

ARTICLE

Positive association between research competitiveness of Chinese academic hospitals and the scale of their biobanks: A national survey

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Abstract

Biobanks are important research infrastructure developed rapidly by Chinese hospitals. The objective of this study is to investigate the association between the comprehensive research competitiveness of hospitals and the development of hospital biobanks. In 2018, we conducted a national survey among Chinese biobank managers and directors. An online questionnaire was used to collect data of biobank characteristics. Of the 70 academic hospital biobanks responded to our survey, 49 of their hospitals were listed in the Science and Technology Evaluation Metrics (STEM) and 46 of their hospitals were listed in the Fudan Hospital Rankings, respectively, in 2018. Hospital scores from the STEM and Fudan Hospital Rankings were identified from their official websites. Multivariate linear regression analyses were used to assess the associations of STEM scores and Fudan Hospital Rankings with the scale of biobanks. The overall STEM score, Scientific and Technological Output, and Academic Impact in hospitals with large-scale biobanks were 48.35%, 55.16%, and 58.65% higher than those with small-scale biobanks, respectively. The scale of biobanks was positively associated with STEM score ($\beta = 0.367$, $p = 0.009$), Scientific and Technological Output ($\beta = 0.441$, $p = 0.001$), and Academic Impact ($\beta = 0.304$, $p = 0.044$) after adjustment for potential confounders. For Fudan Hospital Rankings, the comprehensive score and sustainable development ability score were higher in hospitals with large-scale biobanks. Further analyses showed that the scale of the biobanks was positively associated with a higher comprehensive score ($\beta = 0.313$, $p = 0.037$) and a sustainable development ability score ($\beta = 0.463$, $p < 0.001$). The scale of hospital biobanks was positively associated with the research competitiveness of Chinese hospitals.

Yinan Zhang and Zhouliang Bian contributed equally to this work.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Hospital-based biobanks are expected to promote high-quality scientific research. However, the relationship between the comprehensive research competitiveness of hospitals and the development of hospital biobanks remains unknown.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study revealed the relationship between the comprehensive research competitiveness of hospitals and the development of hospital biobanks.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The scale of hospital biobanks was positively associated with the research competitiveness of Chinese hospitals.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

From our study, we wish more and more scientists will be aware that biobanks play a pivotal role in scientific studies. With the continuous development of biobanks, the quality of the clinical pharmacology and translational science is expected to be improved.

INTRODUCTION

Biobanks are infrastructures that accept, store, process, and distribute human biological samples, such as blood, tissues, or DNA, and related clinical data for various purposes.¹ Biobanks play a significant role in a wide range of scientific research, including biomarker detection and drug discovery.² Biobanks can be broadly classified as population-based and disease-oriented.³ For example, the UK biobank is a population-based biorepository established to study the disabling diseases (such as heart diseases, cancer, stroke, etc.) and improve public health.⁴ This prospective study built an unparalleled resource of biospecimens and personal data on lifestyle, environment, medical history, allowing the identification of relationships between different exposures, and health outcomes. The database is open to all scientists around the world for medical research of public interest. Until 2019, the UK biobanks have become a crucial resource for medical research and more than 600 peer-reviewed articles were published.⁵ With their deep genetic and phenotypic data, biobanks have been accelerating global research and innovation.

As medical institutions provide ethically approved, high-quality biological material, and clinical data, biobanks were rapidly developed in academic hospitals. For example, the Mayo Clinic Biobank was established in 2009 with a recruitment goal of 50,000 participants.⁶ Until 2019, more than 200,000 aliquots have been distributed for over 270 projects. Biological samples from the biobank have been used to identify genetic effects on bipolar disorder and enhance genotype-driven translational research. At

Massachusetts General Hospital, the Partners Healthcare Biobank was founded to improve the practice of medicine in various fields.⁷ Diverse biospecimens and data were collected from 75,000 patients at two academic medical centers.

