 (19.7)	
Fruit (times/week)				0.554
≤3	173 (5.2)	146 (84.4)	27 (15.6)	
4–6	637 (19.3)	518 (81.3)	119 (18.7)	
>6	2,492 (75.5)	2,020 (81.1)	472 (18.9)	
Soybean (times/week)				0.652
≤3	1,898 (57.9)	1,553 (81.8)	345 (18.2)	
4–6	865 (26.4)	698 (80.7)	167 (19.3)	
>6	514 (15.7)	413 (80.4)	101 (19.6)	

Abbreviation: GDM=gestational diabetes mellitus; BMI=body mass index.

* The total value differs from the sum of subgroups due to the exclusion of cases with missing data.

† Differences in prevalence of GDM by subcategory were examined with the Chi-square test.

§ Smoking included exposure to passive smoking.

to those on FAO (adjusted *OR*=1.34, 95% *CI*: 1.05–1.72). No significant difference in GDM prevalence was observed between women taking FAO and those without FA supplementation (adjusted *OR*=0.76, 95% *CI*: 0.37–1.55). Furthermore, no associations were detected between the initial time or frequency of FA supplementation and GDM, regardless of stratification by type (all *P*>0.05).

When analyzing the association between FA supplementation and GDM subtypes, the results showed that the increased risk for GDM in pregnant women supplemented with MMFA compared to FAO was primarily due to changes in FPG (adjusted *OR*=1.40, 95% *CI*: 1.02–1.92). FA supplementation type was not associated with 1 h PG-GDM and 2 h PG-GDM (all *P*>0.05). (Figure 1).

DISCUSSION

We investigated the association between maternal FA supplementation and GDM using a prospective cohort in Haidian District, Beijing. Our results revealed that the GDM prevalence in Beijing was 18.8%, which was slightly higher than the reported prevalence in Beijing in 2017 (17.2%) (*5*), and surpassing that in China (14.8%) (*2*). This suggests that GDM prevalence in Beijing is relatively high and continues to increase. Furthermore, only 3.2% of participants did not take FA periconceptionally, and more women opted for MMFA than FAO, which aligns with another survey conducted in Beijing (*6*). These findings underline the importance of exploring the effects of FAO/MMFA supplementation on GDM.

Our study found that pregnant women taking MMFA had a higher likelihood of developing GDM compared to those taking FAO. We observed no significant difference in GDM risk between women who took FAO and those without supplementation, suggesting that appropriate FA supplementation does not increase GDM risk. Several possible explanations for this association exist.

TABLE 2. Association between folic acid supplementation and GDM in pregnant women in Beijing, China, 2017–2021.

FA supplementation	Total	GDM	Crude *OR* (95% *CI*)*	Adjusted *OR* (95% *CI*)†
Total	3,421	643 (18.8)	–	–
FA supplementation				
No	109	15 (13.8)	Reference	Reference
Yes	3,312	628 (19.0)	1.47 (0.84–2.55)	1.52 (0.80–2.87)
Type				
FAO	880	145 (16.5)	Reference	Reference
MMFA	2,432	483 (19.9)	1.26 (1.02–1.54)	1.34 (1.05–1.72)
Nonusers	109	15 (13.8)	0.81 (0.46–1.44)	0.76 (0.37–1.55)
Initial time				
Nonusers	109	15 (13.8)	Reference	Reference
Before conception	1,689	317 (18.8)	1.45 (0.83–2.53)	1.60 (0.80–3.22)
After conception	1,623	311 (19.2)	1.49 (0.85–2.60)	1.64 (0.82–3.30)
Supplement frequency				
Nonusers	109	15 (13.8)	Reference	Reference
≤24 capsules per month	675	141 (20.9)	1.66 (0.93–2.94)	1.82 (0.89–3.72)
>24 capsules per month	2,557	472 (18.5)	1.42 (0.82–2.47)	1.55 (0.77–3.10)
Stratified by types				
Initial time				
FAO				
Nonusers	109	15 (13.8)	Reference	Reference
Before conception	465	69 (14.8)	1.09 (0.60–1.99)	1.36 (0.72–2.59)
After conception	415	76 (18.3)	1.41 (0.77–2.56)	1.60 (0.85–3.00)
MMFA				
Nonusers	109	15 (13.8)	Reference	Reference
Before conception	1,224	248 (20.3)	1.59 (0.91–2.80)	1.78 (0.88–3.60)
After conception	1,208	235 (19.5)	1.51 (0.86–2.66)	1.68 (0.83–3.39)
Supplement frequency				
FAO				
Nonusers	109	15 (13.8)	Reference	Reference
≤24 capsules per month	190	37 (19.5)	1.52 (0.79–2.91)	1.87 (0.81–4.31)
>24 capsules per month	658	105 (16.0)	1.19 (0.66–2.13)	1.48 (0.68–3.21)
MMFA				
Nonusers	109	15 (13.8)	Reference	Reference
≤24 capsules per month	485	104 (21.4)	1.71 (0.95–3.08)	1.88 (0.91–3.90)
>24 capsules per month	1,899	367 (19.3)	1.50 (0.86–2.62)	1.65 (0.82–3.32)

Abbreviation: FA=Folic acid; GDM=gestational diabetes mellitus; *OR*=odds ratio; *CI*=confidence interval; FAO=folic acid only; MMFA=multiple micronutrients containing folic acid.

* crude *OR*: logistic regression. No confounders were adjusted.

† adjusted *OR*: logistic regression. Adjusted for maternal age, pre-pregnancy BMI, occupation, education, parity, smoking, and consumption of eggs, milk, vegetables, and fruits.

"–" means data not available.

First, a dose-response relationship may exist between FA and GDM. The main brand of MMFA contains twice the amount of FA (0.8 mg/tablet) as a simple FA tablet (0.4 mg/tablet) (*6*). Excessive FA can lead to increased circulating unmetabolized folate, which in turn elevates homocysteine levels. This elevation has

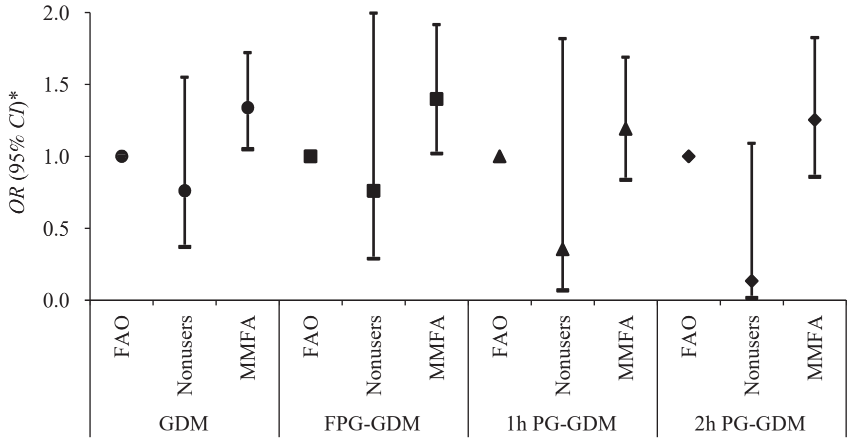

FIGURE 1. Association between folic acid supplementation and various subtypes of gestational diabetes mellitus among pregnant women in Beijing, China, 2017–2021.

Abbreviation: GDM=gestational diabetes mellitus; *OR*=odds ratio; FAO=folic acid only; MMFA=multiple micronutrients containing folic acid; FPG-GDM=GDM diagnosed by fasting plasma glucose; 1 h PG-GDM=GDM diagnosed by 1-hour plasma glucose during OGTT; 2 h PG-GDM=GDM diagnosed by 2-hour plasma glucose during OGTT.

