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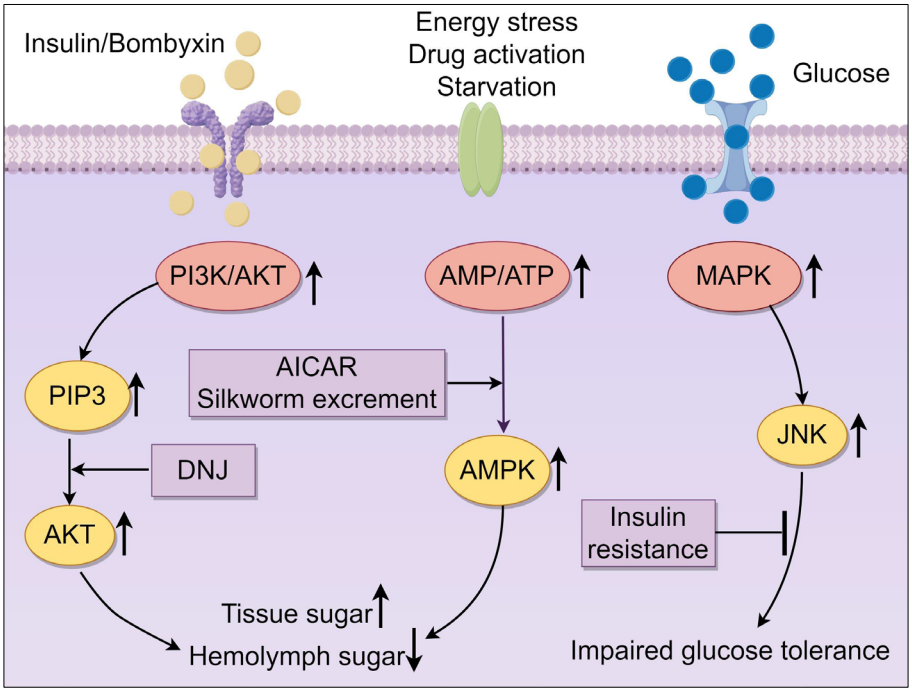

Key signaling pathways in the silkworm diabetes model (Page 205)

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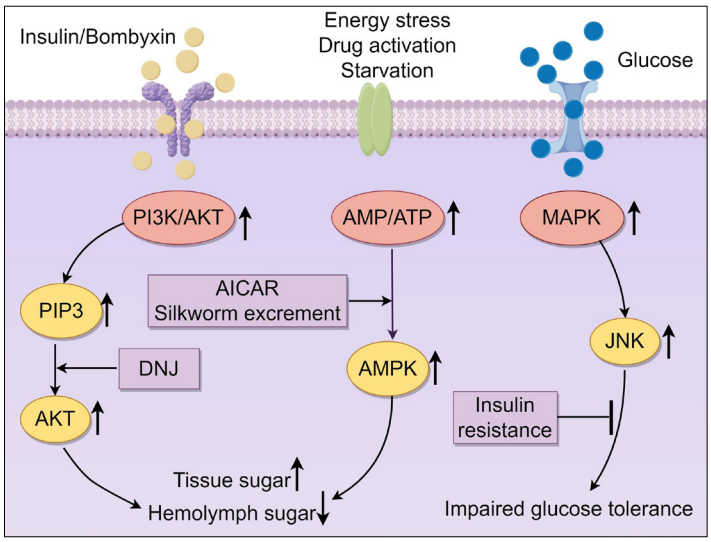

Key signaling pathways in the silkworm diabetes model. The figure shows the interactions between the insulin signaling pathway, PI3K/Akt pathway, AMPK pathway, and MAPK pathway in the silkworm diabetes model. These pathways are activated through molecular cascades and jointly regulate sugar levels in tissues and hemolymph, revealing the mechanism of insulin resistance. (Page 205)

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Asymmetric amplification: New lens for China's e-cigarette policies on youth influence

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Abstract: China introduced universal e-cigarette regulations in 2018 to curb youth vaping, including flavor bans, online sales prohibitions, and taxation. While these policies are not explicitly age-targeted, their design disproportionately impacts adolescents due to young people's price sensitivity, preference for flavored products, and reliance on online purchases. This study examines how such regulations achieve outcomes akin to age-based bans without directly restricting moral agency or risking discrimination. We believe that universal measures like flavor restrictions and taxes amplify their impact on youth through behavioral and economic mechanisms — termed "asymmetric amplification". Results suggest these policies effectively reduce youth vaping while sidestepping ethical controversies tied to generational bans. However, challenges like informal sales channels and adolescent stigma require complementary enforcement. This paper highlights a pragmatic and ethically sound approach to youth tobacco control and offers new insights into policy design for public health practitioners and regulators worldwide.