Human biospecimens are also critical in advancing biomedical research for Chinese researchers.⁸ In 2009, Biobank Branch, China Medicinal Biotechnology Association, was established to promote the standardization of Chinese biorepositories. Since then, the Chinese government has focused more on the development of biobanks. In 2010, the Ministry of Science and Technology initiated a national biobanking project for supporting the Significant New Drugs Development.⁹ Focused on four major types of diseases, this project was led by principal investigators from 10 academic hospitals in Beijing, Shanghai, and Tianjin.

Many Chinese hospitals pay more and more attention to innovative scientific research while pursuing state-of-the-art clinical care. In addition, hospital-based biobanks are expected to promote high-quality scientific research.

To evaluate the capabilities of academic and scientific research among the hospitals, different metrics were designed in China. For example, the Science and Technology Evaluation Metrics (STEM) were developed by the Institute of Medical Information at Chinese Academy of Medical Sciences in 2018. More than 1000 hospitals were rated and ranked annually according to the metrics. Interestingly, another influential ranking system (i.e., “Chinese Hospital Rankings”) has been released by the Hospital Management Institute of Fudan University (Fudan Hospital Rankings) since 2010. This ranking

system evaluates research capability as well as hospital reputation.¹⁰

Despite the important role of biological samples in translational medicine and biological research, the relationship between the comprehensive research competitiveness of hospitals and the development of hospital biobanks remains unknown. In 2018, we conducted an online survey to learn the current conditions of Chinese academic hospital biobanks.¹¹ In the present study, we mainly investigated whether the science and technology capacity, evaluated by the STEM scores or Fudan Hospital Rankings, was associated with the scales and other characteristics of biobanks in Chinese hospitals.

METHODS

Participants

In order to investigate the status of the Chinese academic biobanks, we conducted an online questionnaire through a survey platform (SO JUMP) in 2018. The study participants were enrolled from a WeChat group of Chinese biobank managers and directors. Among the 198 identified biobanks, 80 were excluded because they were from non-academic hospitals or third-party specimen storage facilities. As a result, 118 biobanks affiliated with academic hospitals met the inclusion criteria and were invited to complete a questionnaire. A total of 70 biobank managers from the eligible biobanks finished the survey, reaching a response rate of 59.3%. In our previous research, the scales, collections, and biospecimen distribution were analyzed in these tertiary hospital biobanks.¹¹ The hospitals that were listed in the 2018 STEM and 2018 Fudan Hospital Rankings were included in this study. In addition, general hospital characteristics, STEM scores, and Fudan hospital ranking scores were also collected (Figure 1).

General information of hospitals and biobanks

The questionnaire survey of Chinese biobanks in 2018 (detailed in the supplementary information) comprises 59 items which can be further grouped into seven aspects: (1) general characteristics (years of establishment, area of biobanks, number of freezers and liquid nitrogen tanks, etc.); (2) specimen collection (number and range of sample collection, etc.); (3) specimen distribution (number and range of sample distribution, access policies, etc.); (4) information management system; (5) biobanking staff; (6) standard operation procedures and quality control; and (7) ethical issues and certifications.