* *OR*: logistic regression. Adjusted for maternal age, pre-pregnancy BMI, occupation, education, parity, smoking, and consumption of eggs, milk, vegetables, and fruits.

been associated with increased oxidative stress and impaired pancreatic β-cell function (*7*). As we did not investigate FA supplementation quantity and dosage, further research should examine the dose-response relationship between FA and GDM.

Second, other nutrients play important roles in numerous cellular and physiological processes. Excessive levels of certain micronutrients in MMFA, such as iron, have been associated with GDM (*8*). WHO guidelines do not recommend promoting MMFA in pregnant women due to insufficient evidence of its benefits for neonatal survival, growth, or cognitive function compared to FAO. Additionally, MMFA supplementation may pose an increased economic burden for pregnant women (*9*). Although we did not investigate the specific nutrient contents and doses of MMFA, our results support prioritizing FAO supplementation for GDM prevention. Our study supports the WHO's recommendation by emphasizing the potential risks of MMFA for women's health.

Previous research examining the relationship between FA supplementation and GDM has yielded inconsistent findings; some studies have reported a protective effect, while others have found no association or even harmful outcomes (*3*). These discrepancies are generally attributed to variations in study populations with regard to GDM prevalence, diagnostic criteria, as well as dietary and lifestyle differences. Notably, few investigations have distinguished between types of FA supplementation or considered the influence of other vitamins and minerals. In our cohort, the majority of pregnant women opted for MMFA supplementation, and a significant difference in GDM risk was observed between those taking FAO and those using MMFA. To the best of our knowledge, this study is the first to illuminate the distinct effects of FAO and MMFA on GDM risk, laying the groundwork for future research exploring the relationship between FA supplementation and GDM.

We further compared the effects of FA supplementation on various subtypes of GDM. The findings indicated that MMFA supplementation primarily affected FPG levels, increasing the risk of developing GDM. Previous studies have demonstrated a relationship between vitamin B12 levels and FPG; however, no significant associations were observed between vitamin B12 and either 1 h PG or 2 h PG (*10*). This may suggest that FPG serves as a more sensitive indicator for GDM diagnosis and predicting risk factors.

Our study exhibited multiple strengths. First, as a prospective cohort study, it excluded women with a history of diabetes mellitus, allowing for the prospective determination that FA supplementation significantly contributed to the heightened risk for GDM. Second, by controlling the consumption frequency of fruits, vegetables, and other foods, we effectively eliminated the influence of dietary FA intake on the results. Lastly, through stratification of the FA supplementation types, we were able to investigate the associations between specific characteristics of FA supplementation and GDM.

This study, however, is subject to several limitations. The population was drawn from Beijing, which has a high standard of living and nutritional status, potentially limiting the generalizability of the results. The older maternal age and prevalence of GDM, as well as potential genetic and environmental factors, may also affect the findings. Additionally, we were unable to obtain and compare the specific components of the MMFA, and our analysis did not investigate the duration or dose of FA supplementation, although we did incorporate frequency. Lastly, we did not examine the association between blood FA levels and GDM; further research is warranted in this area.

In conclusion, our study suggests that maternal periconceptional supplementation with MMFA may result in an increased risk for GDM when compared to FAO supplementation. Pregnant women ought to be cognizant of the potential issues related to over supplementation of certain micronutrients. As new population policies are implemented, the proportion of pregnant women of advanced age continues to rise. Concurrently, improved nutritional status among pregnant women has been observed, as evidenced by increased instances of overweight and excessive gestational weight gain during pregnancy. These factors may contribute to a heightened prevalence of GDM among expectant mothers. Our findings indicate that pregnant women should prioritize FAO supplementation as a preventive measure against GDM. Further research is warranted to inform clinical practice and aid women in reducing the risk of GDM and other associated metabolic diseases.

Conflicts of interest: No conflicts of interest.

Acknowledgements: The authors would like to thank all the participants in this study. The authors also thank the health care workers at Haidian Maternal and Child Health Hospital for their assistance with data collection.

Funding: The Fundamental Research Funds for the Central Universities (BMU2021YJ034); CNS-ZD Tizhi and Health Fund (CNS-ZD2020-115); National Natural Science Foundation of China (81673177).

doi: 10.46234/ccdcw2023.095

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Submitted: April 07, 2023; Accepted: May 06, 2023

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Preplanned Studies

A Comparison of Clinical Characteristics of Infections with SARS-CoV-2 Omicron Subvariants BF.7.14 and BA.5.2.48 — China, October–December 2022

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Summary

What is already known about this topic?

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to evolve, the clinical manifestations resulting from different SARS-CoV-2 variants may demonstrate significant variation.

What is added by this report?

We conducted a comparative analysis of the clinical features associated with SARS-CoV-2 Omicron subvariants BF.7.14 and BA.5.2.48 infections. The results of our study indicate that there are no substantial differences in clinical manifestations, duration of illness, healthcare-seeking behaviors, or treatment between these two subvariants.

What are the implications for public health practice?

Timely identification of alterations in the clinical spectrum is crucial for researchers and healthcare practitioners in order to enhance their comprehension of clinical manifestations, as well as the progression of SARS-CoV-2. Furthermore, this information is beneficial for policymakers in the process of revising and implementing appropriate countermeasures.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has demonstrated ongoing adaptations in humans and its infections display a wide array of clinical manifestations (*1*). Although the symptoms caused by various SARS-CoV-2 variants may be similar (*2*), certain variants have been associated with increased severity or heightened transmissibility (*3–4*).

According to surveillance data from the China CDC (*5*), the proportions of the Omicron subvariants BF.7.14 and BA.5.2.48 have increased since late September 2022 in China. The BF.7.14 variant has become widespread in Beijing Municipality, Tianjin Municipality, and Inner Mongolia Autonomous Region, whereas the BA.5.2.48 variant has been predominant in other provincial-level administrative divisions (PLADs). Public controversy arose if infected individuals in Beijing exhibited more severe symptoms than their counterparts in Shanghai Municipality, Guangdong Province, and other PLADs in southern China. To address these concerns, we conducted a retrospective study employing a telephone survey to examine the differences in clinical characteristics of infections with BF.7.14 and BA.5.2.48 subvariants.

In Beijing, respiratory samples from both imported and local cases have been routinely collected. These samples include nasopharyngeal swabs, oropharyngeal swabs, and sputum. The sample collection process is detailed in a previous study conducted by our team (*6*).

For this study, we randomly selected samples with sufficient viral load (*Ct* <32) collected from October to December 2022. Utilizing next-generation sequencing, we found all 527 patients were infected with the Omicron variant, with 371 and 156 individuals being infected with the BF.7.14 and BA.5.2.48 subvariants, respectively. Ethics approval for this study was granted by the Ethics Committee of the Beijing Center for Disease Prevention and Control (2021-1G-3012).

The structured questionnaire was created by public health professionals from the Beijing Center for Disease Prevention and Control, as well as clinical experts from Beijing Shijitan Hospital. This 67-question survey addressed participant demographics, coronavirus disease 2019 (COVID-19) vaccination status, comorbidities, duration of illness, clinical manifestations, healthcare-seeking behaviors, and treatment.

A third-party survey company executed the telephone survey which took place between March 2 and 6, 2023. The survey commenced with a brief introduction to the study, and questionnaires were completed by individuals who provided verbal consent to participate. Comorbidities and symptoms were discussed in-depth, with explanations given as necessary. The estimated time for completion ranged from 7 to 15 minutes.

Responses were gathered and entered into a Word Processing System (WPS, version13.33.0; Kingsoft, Beijing, China) spreadsheet. Data analysis was conducted using SPSS software (version 19.0; IBM, Armonk, NY, USA). Descriptive statistics, including frequencies and proportions, were computed for each item in the questionnaire. Median values with interquartile range (*IQR*) and means with standard deviation were reported. Student's *t*-tests were utilized to compare continuous measures. For dichotomous measures, chi-square (χ^2) tests were carried out, and contingency corrections or Fisher's exact tests were employed when data did not fulfill the standard χ^2 test criteria. Mann-Whitney *U* tests were applied to compare median values. A probability value of $P \leq 0.05$ was considered statistically significant, and all statistical tests were two-sided.