***Keywords*:** e-cigarette, regulation, adolescence, China

Introduction

Since 2018, China has introduced several significant policies aimed at regulating e-cigarettes to combat tobacco use, particularly among young people. These regulations, which include taxing e-cigarettes at the same rate as traditional cigarettes, prohibiting online sales, and banning all but traditional tobacco-flavored e-cigarettes (*1*), reflect a concerted effort to reduce the number of e-cigarette users. Although these regulations are not explicitly age-based, they disproportionately impact younger users due to their unique consumption habits and demographic characteristics, namely an "asymmetric amplification" effect.

This paper explores how these policies, while neutral in design, function similarly to policies that restrict access for specific cohorts, avoiding ethical concerns related to moral agency and discrimination while still help achieve significant public health objectives.

Asymmetric amplification

The concept of asymmetric amplification describes the uneven distribution of regulatory effects, where certain groups — typically the more vulnerable — bear the brunt of the policies. In this case, while China's regulations on e-cigarettes are intended to reduce smoking and vaping across all demographics, young people face a disproportionate burden due to their consumption habits. Adolescents are often more price-sensitive than adults and, as a result, may be significantly impacted by the increased costs of e-cigarettes due to the new taxation policies. In addition, youth are more likely to be drawn to flavored e-cigarettes, which are now banned under the current regulations. The appeal of flavored products, which range from fruity to candy-like tastes, has been a key driver of e-cigarette consumption among younger individuals (*2*). By limiting the availability of these flavors, the regulations not only reduce choice but also diminish the attractiveness of e-cigarettes for young people, who may be more inclined to quit using them if their preferred flavors are unavailable. Similarly, the prohibition of online sales curtails access for youth, who rely more heavily on digital platforms for purchases compared to older generations. These restrictions, though aimed at protecting health, create

a situation where young users are disproportionately affected by policies that might otherwise have a more neutral effect on older users (Figure 1).

This asymmetric amplification effect is particularly evident when comparing e-cigarette usage rates between China and other countries. In the U.S. 11.3% of high school students use e-cigarettes in 2021, and 2.8% of middle school students use e-cigarettes (*3*). By 2024 10% of high school students in the U.S. use e-cigarettes and 4.6% of middle school students use e-cigarettes (*4*). In Organisation for Economic Co-operation and Development (OECD) countries, the vaping rate among adolescents was 6.1% in 2021 (*5*), while in China, the rate was 2.4% in 2023, showing a decline from 3.6% in 2021 (*6*). By indirectly targeting the behaviors and preferences of youth, the regulations achieve outcomes similar to policies that explicitly ban tobacco products for specific age groups, without raising the same ethical concerns.

One significant advantage of this approach is its ability to sidestep the contentious debates surrounding generational bans, particularly issues of moral agency and discrimination. Generational bans, as discussed by Kniess, can be criticized for denying moral agency by implying that younger individuals lack the capacity to make informed choices about their health (*7*). Additionally, such bans may be viewed as discriminatory, as they create legal distinctions between individuals based solely on the arbitrary factor of their birth year. These e-cigarette policies in China, by contrast, do not explicitly single out any group based on age or birth cohort. Instead, they rely on universal measures that naturally have a greater effect on youth due to their consumption patterns. This design avoids the perception of paternalism or unfair treatment while still prioritizing the protection of young people's health. More importantly, flavor restrictions and taxes have the strongest evidence to support effective control of e-cigarettes, while age restrictions, which might involve moral issues, needs powerful enforcement and meaningful penalties to ensure effectiveness (*2*).

However, the asymmetric amplification effect is not without its challenges. While it reduces the accessibility and appeal of e-cigarettes among youth, it may also drive some young users to seek alternative, unregulated sources. Informal sales channels (*8*), such as internet cafes, billiard halls, and bars, continue to offer flavored e-cigarettes that are not available through legal means. These products, often sold without oversight, may pose greater health risks than those regulated by the government. Moreover, the stigma associated with restricted access could inadvertently reinforce rebellious attitudes toward tobacco control among adolescents, further complicating public health efforts.

Future outlooks

It is important to stress that China's e-cigarette regulations are not solely based on asymmetric amplification. While the regulatory burden disproportionately affects young users, there are still age-based regulations in place, such as the prohibition of e-cigarette sales to individuals under the age of 18 and restrictions on the location of e-cigarette stores near schools. These measures form an integral part of China's broader regulatory strategy, targeting the reduction of e-cigarette use among youth and providing a more comprehensive approach to tobacco control. These age-based restrictions complement the asymmetric amplification effects and reflect China's commitment to safeguarding the health of younger populations while also addressing broader concerns about public health. Check Figure 2 for whole regulation map.