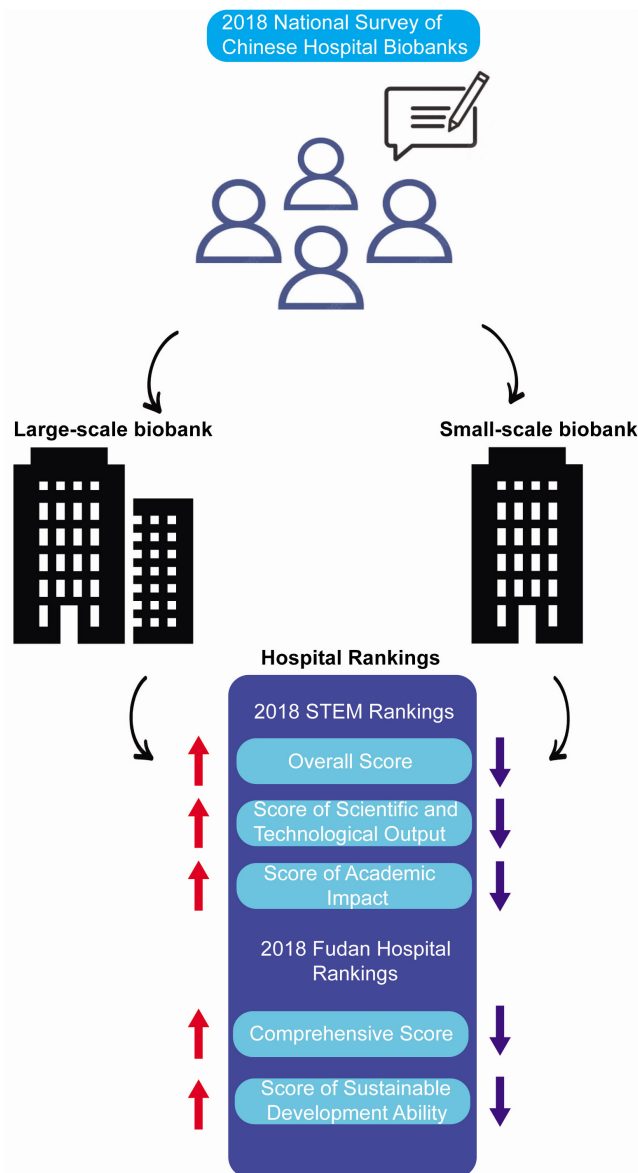


FIGURE 1 Relationship between research competitiveness of Chinese academic hospitals and the scale of their biobanks. STEM, Science and Technology Evaluation Metrics.

In addition, the hospital characteristics, including total beds, inpatient and outpatient volumes, number of surgeries, numbers of PhD and master's degree supervisors of the hospitals were collected from their official websites.

2018 Science and Technology Evaluation Metrics

Since 2018, the Institute of Medical Information, Chinese Academy of Medical Sciences, conducted an annual ranking of the capacity in science and technology of hospitals across China. Scores of three aspects in STEM were used to calculate last year's rankings for each

hospital: (1) score of Scientific and Technological Output based on the hospitals' research achievement, including article publications, scientific awards, innovations and patents, etc.; (2) score of Academic Impact focusing on academic influence of scientists and quality of research; and (3) score of Scientific and Technological Conditions evaluated by the status of research projects and research platforms. The 2018 scores of STEM were identified on the official STEM website (<http://top100.imicams.ac.cn/>).

2018 Fudan Hospital Rankings

Fudan Hospital Rankings provide tools for aiding the decision making of patients and evaluate different aspects of the competitiveness of Chinese hospitals. The comprehensive score is based on a weighted average of individual scores, including (1) hospital reputation score based on subjective assessment and (2) sustainable development ability score based on objective indicators. The hospital reputation score was calculated by medical experts using a standard questionnaire. On the other hand, the sustainable development ability score was primarily based on research output, such as Science Citation Index article publications and national science and technology awards. The comprehensive score is a weighted average of these two individual scores, where the reputation score accounts for 80% and the sustainable development ability score accounts for 20%. The 2018 Fudan Hospital Rankings were identified from the website of Hospital Management Institute, Fudan University (<http://www.fudanmed.com/institute/news222.aspx>).

Statistical analysis

Biobanks were categorized by storage capacity according to our previous study: biobanks with greater than or equal to 200,000 specimens in storage were categorized as large-scale, whereas those with less than 200,000 specimens in storage were categorized as small-scale biobanks. Continuous variables with approximately normal distribution were presented as mean \pm SD, categorical variables were presented as percentages. The Student's *t*-test and the Pearson χ^2 test were used to compare the differences in the continuous and categorical variables, respectively. Multivariate linear regression analyses were used to assess the associations of STEM scores/Fudan Hospital Rankings with the scale of biobanks after adjusting for covariants. Statistical analyses were performed using SPSS 21.0 (SPSS Inc.) and all reported *p* values were two-tailed and $p \leq 0.05$ were considered statistically significant.