Among the 527 patients who were contacted via telephone, a total of 339 (64.3%) responded and completed the questionnaire. The response rate for the BF.7.14 infection group was 65.2% (242/371), and for the BA.5.2.48 group, it was 62.2% (97/156, χ^2=0.445, *P*=0.505). In the case of 31 patients under 18 years of age, their parents were surveyed through phone calls as proxies for the patients themselves.

Table 1 displays the participants' background characteristics. No statistically significant differences were observed in terms of age or sex. Additionally,

TABLE 1. Background characteristics of the patients.

Characteristic	BF.7.14 infection	BA.5.2.48 infection	Statistic	*P* value
Age [years old, (M, *IQR*)]	41 (30.8–55.3)	41 (29.5–52.0)	11454.500*	0.729
Male (*n*, %)	150 (62.0)	60 (61.9)	<0.001*	0.983
BMI [kg/m², ($\bar{X}$, SD)]	24.7 (3.9)	24.5 (4.4)	−0.353†	0.724
COVID-19 vaccination (*n*, %)			0.402§	0.526
None	21 (8.9)	8 (8.3)		
1 dose	4 (1.7)	1 (1.0)		
2 doses	47 (20.0)	18 (18.8)		
≥3 doses	163 (69.4)	69 (71.9)		
Comorbidities (*n*, %)				
Hypertension	44 (18.2)	11 (11.3)	2.385*	0.123
Metabolic disorders	23 (9.5)	9 (9.3)	0.004*	0.949
Cardiovascular diseases	14 (5.8)	5 (5.2)	0.052*	0.820
Cerebrovascular diseases	7 (2.9)	1 (1.0)	0.390*	0.532
Lung diseases	8 (3.3)	3 (3.1)	<0.001§	>0.999
Tumors	3 (1.2)	2 (2.1)	0.005§	0.945
Rheumatic diseases	1 (0.4)	3 (3.1)	2.276§	0.131
Health-related behaviors				
Smoking	61 (25.2)	15 (15.5)	3.779*	0.052
Alcohol consumption	65 (26.9)	19 (19.6)	1.965*	0.161
Routine exercise	136 (56.2)	48 (49.5)	1.258*	0.262
Education level (*n*, %)			4.661*	0.198
Junior high school or below	97 (40.1)	31 (32.0)		
Senior high school (or equivalent)	63 (26.0)	21 (21.6)		
Undergraduate	70 (28.9)	38 (39.2)		
Postgraduate	12 (5.0)	7 (7.2)		

Abbreviation: M=median; *IQR*=interquartile range; BMI=body mass index (only applied to ≥18 years old); $\bar{X}$=average; SD=standard deviation; COVID-19=coronavirus disease 2019.

* χ^2 test.

† Student's *t*-test.

§ χ^2 test with contingency correction.

there was no significant difference in body mass index (BMI, weight/height^2) calculated for adults (i.e., age ≥ 18 years). Approximately 70% of the patients reported having received three or more doses of the COVID-19 vaccine, though vaccination completion rates did not significantly impact infection rates.

The three most common comorbidities in both the BF.7.14 and BA.5.2.48 infection groups were hypertension (18.2%, 44/242 *vs.* 11.3%, 11/97), metabolic disorders (9.5%, 23/242 *vs.* 9.3%, 9/97), and cardiovascular diseases (5.8%, 14/242 *vs.* 5.2%, 5/97), with no significant differences observed between the groups. Health-related behaviors such as smoking, alcohol consumption, and regular exercise showed no statistically significant differences between the two groups. Furthermore, the difference in education levels between the groups was not statistically significant.

Table 2 presents the patients' clinical characteristics. All manifestations were thoroughly examined, and no significant differences in symptoms between the groups were found, with the exception of fever. More than

TABLE 2. Clinical characteristics of the patients.

Characteristic	BF.7.14 infection	BA.5.2.48 infection	Statistic	*P* value
Symptoms (*n*, %)				
Fever			12.273*	0.007
No fever (<37.3 °C)	111 (35.0)	25 (27.8)		
Low-grade fever (37.3 °C–38.0 °C)	68 (21.5)	14 (15.6)		
Middle-grade fever (38.1 °C–39.0 °C)	96 (30.3)	31 (34.4)		
High fever (≥39.1 °C)	42 (13.2)	20 (22.2)		
Cough	128 (52.9)	46 (47.4)	0.829*	0.362
Swallowing difficulty	95 (39.6)	28 (28.9)	3.423*	0.064
Fatigue or muscle weakness	70 (29.2)	23 (23.7)	1.029*	0.310
Muscle pain	58 (24.2)	18 (18.6)	1.245*	0.265
Difficulty in movement	40 (19.8)	16 (19.0)	0.021*	0.884
Headache	39 (16.3)	13 (13.4)	0.448*	0.503
Taste or smell disorder	38 (15.9)	11 (11.3)	1.151*	0.283
Sleep disorder	39 (16.3)	10 (10.3)	1.962*	0.161
Joint pain	30 (12.6)	11 (11.3)	0.095*	0.758
Vomiting or diarrhea	23 (9.6)	10 (10.3)	0.041*	0.839
Breathing difficulties	31 (12.9)	6 (6.2)	3.202*	0.074
Cognitive impairment	20 (8.3)	9 (9.3)	0.078*	0.779
Dizziness	17 (7.1)	6 (6.2)	0.093*	0.760
Personality change	22 (9.2)	3 (3.1)	3.711*	0.054
Chest pain	14 (5.8)	4 (4.1)	0.399*	0.527
Hair loss	7 (2.9)	1 (1.0)	0.402†	0.526
Conjunctivitis	4 (1.7)	0 (0.0)	0.524†	0.469
Skin rash	3 (1.3)	0 (0.0)	–§	0.560
Number of symptoms			2.839*	0.242
None	40 (16.5)	13 (13.4)		
1–3 symptoms	98 (40.5)	49 (50.5)		
≥4 symptoms	104 (43.0)	35 (36.1)		
Length of illness [day, (M, *IQR*)]	10.0 (5.0–18.5)	7.5 (3.0–26.8)	8656.000¶	0.619

Abbreviation: M=median; *IQR*=interquartile range.

* χ^2 test.

† χ^2 test with contingency correction.

§ Fisher exact test.

¶ Mann-Whitney *U* test.

60% of participants reported fever measured by a body temperature of ≥37.3 °C. The research classified fever into four categories: no fever (<37.3 °C), low-grade fever (37.3 °C–38.0 °C), middle-grade fever (38.1 °C–39.0 °C), and high fever (≥39.1 °C). A significant difference was discovered among the fever categories (χ^2=12.273, *P*=0.007). Patients infected with BA.5.2.48 had a higher prevalence of high fever compared to those infected with BF.7.14 (22.2%, 20 cases *vs*. 9.7%, 22 cases).

Cough was exhibited by approximately half of the participants in both the BF.7.14 (52.9%, 128/242) and BA.5.2.48 (47.4%, 46/97) groups. Additionally, 39.6% (95/240) and 28.9% (28/97) of patients in the BF.7.14 and BA.5.2.48 infection groups, respectively, reported a sore throat or difficulty swallowing. These symptoms ranked among the top three, while 16.5% (40/242) of individuals infected with BF.7.14 and 13.4% (13/97) of those infected with BA.5.2.48 remained asymptomatic. No significant difference in symptoms was noted between the groups. Participants infected with BF.7.14 experienced symptoms for a median duration of 10.0 days (*IQR*: 5.0–18.5), while those infected with BA.5.2.48 reported symptom relief after a median duration of 7.5 days (*IQR*: 3.0–26.8).