China's e-cigarette regulations also raise important questions about the role of public health policies in shaping behavior across different demographic groups. By targeting specific behaviors and preferences rather than demographic characteristics, these policies achieve similar outcomes to age-based restrictions while avoiding the ethical dilemmas associated with explicit

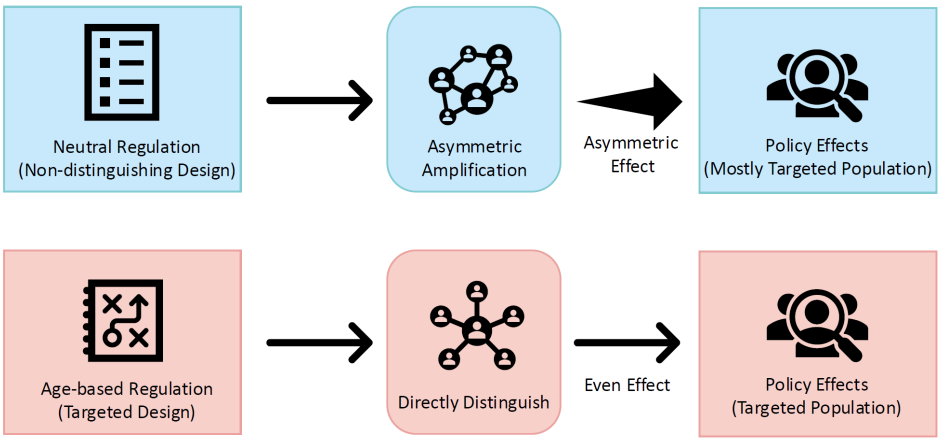

Figure 1. Exhibition of asymmetric amplification effect.

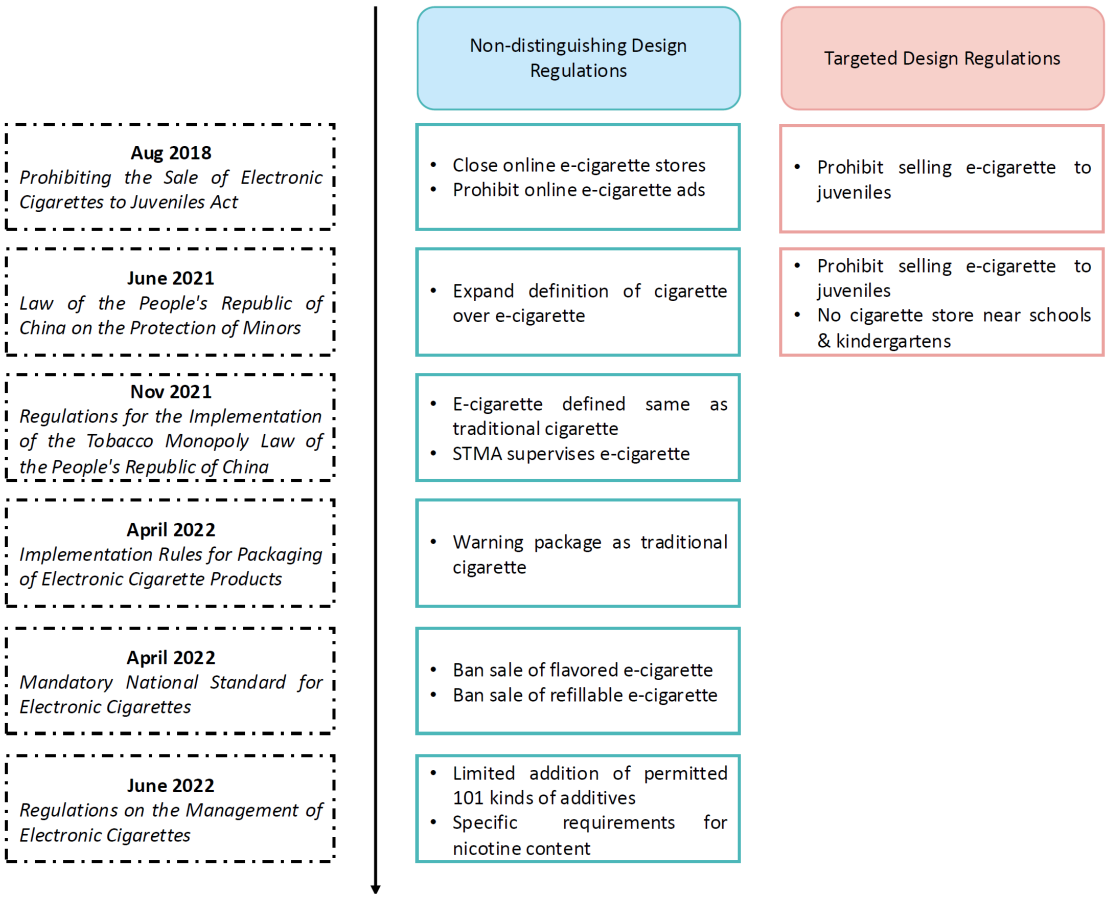

Figure 2. Chinese e-cigarette regulation map. STMA: State Tobacco Monopoly Administration.

discrimination or denial of agency. This approach represents a pragmatic balance between public health objectives and ethical considerations, demonstrating that it is possible to design policies that protect vulnerable populations without creating perceptions of unfair treatment (*9*).