RESULTS

General characteristics of hospitals and their biobanks listed in 2018 STEM

Among the 70 biobanks involved in our survey, 49 of their hospitals were listed in the 2018 STEM. General information and STEM scores of these hospitals and biobanks are shown in [Table 1](#). These biobanks were classified into large-scale and small-scale biobanks, as previously described.¹¹ Compared with small-scale biobanks, large-scale biobanks of top-ranked hospitals in 2018 STEM were equipped with more ultra-low temperature freezers, distributed and used a larger number of specimens annually during 2015–2017 (all *p* values < 0.05). On the other hand, no differences were found in the number of new specimens in storage annually, area of biobanks, number of liquid nitrogen storage equipment, specimen sources, and types of specimens in storage between these two groups of biobanks (all *p* values > 0.05).

Analysis of general characteristics of the hospitals, showed that the number of hospital beds, outpatient and emergency department visits, inpatient visits, and annual volumes of the surgeries were comparable between hospitals with large-scale and small-scale biobanks (all *p* values > 0.05).

Hospitals with large-scale biobanks had higher overall STEM score than those with small-scale biobanks (34.70 ± 21.29 vs. 23.39 ± 8.64 , $p = 0.018$). Analyses of individual scores showed that hospitals with large-scale biobanks had higher scores in Scientific and Technological Output (16.54 ± 10.04 vs. 10.66 ± 4.50 , $p = 0.013$) and Academic Impact (10.36 ± 7.17 vs. 6.53 ± 3.01 , $p = 0.018$). However, the score of Scientific and Technological Conditions was comparable between these two groups of hospitals (7.80 ± 5.02 vs. 6.20 ± 3.54 , $p = 0.208$).

Correlations between 2018 STEM scores of hospitals and scale of their affiliated biobanks

We further examined the correlation between the 2018 STEM scores of hospitals and the scale of their affiliated biobanks using multiple linear regression models. As shown in [Table 2](#), the overall STEM scores were positively associated with the scale of biobanks ($p = 0.021$) in the crude model. In addition, the association remained statistically significant after controlling for hospital beds, inpatient and outpatient visits, number of new samples in storage, and the number of samples for distribution ($p = 0.009$). Further analysis confirmed that hospitals with larger biobanks tend to have higher STEM ranking ($p = 0.013$).

For individual scores of the STEM rankings, the scale of biobanks was positively associated with the scores of Scientific and Technological Output ($p = 0.013$) and Academic Impact

TABLE 1 General information and STEM scores of hospitals and their biobanks

| | Large-scale biobank (n = 26) | Small-scale biobank (n = 23) | p value |
|---|------------------------------|------------------------------|---------|
| Area of biobank | | | 0.744 |
| $\leq 100 \text{ m}^2$ | 65.40% | 60.90% | |
| $> 100 \text{ m}^2$ | 34.60% | 39.10% | |
| Number of ultra-low temperature freezers | | | 0.005 |
| ≤ 50 | 53.80% | 91.30% | |
| > 50 | 46.20% | 8.70% | |
| Number of liquid nitrogen storage equipment | | | 0.367 |
| ≤ 5 | 57.70% | 73.90% | |
| > 5 | 42.30% | 26.10% | |
| Number of new specimens in storage annually 2015–2017 | | | 0.086 |
| $\leq 10,000$ | 11.50% | 34.80% | |
| $> 10,000$ | 88.50% | 65.20% | |
| Number of specimens for distribution annually 2015–2017 | | | 0.001 |
| ≤ 5000 | 34.60% | 82.60% | |
| > 5000 | 65.40% | 17.40% | |
| Types of specimens in storage | 9.46 \pm 3.10 | 9.17 \pm 3.55 | 0.763 |
| Number of hospital beds | 2265.23 \pm 1062.69 | 2966.87 \pm 2175.67 | 0.151 |
| Outpatient and emergency department visits (thousands) | 2923.9 \pm 1671.1 | 3210.95 \pm 1470.4 | 0.546 |
| Inpatient visits (thousands) | 107.1 \pm 59.7 | 117.0 \pm 59.0 | 0.610 |
| Surgical volumes (thousands) | 57.4 \pm 40.5 | 78.0 \pm 47.6 | 0.129 |
| STEM ranking | | | |
| Scientific and technological output | 16.54 \pm 10.04 | 10.66 \pm 4.50 | 0.013 |
| Academic Impact | 10.36 \pm 7.17 | 6.53 \pm 3.01 | 0.018 |
| Scientific and technological conditions | 7.80 \pm 5.02 | 6.20 \pm 3.54 | 0.208 |
| STEM | 34.70 \pm 21.29 | 23.39 \pm 8.64 | 0.018 |