The healthcare-seeking behaviors of participants are depicted in Table 3. The majority of the BF.7.14 (76.9%, 186/242) and BA.5.2.48 (77.3%, 75/97) infected participants were admitted to hospitals or Fangcang alternative care sites. The median hospital stay for both groups was 12.0 days. A small percentage of patients infected with BF.7.14 (4.5%, 11/242) and BA.5.2.48 (1.0%, 1/97) required admission to intensive care units for further treatment.

DISCUSSION

To the best of our knowledge, this study is the first to compare the clinical characteristics of infections with SARS-CoV-2 Omicron subvariants BF.7.14 and BA.5.2.48, addressing public concerns about disparities in clinical severity. The results indicate that the baseline characteristics of the two infection groups were comparable, with no significant differences found in age, sex, BMI, vaccination status, comorbidities, health-related behaviors, or education levels. Furthermore, our findings suggest no significant differences in clinical manifestations, duration of illness, healthcare-seeking behaviors, or treatment.

In this study, the researchers investigated a broad spectrum of clinical manifestations, encompassing both physical and mental symptoms, as documented in previous studies (*1*,*7*). However, no noteworthy differences were observed across the groups, with the exception of fever severity. The duration of hospitalization for patients in this study was considerably shorter than that reported in an Italian study, where the median hospital stay was 30 days (*IQR*: 12–80) (*8*). This outcome may be attributed to the dynamic zero-COVID-19 policy implemented in Beijing, which mandated medical isolation for infected individuals in order to mitigate community transmission. Consequently, several patients with mild disease severity were admitted to hospitals.

The BA.5.2.48 and BF.7.14 subvariants exhibited 59 and 57 high-frequency non-synonymous mutations, respectively, both originating from the BA.5 lineage of the Omicron variant (*9*). The spike protein, situated on the surface of the SARS-CoV-2 virus, plays a crucial role in virus attachment and entry into host cells (*10*). Numerous mutations within the spike protein have been directly linked to infectivity, transmissibility, and immune evasion capabilities (*11*). Notably, the BF.7.14 and BA.5.2.48 subvariants shared identical mutation sites in the spike protein, with the exception of R346T and C1243F. Prior research has suggested that the symptoms of BF.7 infection are analogous to those connected to infections with other Omicron subvariants (*12*).

Our study presents several limitations. First,

TABLE 3. Healthcare-seeking behaviors and treatment of the patients.

Behaviors or treatment	BF.7.14 infection	BA.5.2.48 infection	Statistic	*P* value
Outpatient treatment (*n*, %)	5 (2.1)	4 (4.1)	0.478*	0.489
Admission to hospitals or Fangcang ACS (*n*, %)	186 (76.9)	75 (77.3)	0.008†	0.928
Length of hospital stay [day, (M, *IQR*)]	12 (8.0–15.0)	12 (10.0–15.0)	8277.500§	0.745
Admission to ICU (*n*, %)	11 (4.5)	1 (1.0)	1.581†	0.209

Abbreviation: ACS=alternative care site; M=median; *IQR*=interquartile range; ICU=intensive care unit.
* χ^2 test with contingency correction;
† χ^2 test;
§ Mann-Whitney *U* test.

participants received the survey via telephone approximately four months after their infection, which may introduce recall bias. Consequently, they might not accurately remember pertinent details of their illness, resulting in potential under-reporting of manifestations. Longitudinal studies could provide valuable information for researchers and healthcare practitioners to better comprehend the clinical manifestations and evolution of SARS-CoV-2, as well as to identify changes in the clinical spectrum in a timely manner. Second, our study represents a small subset of the infected population in Beijing. Although the limited sample size might not precisely reflect the broader population, it still offers insights into the clinical manifestations caused by subvariants of SARS-CoV-2, especially considering the scarcity of evidence from previous studies.

Conflicts of interest: No conflicts of interest.

Acknowledgements: Health care professionals who participated in the epidemiological survey, sample collection, and transportation.

Funding: Supported by the National Key Research and Development Program of China (2021ZD0114103).

doi: 10.46234/ccdcw2023.096

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Submitted: April 09, 2023; Accepted: May 30, 2023

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Perspectives

Sentinel Community-Based Surveillance: An Innovative Mode of Proactive Surveillance on Infectious Disease

Jue Liu[1,2]; Qun Li[3,#]; Wannian Liang[4,5,#]; Min Liu[1,2,#]

BACKGROUND

Surveillance is a critical component of epidemiological and public health practice, playing a significant role in the prevention, control, and management of major public health risks (*1*). Historically, surveillance methods were primarily based on hospital data (e.g., sentinel hospital monitoring for influenza) or specific populations [such as the human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) population] for sentinel surveillance. However, for newly emerging infectious diseases or major infectious diseases with pandemic potential, traditional methods based on hospitals or specific populations may be insufficient for meeting the requirements of multi-source information, active monitoring, and early warning. For instance, the reported number of coronavirus disease 2019 (COVID-19) cases represents passive reporting data, as there is a certain proportion of asymptomatic infected individuals and those who have not been tested. As most countries have relaxed or eliminated COVID-19 testing strategies, the number of reported cases may not accurately or comprehensively reflect the global prevalence levels and dynamic trends of COVID-19 in the general population.

Following the early outbreak phase of COVID-19, China entered a normalization stage of prevention and control on April 29, 2020. During this stage, by adopting a strategy to prevent both imported cases and domestic resurgences, China effectively controlled the epidemic's spread and significantly reduced the number of deaths. On December 7, 2022, China implemented the "Ten New Measures" to optimize COVID-19 prevention and control efforts further. Against this backdrop, China quickly and urgently established the nationwide Sentinel Community-Based Surveillance (SCS) by the end of 2022 (*2*), an innovative method for actively detecting infectious diseases, which aims to dynamically monitor the incidence rate of COVID-19 within the general population and provide an evidence-based foundation for estimating healthcare resource needs and allocating resources scientifically. SCS has played an essential, necessary, and irreplaceable role in actively tracking the COVID-19 epidemic situation and effectively managing public health risks in the general population in China. This study analyzes and describes the definition, characteristics of community-based surveillance, and practical experiences in China, providing a model reference for proactive surveillance in other countries or for other infectious diseases.

DEFINITION

SCS represents a proactive approach to surveillance, involving the systematic and ongoing collection, analysis, and interpretation of data related to community populations. It is closely integrated with the prompt and consistent dissemination of results and evaluations to relevant stakeholders, thus enabling the initiation of appropriate actions (*1*).

CHARACTERISTICS

The SCS represents a significant departure from prior surveillance methods through four key advancements. First, the surveillance approach has shifted from passive to proactive, whereby the SCS actively acquires pertinent information regarding potential infectious diseases on a regular basis, drawing upon a national prospective community-based cohort. Second, the focus of surveillance has transitioned from confirmed or suspected patients (patient-centered) to the general population (people-centered). Traditional hospital-based surveillance typically collects data on patients with specific conditions such as influenza or HIV/AIDS, which, despite its relative ease, may not accurately represent the general population due to inherent selection bias. Third, the SCS now encompasses the comprehensive life-cycle management of infectious diseases, including aspects of prevention, screening, diagnosis, treatment, rehabilitation, and social support. Forth, the SCS merges public health, medical care, and social care in a cohesive fashion. The system garners support from a variety of organizations such as the CDCs, healthcare service delivery departments, community centers, and other related departments, ultimately bridging the gaps in fragmented public health and medical surveillance systems.

Consequently, we have distilled these transformations into five core attributes of the SCS model: proactive, people-centered, life-cycle management, integration, and coordination, collectively referred to as the "PELIC" theoretical framework (Figure 1).