While the concept of "asymmetric amplification" has not been explicitly used in other countries, several international policy measures reflect similar dynamics. For example, high excise taxes on e-cigarettes in U.S. have disproportionately affected youth at different age groups, who are more price-sensitive than adults (*8,10*). Similarly, flavor bans adopted in countries like Finland and Hungary target all users but have the greatest impact on adolescents due to their flavor preferences (*11,12*). Canada's nicotine cap, though universally applied, also limits access to products favored by young users (*13*). These policies share a common feature: universal designs that generate amplified effects on youth through behavioral or economic mechanisms, aligning with the asymmetric amplification framework proposed in this paper.

Conclusions

In conclusion, China's asymmetric amplification-based e-cigarette regulations offer a compelling case study in the design of public health policies. By leveraging universal measures that naturally affect younger users more significantly, these policies avoid the ethical controversies associated with age-based bans while achieving meaningful reductions in youth e-cigarette use. However, the challenges posed by informal markets and potential stigma highlight the need for complementary measures to address unintended consequences. As governments worldwide continue to grapple with the public health challenges posed by e-cigarettes, China's approach offers valuable insights into how regulatory frameworks can balance effectiveness with ethical integrity.

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Creation and use of an index of the emergency resilience of urban public health management in China

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Abstract: This article proposes a framework for emergency resilience based on a review of the literature and theoretical analysis. On this basis, the Delphi method and the Analytic Hierarchy Process have been used to create an index of the emergency resilience of urban public health management. This index includes 6 primary indicators, 22 secondary indicators, and 93 tertiary indicators. An evaluation using the created index indicated that Shanghai's public health emergency management scored 82 out of 100, which is generally a good score. However, there are still problems such as the lack of specificity and implementability in emergency plans, the lack of diversification of reserves of emergency supplies, the low degree of sharing emergency information and cooperation, failure to capitalize on the advantages of traditional Chinese medicine, and the shortage of public health personnel in local communities. Overall, the index of the emergency resilience of urban public health management as was created from the perspective of preventing and controlling major infectious diseases is scientific and reliable, and it can effectively evaluate the current state of emergency management in urban public health.

***Keywords*:** prevention and control of major infectious diseases, emergency resilience, public health emergency management, creation of an index

Introduction

When a public health emergency occurs, the healthcare system is the first line of defense against the crisis. Kieny *et al.* published "Beyond Ebola: a new agenda for resilient health systems" in the Lancet in January 2015, marking the beginning of systematic research based on healthcare system resilience (*1*). The World Health Organization defines disaster resilience as "the ability of a system, community, or society to resist, absorb, adapt, and quickly and effectively recover from disasters when exposed to danger, while maintaining the basic structure and functions of the system" (*2*). In today's society, responding to major public health emergencies is no longer an internal matter for the healthcare system. It requires close cooperation with and a joint response by the government, social organizations, and other stakeholders from the perspective of urban governance.

Therefore, this study proposes an emergency resilience framework based on a review of the literature and theoretical analysis from the perspective of an urban response to major public health emergencies, and it created an index of the emergency resilience of urban public health management in order to provide a reference to improve public health emergency management and enhance public health resilience in Chinese cities.

Method by which an index was created

Creating an initial index

An initial index was created by conducting a review of the literature and performing a theoretical analysis. Based on emergency management theory, resilience theory, and urban governance theory, the emergency resilience framework is first proposed. There are separate dimensions on which to evaluate the emergency resilience of urban public health management, and they are the target layer. That layer is used as to further analyze the key factors influencing urban prevention and control of major public health emergencies, which are the criterion layer. Those criteria are then refined into indicators that are easy to measure, and they are used as the indicator layer.

At present, there are many frameworks with which to evaluate public health emergency response capabilities

both domestically and internationally. Zheng *et al.* used the Delphi method to create indicators of resilience to evaluate epidemic prevention and control by local disease prevention and control facilities (*3*). Based on emergency management theory and resilience theory, Wang *et al.* created indicators with which to evaluate local medical and healthcare facilities' emergency response to major infectious disease outbreaks (*4*). In 2018, the European Centre for Disease Control and Prevention (ECDC) released the Health Emergency Preparedness Self-Assessment (HEPSA) Tool (*5*). Through a review of the literature, Fallah-Aliabadi *et al.* divided disaster resilience into constructive resilience, infrastructural resilience, and administrative resilience, and they developed indicators with which to evaluate the disaster resilience of hospitals (*6*). Zhou *et al.* used the Delphi expert consultation method to create an index with which to evaluate the resilience of the healthcare system in the context of a surge in catastrophic medical demand based on entropy theory (*7*), providing a reference for improving China's disaster risk management capabilities. Cai Y *et al.* used a synthetic control method to evaluate the impact of a trial policy of equalization of healthcare services for migrant populations on the resilience of public health systems in mega cities (*8*). According to the studies above, scholars have begun to apply emergency management theory and resilience theory to jointly solve public health problems, and the research focus has also shifted from specific facilities to the healthcare system and the urban public health system.