Abbreviation: STEM, Science and Technology Evaluation Metrics.

($p = 0.021$) in the crude model. In addition, the association remained statistically significant after controlling for potential confounding variables (all p values < 0.05). However, the score of Scientific and Technological Conditions was not associated with the scale of biobanks.

General characteristics of hospitals and their biobanks in 2018 Fudan Hospital Rankings

Among the surveyed biobanks, 46 of their hospitals were listed in the 2018 Fudan Hospital Rankings. As shown

in Table 3, compared with small-scale biobanks, large-scale biobanks of hospitals listed in Fudan Hospital Rankings also owned more ultra-low temperature freezers ($p = 0.004$), stored more specimens annually ($p = 0.021$), and distributed more specimens annually during 2015–2017 ($p = 0.045$). On the other hand, the number of liquid nitrogen storage equipment ($p = 0.346$) and types of specimens in storage ($p = 0.542$) were similar between these two groups of hospitals.

There were also no significant differences on hospital-level characteristics, including the number of hospital beds, outpatient and emergency department visits, inpatient visits, and annual volumes of the surgeries between

TABLE 2 Correlations between STEM scores of hospitals and scale of their affiliated biobanks

| | Model 1 | | Model 2 | |
|---|---------------------------|----------|---------------------------|----------------|
| | β (95% CI) | <i>p</i> | β (95% CI) | <i>p</i> value |
| Scientific and technological output | 5.881 (1.307, 10.456) | 0.013 | 7.935 (3.619, 12.250) | 0.005 |
| Academic impact | 3.830 (0.594, 7.066) | 0.021 | 3.868 (0.108, 7.628) | 0.044 |
| Scientific and technological conditions | 1.603 (−0.924, 4.130) | 0.208 | 1.485 (−1.8, 4.769) | 0.365 |
| STEM | 11.314 (1.747, 20.882) | 0.021 | 13.781 (3.660, 23.902) | 0.009 |
| STEM ranking | −19.528 (−33.461, −5.596) | 0.007 | −20.292 (−36.057, −4.526) | 0.013 |

Notes: Model 1: Crude.

Model 2: Model 1 + hospital beds + inpatient visits and outpatient visits + number of new samples in storage and number of samples for distribution.

Abbreviations: CI, confidence interval; STEM, Science and Technology Evaluation Metrics.

hospitals with small- and large-scale biobanks in 2018 Fudan Hospital Rankings (all *p* values > 0.05).

For Fudan Hospital Rankings, the comprehensive score (25.56 ± 24.20 vs. 14.64 ± 7.49 , *p* = 0.045) and sustainable development ability score (10.89 ± 3.16 vs. 8.15 ± 2.87 , *p* = 0.004) were higher in hospitals with large-scale biobanks compared with small-scale biobanks. However, the hospital reputation score remained similar between these two groups (*p* > 0.05).

Correlations between 2018 Fudan Hospital Rankings and scale of their affiliated biobanks

The correlation between 2018 Fudan Hospital Rankings and the scale of their affiliated biobanks was also investigated. As shown in Table 4, multivariate linear regression analyses indicated that the comprehensive score (*p* = 0.049) and sustainable development ability score (*p* = 0.004) were positively associated with larger scale of affiliated biobanks in the crude model. These associations remained significant after adjustment for potential confounders (all *p* values < 0.05). Not surprisingly, hospitals with larger biobanks tend to have higher hospital comprehensive ranking. However, no linear association was found between hospital reputation score and the size of biobanks in both crude and adjusted models (*p* values > 0.05).