PRACTICAL EXPERIENCE IN CHINA

In December 2022, the Omicron variant strain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) rapidly spread in China (*3*). To dynamically monitor the epidemic trends and disease burden of COVID-19 in the general population and to promptly understand changes in public medical needs, the National Sentinel Community-Based Surveillance (NSCS) was launched under the support of the National Bureau of Disease Control and Prevention. This aimed to provide scientific evidence for improved prevention, control, and management of COVID-19 and enable the rational allocation of medical and health resources (*2*).

NSCS is a national community-based sentinel surveillance cohort consisting of a sample size of 0.42 million participants. It employed multistage stratified cluster sampling from all 31 provincial-level administrative divisions (PLADs) and the Xinjiang Production and Construction Corps (XPCC). Each PLAD selected one provincial capital city, one other large city, and one county. At least 2,000 households (≥5,000 individuals) were sampled in each provincial capital city; at least 1,500 households (≥3,000 individuals) were sampled in each selected large city; and at least 1,000 households (≥2,500 individuals) were sampled in each selected county (*2*). The minimum sampling unit was the household, and all selected households were included in the cohort. Each site conducted nucleic acid or antigen testing twice a week for every household. Additionally, information on symptoms, hospital visits, and other basic data were collected. NSCS collected data and provided feedback through multi-department collaboration. Community or village committees in each surveillance sentinel site were responsible for implementing the investigation

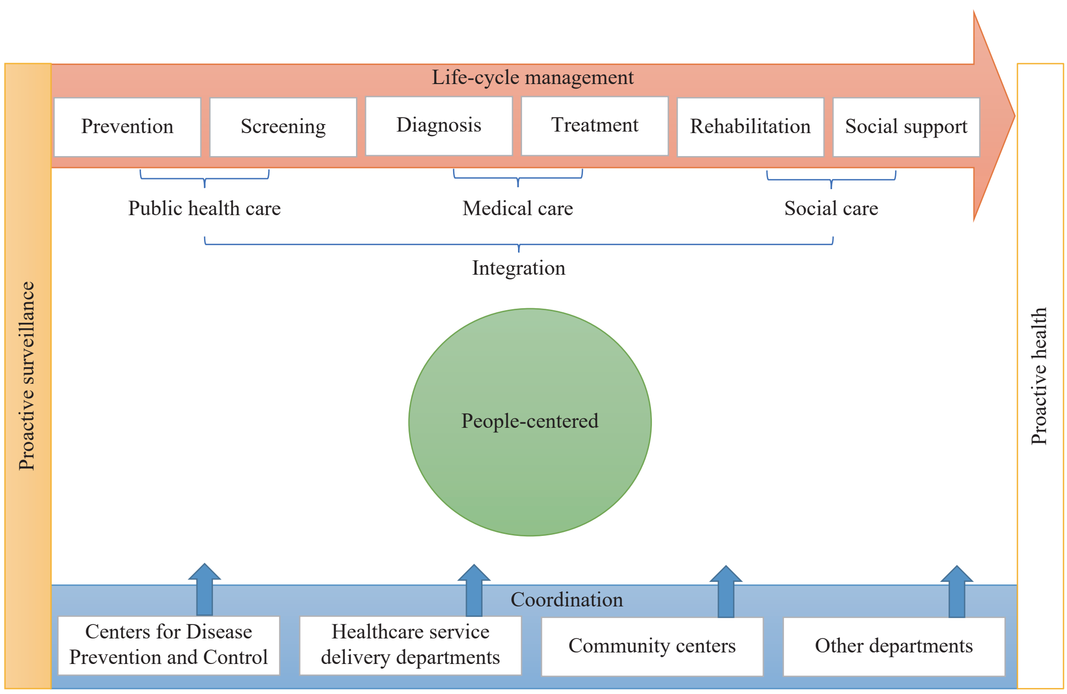

FIGURE 1. Theoretical framework of sentinel community-based surveillance using the PELIC model.
Note: "PELIC" denotes the five fundamental attributes of Sentinel Community-Based Surveillance, which encompass proactive, people-centered, life-cycle management, integration, and coordination.

and reporting data. The district CDC of each sentinel site was responsible for collecting information and reporting to other levels.

All participants in the monitored communities were tested for infection twice a week from December 16, 2022, to January 12, 2023. Data from the NSCS showed that the peak of SARS-CoV-2 infection in China had passed, and SARS-CoV-2 infection in community populations is currently at a low epidemic level (*2*). Specifically, the daily average newly positive rate of SARS-CoV-2 infection decreased from 4.13% in Round 1 (December 16–19, 2022) to 0.69% in Round 8 (January 10–12, 2023). The epidemic peak occurred in Round 2 (December 20–22, 2022) (*2*). In rural areas, the epidemic wave also peaked between December 20–22, 2022, and passed quickly following the optimization of prevention and control measures (*4*). Since January 13, participants have been tested once a week, given the low epidemic level of SARS-CoV-2 infection. The time interval and content of community-based surveillance have been adjusted and optimized according to the needs of disease prevention and control.

PROSPECTIVE

The practical experience in China has demonstrated that the SCS model plays a crucial, necessary, and irreplaceable role in actively monitoring the COVID-19 epidemic and effectively managing public health risks among the general population (*2*,*4*). The SCS model is particularly well-suited for situations where an infectious disease is in the community-transmission stage (or widely prevalent), or where asymptomatic infections and mild cases constitute a significant proportion of the infected population, and appropriate testing methods are available for screening. This approach enables stakeholders, such as the government, health sector policymakers, CDCs, health workers, communities, and the public, to timely and dynamically assess the incidence rate, cumulative infection rate, and estimate the demand for health resources among the general population. As an innovative method of proactive surveillance for emerging and widespread infectious diseases, the SCS model can also provide a useful reference for proactive surveillance in other countries and for other infectious diseases.

In 2021, China released the Outline of the 14th Five-Year Plan and the Vision 2035 of the National Economic and Social Development of the People's Republic of China, which explicitly emphasized proactive health intervention technologies (*5*). As a means of achieving proactive health, proactive surveillance will play a critical role in preparing for and responding to future outbreaks of infectious diseases and other major infectious diseases. Community-based surveillance platforms can also serve a multidimensional role in proactive surveillance (such as symptom surveillance, disease surveillance, and surveillance of health resource demand), early warning, resource preparation and allocation, medical and social support, and community governance. This approach, based on community populations, enhances the preparation and response for future outbreaks of emerging infectious diseases and other significant infectious diseases.

Conflicts of interest: No conflicts of interest.

Funding: National Natural Science Foundation of China (72122001; 72211540398; 71934002), Beijing Natural Science Foundation of China (L222027), National Key Research and Development Program of China (2021ZD0114105; 2021ZD0114104; 2021ZD0114101).

doi: 10.46234/ccdcw2023.097

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Submitted: April 07, 2023; Accepted: May 24, 2023

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Perspectives

A Visualization Analysis of Medical and Prevention Fusion Research in China via CiteSpace

Chen Jin[1]; Sijing Tu[1,2]; Yu Qian[1]; Xiaoyu Chen[1]; Zhiyi Peng[1]; Xiaohe Wang[1,#]

Since the 1990s, the acceleration of population aging has led to an increased prevalence of chronic diseases and enhanced public health awareness. Numerous countries have proposed healthcare reforms, with a focus on creating an "integrated care" model that aims to improve the quality of medical services and reduce costs (*1*–*2*). In 2008, the World Health Organization (WHO) put forward the concept of Integrated Delivery Systems (IDS), advocating for continuous, timely and integrated medical services. In 2016, the WHO introduced the people-centered and integrated healthcare (PCIC) global health strategy model, which is highly compatible with the core concept of "shifting from disease treatment to overall health promotion" in the "Healthy China" strategy. Medical prevention fusion (MPF) represents the practical application of PCIC in China and serves as a significant goal for the country's ongoing healthcare system reform. Furthermore, MPF is a crucial initiative for implementing the Healthy China Strategy.