Based on previous experience in preventing and controlling major public health emergencies (*9,10*), we believe that emergency resilience means having a system with resilience when responding to emergencies so that the system can effectively respond to shocks at various stages of the emergency response, including advance preparations, in-process handling, and post-incident recovery. This reduces vulnerability in the emergency response process, thus reducing casualties and economic losses, and it allows a quick return to normal production and life. The system's ability to respond to emergencies can grow incrementally, and sufficient preparations can be made for the system to respond to the next emergency. An emergency resilience framework should include six dimensions: organizational resilience, institutional resilience, facility resilience, social resilience, occupational resilience, and technological resilience (*11-16*) (Figure 1). The six dimensions of the emergency resilience framework served as primary indicators, ultimately constituting an initial index that included 6 primary indicators, 21 secondary indicators, and 89 tertiary indicators.

Delphi method

The Delphi method is a structured process that uses a series of questionnaires and "rounds" to collect information, with rounds conducted until a group consensus is reached (*17*). The Delphi method does not have specific requirements for the minimum number of experts, and in general having 15 to 50 experts is advisable (*18*). We selected 34 experts from institutions of higher education, disease prevention and control centers at the city and district level, secondary and primary-tier hospitals, health commissions, and other government agencies and grassroots organizations in Shanghai, Nanjing, Guangzhou, and Haikou to consult. The experts had worked in administration, teaching, and research related to health emergency management, health policy research, and urban governance for at least 5 years and voluntarily participated in this study. This study conducted two rounds of expert consultation *via* e-mail and created an index of the emergency resilience of urban public health management based on expert opinions.

Analytic Hierarchy Process

The Analytic Hierarchy Process (AHP) is a decision-making technique proposed by the American operations

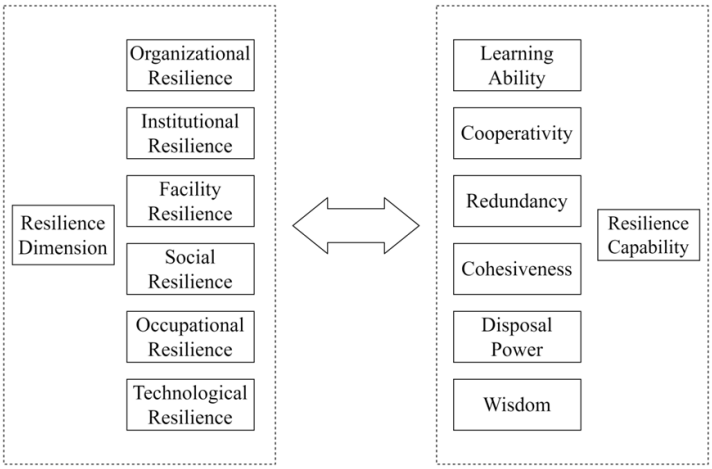

Figure 1. Dimensions and capabilities of "emergency resilience".

researcher Thomas Saaty in the 1970s. It combines qualitative and quantitative analysis and is mainly used to solve complex multi-objective decision-making problems (*19*). The AHP can be roughly divided into five steps (*20*): *i*) establishing a hierarchical structure model, *ii*) constructing a pairwise comparison matrix, *iii*) calculating eigenvalues and eigenvectors; *iv*) consistency of inspection indicators, and *v*) calculating the weights of the indicators.

Fuzzy comprehensive evaluation

Fuzzy comprehensive evaluation is a method of comprehensive evaluation based on fuzzy mathematics. By applying the principle of fuzzy relation synthesis, factors with unclear boundaries and that are difficult to quantify are quantitatively processed to comprehensively evaluate practical problems. The three levels of indicators from the index we created were used to conduct a survey, and the questionnaire was distributed to 25 experts with a wealth of work or research experience in public health emergency management, urban governance, or health policy research and who are familiar with the creation of Shanghai's public health emergency management. These experts were communicated with *via* e-mail to have them evaluate Shanghai's public health emergency management.