DISCUSSION

Our study was the first to reveal the relationship between hospital rankings and the scale of their affiliated biobanks in China. The overall STEM score, individual scores of Scientific and Technological Output, and Academic Impact in hospitals with large-scale biobanks were 48.35%, 55.16%, and 58.65% higher than those with

small-scale biobanks, respectively. This implied that the biobank scale of a hospital is positively associated with the hospital's research competitiveness. This finding was further confirmed when using Fudan Hospital Rankings as the comprehensive score and sustainable development ability score were both higher in hospitals with larger biobanks.

Medicine is undergoing substantial changes in the era of personalized and translational medicine. The diagnosis, management, and prognosis rely more and more on molecular and genotypic information from individuals. As a result, a growing number of hospitals realized that translational research is a dynamic process for new scientific discoveries and will improve patient care. The STEM is one of the most popular hospital evaluation ranking systems in China. This ranking system uses comprehensive data to evaluate hospitals' capacity to conduct scientific research. The Scientific and Technological Output score was evaluated using several indicators, including science and technology awards, research articles, different types of standards, and innovation patents. The development of high throughput technology¹² offers many advantages for biological measurements. For example, to achieve an adequate statistical power, larger sample sizes are necessary in a genomewide association study (GWAS) to detect genetic variation underlying complex traits and diseases.¹³ A GWAS meta-analysis in 433,540 individuals identified 61 novel type 2 diabetes loci.¹⁴ As the largest study in East Asian individuals, the larger sample size increased the study's statistical power and was important for detecting small effect sizes of unidentified variants.¹⁴ Our finding implies that human biobanks take an important role in bridging the gap between basic research and clinical practice. In addition, the score of Academic Impact evaluated in the STEM put a greater emphasis on the quality of scientific research and talent projects. Several parameters, including article citations, academic appointment, outstanding talents, and innovation teams were evaluated. Hospital biobanks can integrate the biological samples and detailed phenotypic

TABLE 3 General information and scores from Fudan Hospital Rankings of hospitals and their biobanks

| | Large-scale biobank (n = 24) | Small-scale biobank (n = 22) | p value |
|---|------------------------------|------------------------------|---------|
| Area of biobank | | | |
| $\leq 100 \text{ m}^2$ | 62.50% | 45.50% | |
| $> 100 \text{ m}^2$ | 37.50% | 54.50% | |
| Number of ultra-low temperature freezers | | | 0.004 |
| ≤ 50 | 50.00% | 90.90% | |
| > 50 | 50.00% | 9.10% | |
| Number of liquid nitrogen storage equipment | | | 0.346 |
| ≤ 5 | 63% | 77.30% | |
| > 5 | 38% | 22.70% | |
| Number of new specimens in storage annually 2015–2017 | | | 0.021 |
| $\leq 10,000$ | 12.50% | 45.50% | |
| $> 10,000$ | 87.50% | 54.50% | |
| Number of specimens for distribution annually 2015–2017 | | | 0.045 |
| ≤ 5000 | 37.50% | 68.20% | |
| > 5000 | 62.50% | 31.80% | |
| Types of specimens in storage | 9.50 \pm 3.22 | 8.86 \pm 3.81 | 0.542 |
| Number of hospital beds | 2263.3 \pm 1083.2 | 2850.0 \pm 2301.5 | 0.285 |
| Outpatient and emergency department visits (thousands) | 2856.5 \pm 1384.5 | 3124.9 \pm 1499.6 | 0.546 |
| Inpatient visits (thousands) | 108.4 \pm 60.0 | 110.8 \pm 69.0 | 0.909 |
| Surgical volumes (thousands) | 59.6 \pm 40.0 | 76.7 \pm 48.7 | 0.212 |
| Fudan hospital rankings | | | |
| Hospital reputation score | 14.67 \pm 21.58 | 6.49 \pm 5.28 | 0.084 |
| Sustainable development ability score | 10.89 \pm 3.16 | 8.15 \pm 2.87 | 0.004 |
| Comprehensive score of hospitals | 25.56 \pm 24.20 | 14.64 \pm 7.49 | 0.045 |