Following China's reform and opening up, the economic system shift led to an increased focus on the market within public health. The public healthcare system experienced challenges while the orientation of public health work transitioned from "prevention" to "treatment". This separation between prevention and medical treatment has made it difficult for China's public healthcare system to address the increasingly complex public health issues and meet the rising health care demands of the general population (*3*). Consequently, the Chinese government has successively proposed strategies including medical prevention combination (MPCom), medical prevention integration (MPI), medical prevention collaboration (MPCol), and MPF. Analyzing the hotspots and trends in MPF may help clarify its conceptual connotations and related theoretical research.

The data for this study were collected from three major Chinese databases: China National Knowledge Infrastructure (CNKI), Wanfang, and VIP. A comprehensive search was conducted using the keywords "MPCom," "MPI," "MPCol," and "MPF" in order to identify relevant studies published between January 1, 2000, and December 31, 2022. Data from the three databases were imported into NoteExpress (version V3.7; Beijing, China), a literature management software, to ensure the completeness of relevant literature and remove duplicates. The final dataset was then exported from NoteExpress in Refworks-CiteSpace format to CiteSpace for formal data analysis. The detailed screening process is depicted in Figure 1.

CiteSpace (version 6.1.R6; Drexel University, Philadelphia, PA, USA) is a tool utilized for examining current research hotspots and this analysis allows for a comprehensive understanding of the research directions within focal areas (*4*–*5*). In our study, we employed CiteSpace to analyze the co-occurrence and clustering of authors, institutions, and keywords, which we subsequently represented in the form of knowledge graphs. Within the network diagram, distinct nodes symbolize the analyzed elements. The size of these nodes reflects the number or frequency of publications (*6*). The connecting lines between nodes signify mutual relationships, including collaboration, co-occurrence, or co-citation (*7*).

The number of studies published annually serves as an indicator of the activity within a specific research area (*8*). Supplementary Figure S1 (available in https://weekly.chinacdc.cn/) illustrates the temporal distribution of annual publications in the field of MPF. During these two decades, research on MPF can be divided into two distinct phases. Prior to 2016, fewer than twelve articles were published annually, suggesting that the field was in its nascent stage. However, following the WHO's call for PCIC in 2016, China has progressively acknowledged the significance of MPF. Consequently, this phase has exhibited a consistent upward trend in the number of publications.

The visual analysis map of the author collaboration network can be found in Supplementary Figure S2 (available in https://weekly.chinacdc.cn/). The map

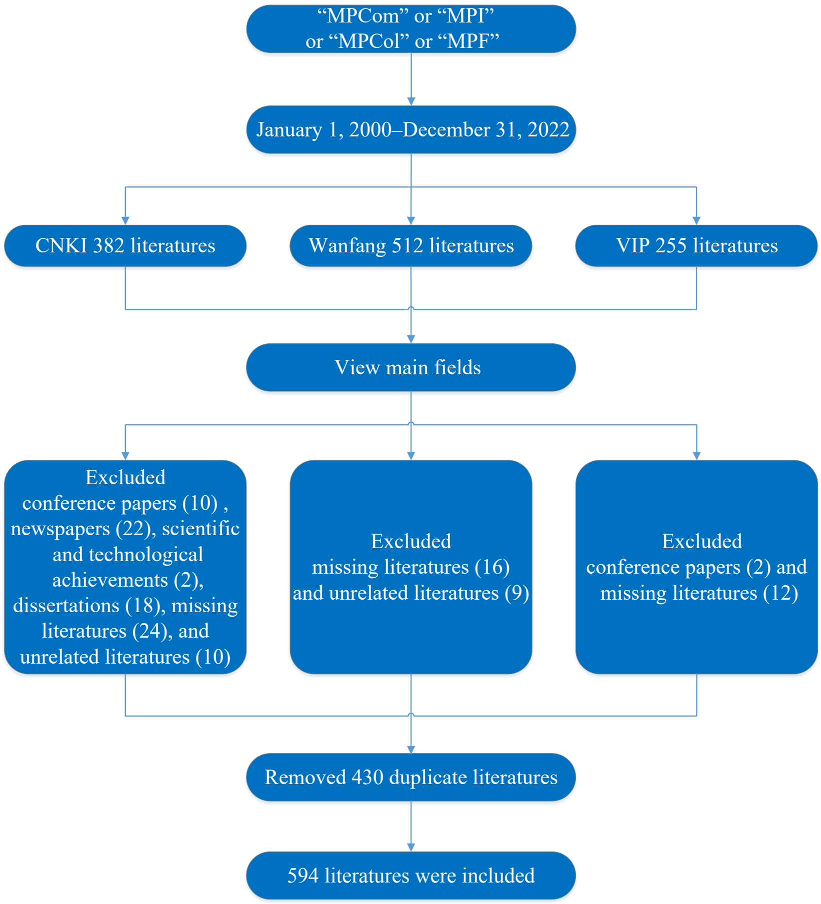

FIGURE 1. The flow chart of search strategy.
Abbreviation: MPCom=medical prevention combination; MPI=medical prevention integration; MPCol=medical prevention collaboration; MPF=medical prevention fusion; CNKI=China National Knowledge Infrastructure.

features 343 nodes and 553 lines, with a network density of 0.0094. Each dot represents an individual author. Larger circles indicate authors with more published articles. Lines represent collaboration between authors, with thicker lines signifying closer collaboration (*5*). One major team is based at the Peking University China Center for Health Development Studies, which includes notable authors such as Menggen Yu and Beibei Yuan, etc. This team primarily investigates influencing factors and cognitive evaluations of MPF in primary care institutions (*9*–*11*).

Supplementary Figure S3 (available in https://weekly.chinacdc.cn/) presents a diagram illustrating research-issuing institutions, which comprises 181 nodes and 63 connecting lines, resulting in a density of 0.0039. The Chinese Center for Disease Control and Prevention holds the top position with eleven publications. Another notable institution, the Center for Health Policy Research and Evaluation at Renmin University of China, has eight publications and is connected to the Sanming Municipal Health Commission. Sanming serves as a national example of China's deepening medical reform and is a representative case of MPF, commonly referred to as the Sanming Model.

Keywords effectively convey the central concept of an article, providing a succinct summary and distillation of the primary content under investigation (*12*). A visualization of keywords is depicted in Figure 2, which includes 279 nodes and 550 research links, with a network density of 0.0142. MPF is a term specific to our country that has gained significant attention within the healthcare field. Over the past two years, it has sparked the research interests of numerous scholars. The term MPF was first officially mentioned in the document titled "The General Office of the National Health Commission on Doing a Good Job of Family Doctor Contracting Services" in 2018 (GuoWeiBan grassroots letter [2018] No. 209). This document emphasized the responsibility of family doctor teams in meeting the requirements of