Creation of an index

Basic information on experts

This study contacted a total of 34 experts, 34 of whom actually participated. Of the experts, 22 were males and 12 were females; 2 were under the age of 30, 16 were between the ages of 30–39, 13 were between the ages of 40–50, and 3 were over the age of 50. Thirteen of the experts have a bachelor's degree or lower level of education, 15 have a master's degree, and 6 have a doctorate. Three of the experts worked in universities, 14 worked in disease control facilities, 5 worked in medical facilities, 6 worked in relevant municipal government agencies, and 6 worked in local communities. Seven of the experts had less than 10 years of work experience, 21 had 10–19 years of work experience, 5 had 20–29 years of work experience, and 1 had more than 30 years of work experience. See Table 1 for details.

Enthusiasm of experts

The valid response rate to the distributed expert consultation form was higher than 70%, indicating that the experts were enthusiastic about participating. A total of 34 copies of the questionnaire were distributed during the first round of consultation in this study, and 34 valid responses were received. In the second round of consultation, questionnaires were still distributed to these 34 experts, and the response rate to the questionnaire was also 100%. This indicates that experts displayed a high level of interest in participating in this study.

Coefficient for expert authority

Calculation of the coefficient for expert authority was determined by averaging two dimensions, familiarity and judgment criteria. Familiarity was divided into five levels: very familiar with a score of 1, somewhat familiar with a score of 0.8, moderately familiar with a score of 0.6, not very familiar with a score of 0.4, and very unfamiliar with a score of 0.2 (*21*). Judgment criteria were classified into four main categories: theoretical analysis, practical experience, the domestic and foreign literature, and intuitive perception (*22*). These categories were divided into the three levels of major (0.3, 0.5, 0.1, 0.1), regular (0.2, 0.4, 0.1, 0.1), and minor (0.1, 0.3, 0.05, 0.05). The average coefficient for two rounds of expert consultation was 0.832 and 0.885, respectively.

Coefficient for coordination among experts

The coefficient for coordination among experts can be used to measure their level of consensus on indicators. In order to quantify the consistency of expert opinions, we used Kendall's coefficient of concordance (W value) as the measurement standard. A higher W value indicates a higher level of coordination among experts, that is, a decrease in the degree of disagreement among expert opinions. As shown in Table 2, the Kendall coefficient for the first round of expert consultation on the indicators overall was 0.243, indicating that experts had differing

Table 1. Basic information on experts

Project	Frequency	Proportion (%)
Sex		
Male	22	64.7
Female	12	35.3
Age (years)		
< 30	2	5.9
30~	16	47.1
40~	13	38.2
≥ 50	3	8.8
Highest level of education		
Undergraduate or lower	13	38.2
Postgraduate	15	44.1
Ph.D. Student	6	17.7
Type of workplace		
College or university	3	8.8
Center for disease control	14	41.2
Medical facility	5	14.7
Agency of the municipal government	6	17.6
Grassroots organization	6	17.6
Work experience (years)		
< 10	7	20.6
10~	21	61.8
20~	5	14.7
≥ 30	1	2.9

opinions on the indicators. The Kendall coefficient for the second round of expert consultation on the indicators overall was 0.445, indicating less disagreement compared to the first round and a tendency towards consensus.

Indicators of the emergency resilience of urban public health management and their weights

According to expert ratings and opinions, after the first round of expert consultation, there were no changes in the primary indicators. Three indicators were modified and one indicator was divided into two secondary indicators. Three indicators were added to the tertiary indicators. Thirteen indicators were modified, the numbers of two indicators were adjusted, and one indicator was divided into separate lower level indicators. Of the secondary indicators, B2-6 was modified to the System of Post-incident Recovery and Assessment, B5-3 was modified to Command Coordination and Communication, B6-2 was modified to Translation of Research, and B3-2 was divided into B3-2 Availability of Medical Equipment or Facilities and B3-3 Availability of Emergency Response Equipment. C2-5-1 Creating a System of Joint Meetings for Public Health Work, C3-2-4 Number of Fever Clinics and C3-3-2 Emergency Medical Equipment were added as a tertiary indicator. C1-1-3 was modified to Establishing Graded and Classified Response Standards, C1-2-1 was modified to Extent of Coverage of Infectious Disease Outbreaks by Monitoring, C1-3-1 was modified to Constructing a Network for Medical Treatment of Infectious Diseases, C1-4-1 was modified to Planning to Build and Develop Emergency Capacity, C2-1-2 was modified to Team Structure and Distribution of Professional Ability, C2-2-2 was modified to Formulating a Plan for Annual Emergency Training and Drills, C3-1-1 was modified to The Number of Laboratories with Biosafety Level 3 Protection, C3-2-1 was modified to The Number of Special Vehicles such as Negative Pressure Ambulances, C5-1-1 was modified to Epidemiological Investigations of and the On-site Capacity to Handle Confirmed Cases, C5-2-5 was modified to The Ability to Transport Patients with Infectious Diseases, C5-3-1 was modified to Coordination and Communication between the Command Center and On-site Commander, C5-3-2 was modified to The Ability to Coordinate and Communicate with the Local Garrison and Armed Police, and C6-2-1 was modified to Creating a Mechanism for Cooperation between the CDC, Universities and Research Institutes. The numbers of C3-2-4 and C3-2-5 were changed to C3-3-1 and C3-3-3, respectively. C5-3-3 was divided into C5-3-3 Ability to Coordinate and Communicate across Departments and C5-3-4 Ability of the Yangtze River Delta Region to Coordinate and Communicate with other Regional Provinces and Cities.