TABLE 4 Correlations between Fudan Hospital Rankings of hospitals and scale of their affiliated biobanks

| | Model 1 | | Model 2 | |
|---------------------------------------|---------------------------|---------|---------------------------|---------|
| | β (95% CI) | p value | β (95% CI) | p value |
| Hospital reputation score | 8.174 (−1.359, 17.707) | 0.091 | 9.704 (−2.753, 22.162) | 0.122 |
| Sustainable development ability score | 2.737 (0.936, 4.538) | 0.004 | 3.086 (1.460, 4.712) | 0.000 |
| Comprehensive score of hospitals | 10.913 (0.059, 21.768) | 0.049 | 12.843 (0.804, 24.882) | 0.037 |
| Hospital comprehensive ranking | −17.693 (−31.274, −4.112) | 0.012 | −16.097 (−29.720, −2.475) | 0.022 |

Notes: Model 1: Crude.

Model 2: Model 1 + hospital beds + Inpatient visits and outpatient visits + number of new samples in storage and number of samples for distribution.

information, thus promoting translational research in medicine. In the present study, hospitals with large-scale biobanks had higher scores on Academic Impact. As more

and more Chinese scientists are aware that biobanks play a pivotal role in scientific studies, the quality of the basic and clinical research is expected to be improved.

Interestingly, the STEM score of Scientific and Technological Conditions, which includes status of research projects or research platform of Chinese hospitals, were not associated with the scale of biobanks. Our study showed that under similar supporting conditions, such as research funding and facilities, the development of large-scale biobanks could improve scientific competitiveness in Chinese hospitals.

Fudan Hospital Rankings have gained popularity in supporting patient decision making. This evaluation method is different from STEM because Fudan Hospital Rankings put more emphasis on subjective metrics, such as hospital reputation. In this study, we found that a higher comprehensive score and sustainable development ability score were observed in hospitals with large-scale biobanks. On the other hand, the hospital reputation score was comparable between hospitals with large- and small-scale biobanks. This observation further implied that hospitals with large-scale biobanks promote research competitiveness regardless of their hospital reputation.

The correlation between research competitiveness of hospitals and their biobanks' sizes may be the result of a virtuous cycle. Hospitals with increased science capacity tend to attach importance to constructing large-scale biobanks, which in turn may strengthen their competitiveness in science and technology.

It should be noted that the underuse of biospecimens was obvious in both large- and small-scale biobanks in our study. In fact, insufficient utilization of samples is a global major issue in biobanking. According to a US survey of 456 biobank managers, more than 60% of these managers were concerned about the underutilization of specimens in biobanks.¹⁵ The insufficient utilization challenges the sustainability of biobanks and contribution of biological samples to important translational discoveries will also be questioned.¹⁶ Further improvement in cooperation and sharing of biospecimens may promote the utilization and increase research productivity in those hospitals.¹⁷

Interestingly, we found that large-scale biobanks had more ultra-low temperature freezers than small-scale biobanks, whereas the number of liquid nitrogen storage equipment was comparable. As blood and other fluid biospecimens are usually stored in ultra-low temperature freezers, this result revealed the potentially important role of these samples in research.¹⁸

In conclusion, we found that both the STEM scores and comprehensive scores in Fudan Hospital Rankings were higher in hospitals with large-scale biobanks (Figure 1). As important research infrastructure, the development of large-scale biobanks contributed to the research competitiveness of Chinese hospitals.

AUTHOR CONTRIBUTIONS

Y.Z., Z.B., and C.W. wrote the manuscript. Y.Z. and C.W. designed the research. Y.Z. and Y.C. performed the research. Y.Z., Z.B., Y.C., and T.C. analyzed the data. E.J. contributed new reagents/analytical tools. All authors have read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work. Abbreviation: CI, confidence interval.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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