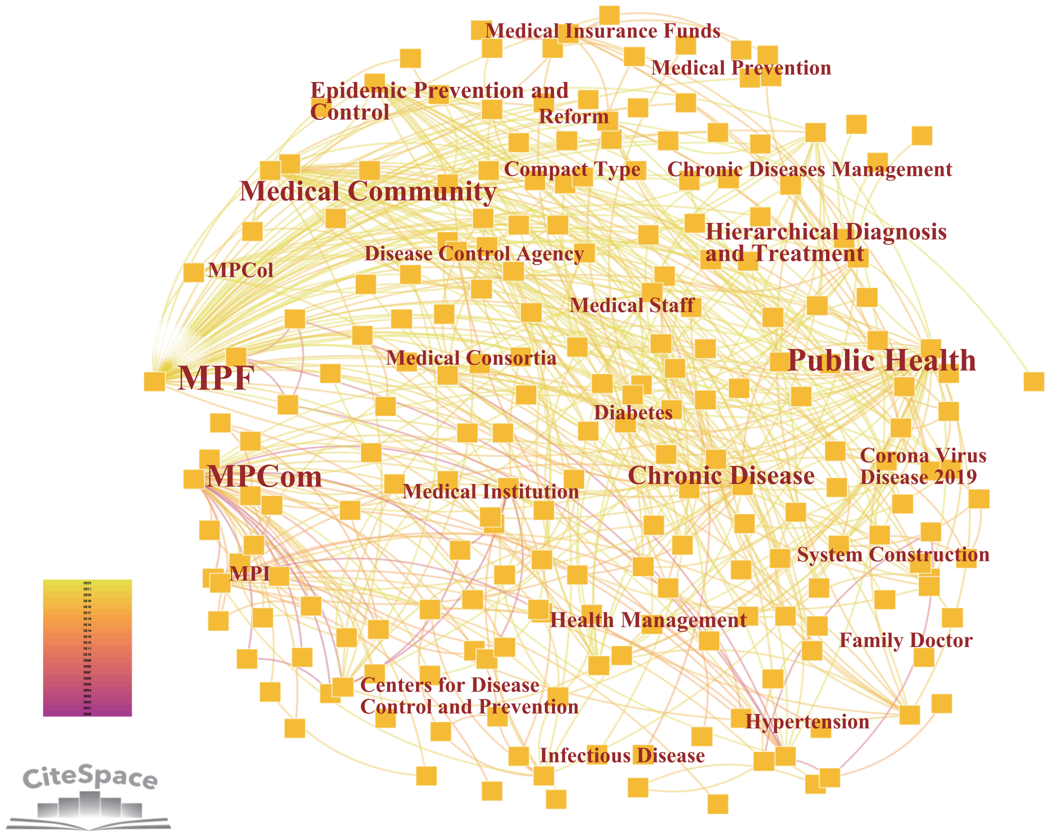

FIGURE 2. The network of keywords.
Abbreviation: MPCom=medical prevention combination; MPI=medical prevention integration; MPCol=medical prevention collaboration; MPF=medical prevention fusion.

contracted residents and providing continuous MPF services. Liu et al. (*2*) proposed that MPF could be interpreted as the integration of medical services and public health services, with a focus on combining and effectively connecting these services during the process. Jie et al. (*13*) viewed MPF as a complex disease management model. In summary, MPF can be described as a combination of services, models, or programs.

Table 1 presents the primary keywords associated with the most significant citation bursts. These keywords were identified based on the increased frequency of publications, independent of their overall usage (*14*). As illustrated in Supplementary Figure S4 (available in https://weekly.chinacdc.cn/), the progression from combination to integration and collaboration to fusion represents a gradual developmental process. When examining the development of MPF, it is essential to consider the stage of separation. Following China's economic reform and opening, the public health sector became increasingly market-driven, resulting in a substantial impact on the public health system. Consequently, the focus of public health work shifted from "prevention" to "medical treatment" (*3*).

MPCom has been in place since 2004. In response to the severe acute respiratory syndrome (SARS) outbreak in 2003, China intensified its focus on public healthcare system development, emphasizing interdisciplinary collaboration among researchers from related academic fields. The MPCom represents the collaboration between medical and public health service personnel or institutions. Generally, the implementation of MPCom has effectively bridged the gap between medical treatment and prevention, both in terms of awareness and practical outcomes (*2*).

The concept of integration was initially introduced by the British philosopher Herbert Spencer and has since been extensively employed in the disciplines of sociology, economics, and political science (*15*). Integration emphasizes the consolidation of assets and ownership as a unifying connection (*16*). In China, the emergence of MPI began in 2006. Domestic scholars have conducted extensive theoretical research and developed unique approaches or academic perspectives for system construction. MPI seeks to deliver prevention, medical treatment, health education, and health promotion services to the population by combining medical and health resources (*17*).

Since the emergence of the coronavirus disease 2019 (COVID-19) pandemic, the awareness of the significance of prevention measures has grown, with increasing attention given to their role alongside medical treatment. The concept of MPCol gained prominence in policy recommendations from 2021 onwards. Although the term collaboration has its origins in Western contexts, the focus of MPCol is to establish a coordinated approach and division of labor between disease control agencies and medical institutions.

In the current state of normalized epidemic prevention and control measures, the role of MPCol is not sufficient. It is essential to create a comprehensive and cohesive framework that merges both medical treatment and prevention strategies. In this context, MPF has emerged as a more effective approach to addressing the present challenges. As compared to terms like "combination", "integration", and "synergy", MPF signifies the highest level of convergence between medical and preventative aspects (*2*).

In order to further investigate research topics within the field of MPF, we conducted a cluster analysis of keywords. This analysis facilitated the identification

TABLE 1. Top keywords with the strongest citation bursts.

Keywords	Year	Strength	Begin	End
Medical prevention combination	2004	2.46	2020	2020
Integration	2006	0.68	2006	2006
Medical prevention integration	2006	3.25	2006	2019
Hierarchical diagnosis and treatment	2016	1.57	2021	2022
Prevention	2018	1.07	2018	2018
Epidemic Prevention and Control	2020	2.80	2020	2020
Medical prevention collaboration	2021	1.13	2021	2022
Fusion	2021	0.79	2021	2022

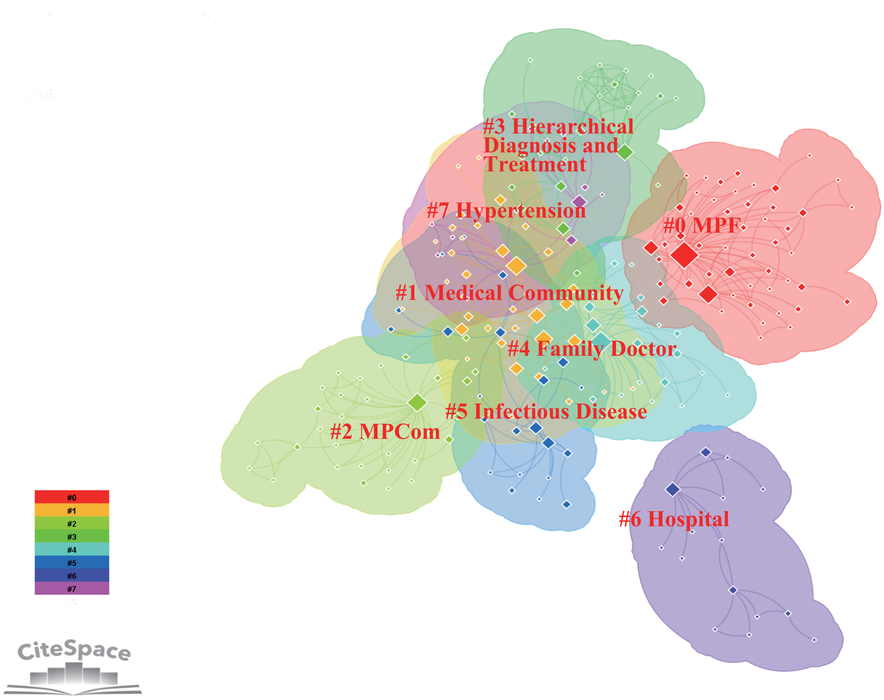

FIGURE 3. Keywords cluster analysis.
Abbreviation: MPCom=medical prevention combination; MPF=medical prevention fusion.

and differentiation of various research topics by generating a keyword clustering map (Figure 3). To evaluate these clusters, the modularity Q value and silhouette value were utilized, with a Q value of 0.6424 and a silhouette value of 0.9085, indicating an efficient and convincing cluster (*18*). A total of eight clusters emerged, including: "#0 MPF", "#1 Medical community", "#2 MPCom", "#3 Hierarchical diagnosis and treatment", "#4 Family doctor", "#5 Infectious disease", "#6 Hospital", "#7 Hypertension".