After the second round of expert consultation, there were no changes in the primary and secondary indicators, and 5 of the tertiary indicators were modified. Specifically, the tertiary indicator C1-1-3 was revised to Establishing Graded and Classified Response Standards, C1-3-1 was revised to Constructing a Network for Medical Treatment of Infectious Diseases, C3-1-4 was revised to The Number of Healthcare Facilities, C4-2-4 was revised to Creating a Mechanism for Coordination with the Village (Community) Public Health Committee, and C6-2-3 was revised to Applied Emergency Research.

Finally, an index of the emergency resilience of urban public health management was created from the perspective of preventing and controlling major infectious diseases. The index consists of 6 primary indicators, 22 secondary indicators, 93 tertiary indicators, and their corresponding weights. See Table 3 for details.

Use of the index

A survey and fuzzy comprehensive evaluation were used to evaluate the current status of the creation of a system to manage public health emergencies in Shanghai within the context of preventing and controlling major public health emergencies. Results indicated that the system to manage public health emergencies in Shanghai scored 82 points (out of 100 points), indicating a good score overall (Table 4).

Shanghai's public health emergency management received a good score overall, but there are also several shortcomings in its resilience. Based on field research, the main issues identified in this evaluation were as follows: first, the emergency plans lack specificity and implementability. Most of the emergency plans in some agencies are based on the requirements of higher-level documents and have not fully incorporated actual local circumstances. At the same time, the revision of the city's emergency plan is progressing slowly and it cannot adapt to the new reality of public health emergency

Table 2. Coefficient for coordination from two rounds of expert consultation

Index	First round			Second round		
	Kendall's coefficient of concordance (W)	c^2	p	Kendall's coefficient of concordance (W)	c^2	p
Primary index	0.378	64.219	< 0.001	0.572	97.181	< 0.001
Secondary index	0.237	161.471	< 0.001	0.487	347.456	< 0.001
Tertiary index	0.225	671.793	< 0.001	0.476	1489.218	< 0.001
Overall index	0.243	950.927	< 0.001	0.445	1817.463	< 0.001

Table 3. Indices and weights of the emergency resilience of urban public health management