The medical community (MC) serves as a crucial foundation for the development of the MPF, a distinctive model of IDS specific to China. The MC facilitates effective vertical integration of medical resources through a hierarchical medical model that is guided by tertiary hospitals and collaborates with secondary and community hospitals within a given region (*19*). This integrated operational approach within MCs offers a conducive environment for the implementation of the MPF.

Hierarchical diagnosis and treatment (HDT) is an effective approach to ensuring the optimal implementation of the MPF system. HDT contributes to increased efficiency in the allocation of medical resources and the reduction of healthcare costs (*20*). The core principles of HDT encompass grassroots first consultation, two-way referral, acute and chronic diseases treatment, and linkage between upper and lower levels, thus fostering the advancement of the MPF system (*21*).

Epidemic prevention and control (EPC) imposes new demands on MPF. The emergence of the COVID-19 pandemic has underscored the increasing significance of MPF. Evidenced by its repeated success in EPC, MPF is a crucial concept in mitigating infectious diseases. To bolster our capacity to address emerging and imported infections, it is vital to continually deepen the integration and collaboration between medical treatment and disease prevention (*22*).

Current researches on MPF predominantly emphasize Western medicine, while traditional Chinese medicine (TCM) receives considerably less attention. Historically, TCM has facilitated a comprehensive approach to healthcare, encompassing prevention, treatment, and rehabilitation. MPF and TCM share similar objectives, and exploring the integration of both approaches to enhance chronic disease management presents a significant direction for future academic research.

To the best of our knowledge, this is the first systematic and comprehensive study examining the progress and trends of MPF research in China. This study offers invaluable insights for scholars in this domain, assisting them to explore the future direction of MPF. However, the study inevitably has some limitations. Firstly, lack of access to English databases may lead to incomplete analysis. Secondly, the presence of synonyms makes some data overlap in the keyword clustering process, leading to potentially biased analysis outcomes.

Conflicts of interest: No conflicts of interest.

Funding: This work was supported by the National Natural Science Foundation of China (71974050 and 72274051).

doi: 10.46234/ccdcw2023.098

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Submitted: January 03, 2023; Accepted: March 14, 2023

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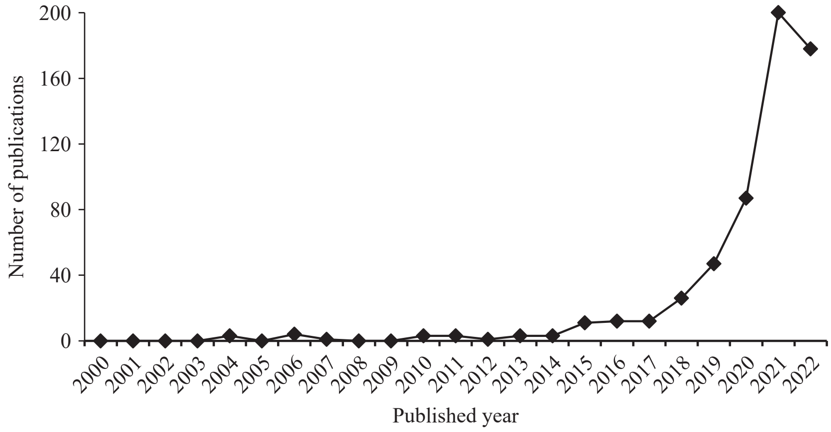
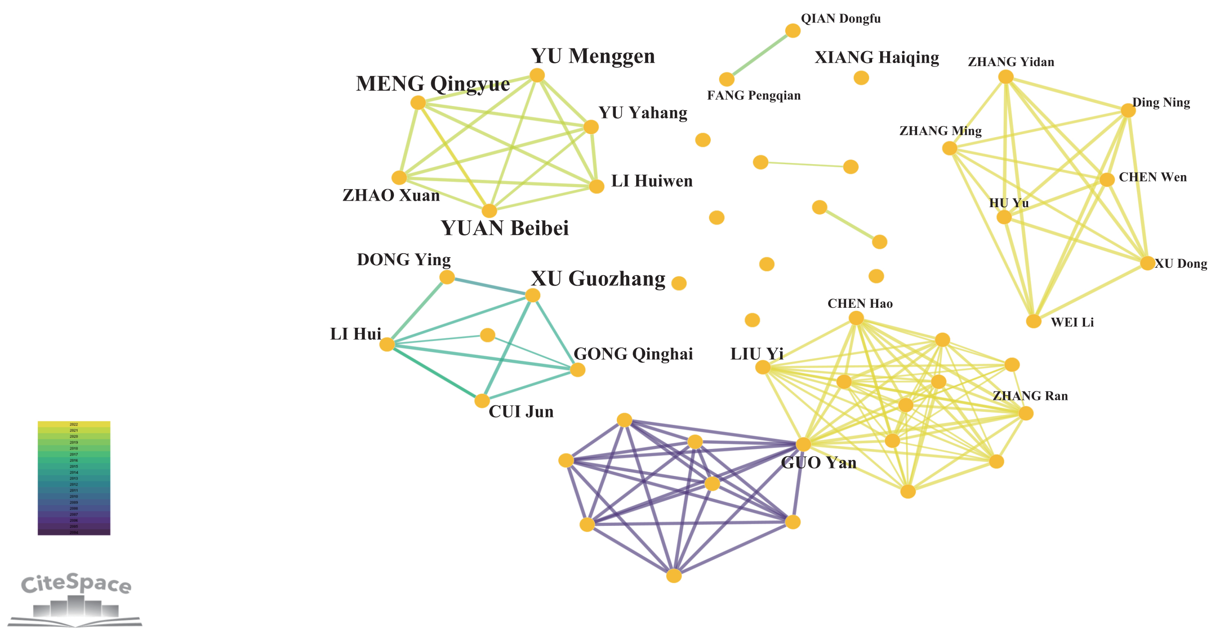
SUPPLEMENTARY MATERIAL

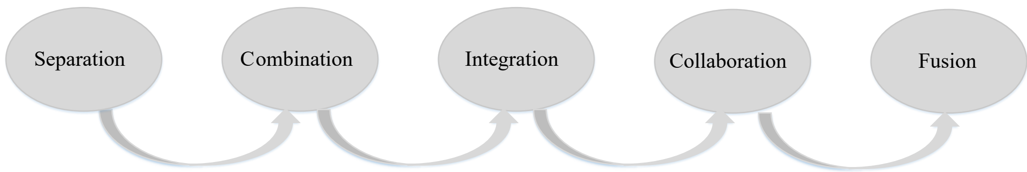


SUPPLEMENTARY FIGURE S1. Temporal distribution of the publications.



SUPPLEMENTARY FIGURE S2. Author cooperation visualization map.

SUPPLEMENTARY FIGURE S3. Institution cooperation visualization map.



SUPPLEMENTARY FIGURE S4. The words development chart.

Indexed by Science Citation Index Expanded (SCIE), Social Sciences Citation Index (SSCI), PubMed Central (PMC), Scopus, Chinese Scientific and Technical Papers and Citations, and Chinese Science Citation Database (CSCD)

The inauguration of *China CDC Weekly* is in part supported by Project for Enhancing International Impact of China STM Journals Category D (PIIJ2-D-04-(2018)) of China Association for Science and Technology (CAST).

CCDC weekly

Vol. 5 No. 23 Jun. 9, 2023

Responsible Authority

National Health Commission of the People's Republic of China

Sponsor

Chinese Center for Disease Control and Prevention

Editing and Publishing

China CDC Weekly Editorial Office
No.155 Changbai Road, Changping District, Beijing, China
Tel: 86-10-63150501, 63150701
Email: weekly@chinacdc.cn

CSSN

ISSN 2096-7071
CN 10-1629/R1