Primary indicator (weight)	Secondary indicator (weight)	Combined (weight)	Tertiary indicator (weight)	Combined (weight)
A1 Organizational Resilience (0.256)	B1-1 Emergency Command System (0.294)	0.075	C1-1-1 Establishing an Emergency Command Group (0.226)	0.066
			C1-1-2 Establishing Public Health Emergency Command Centers with Two Levels in Urban Areas (0.049)	0.014
			C1-1-3 Establishing Graded and Classified Response Standards (0.290)	0.085
			C1-1-4 Establishing an Emergency Command System for Multi-departmental Collaboration (0.049)	0.014
			C1-1-5 Creating a System for Public Health Emergency Command Information (0.385)	0.113
	B1-2 Monitoring and Early Warning System (0.417)	0.107	C1-2-1 Extent of Coverage of Infectious Disease Outbreaks by Monitoring (0.077)	0.032
			C1-2-2 Mechanism for Reporting Infectious Disease Outbreaks (0.437)	0.182
			C1-2-3 Handling of Warning Information (0.053)	0.022
			C1-2-4 Conducting a Risk Assessment (0.333)	0.139
	B1-3 Medical Treatment System (0.213)	0.055	C1-3-1 Constructing a Network for Medical Treatment of Infectious Diseases (0.498)	0.106
			C1-3-2 Establishing a Hierarchical System for Diagnosis and Treatment during Major Epidemics (0.354)	0.075
			C1-3-3 Creating a "Reserve" System for Urgent Treatment (0.087)	0.019
			C1-3-4 Building Capacity for Urgent Treatment in Traditional Chinese Medicine (0.061)	0.013
	B1-4 Organizational Support System (0.076)	0.019	C1-4-1 Planning to Build and Develop Emergency Capacity (0.053)	0.004
			C1-4-2 Preparing a List of Public Health Responsibilities for Disease Control, Medical Care, and Relevant Municipal Government Committees and Bureaus (0.098)	0.007
			C1-4-3 Devising Incentive and Penalty Policies for Illegal Activities such as Obstructing Epidemic Prevention and Control, Inflating Prices, and Spreading Rumors (0.389)	0.030
			C1-4-4 Creating a System to Reduce and Exempt Residents' out of Pocket Expenses During Emergencies (0.389)	0.030
			C1-4-5 Devising Policies to Assist Key Industries and Small and Medium-sized Companies in Emergencies (0.071)	0.005
A2 Institutional Resilience (0.335)	B2-1 System for Forming and Managing Emergency Teams (0.131)	0.044	C2-1-1 Forming Expert Emergency Response Teams for Disease Prevention and Control, Medical Treatment, *etc.* (0.227)	0.030
			C2-1-2 Team Structure and Distribution of Professional Ability (0.059)	0.008
			C2-1-3 Building a Database of Experts on the Treatment of Major Infectious Diseases (0.335)	0.044
			C2-1-4 Creating a System to Manage Emergency Teams (0.044)	0.006
			C2-1-5 Special Funds for Emergency Teams (0.335)	0.044
	B2-2 Emergency Training and Drill System (0.204)	0.068	C2-2-1 Completeness of Emergency Plan (0.133)	0.027
			C2-2-2 Formulating a Plan for Annual Emergency Training and Drills (0.424)	0.086
			C2-2-3 Frequency of Emergency Training and Drills (0.073)	0.015
			C2-2-4 Developing Training Materials and Formulating Drill Plans (0.321)	0.065
			C2-2-5 Creating a System to Evaluate the Effectiveness of Training and Drills (0.050)	0.010
	B2-3 Emergency Supplies and Fund Management System (0.294)		C2-3-1 Amassing a Reserve of Emergency Supplies (0.226)	0.066
			C2-3-2 Inventorying and Dynamic Management of Reserves of Medical Supplies (0.049)	0.014
			C2-3-3 The Degree of Concordance between the Quantity of Reserves of Emergency Supplies and Demand During Emergencies (0.385)	0.113
			C2-3-4 Status of Annual Emergency Reserve Funds (0.049)	0.014
			C2-3-5 Emergency Procurement of Supplies (0.290)	0.085
	B2-4 Mechanism to Integrate Activities During Normal Times and Emergencies (0.131)	0.098	C2-4-1 Creating a Mechanism for Allocation and Regional Mobilization of Emergency Personnel (0.100)	0.013
			C2-4-2 Creating an Emergency Mechanism to Open up Beds to Treat Patients with Infectious Diseases (0.437)	0.057
			C2-4-3 Constructing a Network of Laboratories among the CDC, Medical Facilities, Universities, Research Institutes, Customs and Third-party Testing Agencies (0.077)	0.010
			C2-4-4 Increasing and Changing over Production by Companies during Emergencies (0.053)	0.007

Table 3. Indices and weights of the emergency resilience of urban public health management (continued)

Primary indicator (weight)	Secondary indicator (weight)	Combined (weight)	Tertiary indicator (weight)	Combined (weight)
			C2-4-5 Creating a Mechanism for Repurposing of Large Venues During Emergencies (0.333)	0.044
	B2-5 Joint Prevention and Control Mechanism (0.204)	0.044	C2-5-1 Creating a System of Joint Meetings for Public Health Work (0.297)	0.061
			C2-5-2 Creating a Mechanism of Joint Prevention and Control among Medical and Healthcare Facilities (0.056)	0.011
			C2-5-3 Creating a Mechanism of Joint Prevention and Control between Medical and Non-medical facilities (Education, Agriculture, Forestry, Animal CDC, Airports, *etc.*) (0.421)	0.086
			C2-5-4 Creating a Mechanism for the Yangtze River Delta Region to Coordinate and Work with other Provinces and Cities (0.169)	0.034
			C2-5-5 Actively Participating in Global Public Health Governance (0.056)	0.011
	B2-6 System of Post-incident Recovery and Assessment (0.038)	0.068	C2-6-1 Resuming Work and Production as soon as possible (0.221)	0.008
			C2-6-2 Participating in a Mechanism of Amenities and Compensation for Personnel (0.363)	0.014
			C2-6-3 Creating a Mechanism for a Post-Incident Summary and Assessment (0.053)	0.002
			C2-6-4 The Improvement of Subsequent Systems, Mechanisms, Emergency Plans, and Levels of Prevention (0.363)	0.014
A3 Facility Resilience (0.050)	B3-1 Construction of Infrastructure (0.312)	0.013	C3-1-1 The Number of Laboratories with Biosafety Level 3 Protection (0.053)	0.017
			C3-1-2 The Number of Large Indoor Venues such as Stadiums (0.447)	0.139
			C3-1-3 The Number of Facilities that can be used as Centralized Isolation Sites (0.099)	0.031
			C3-1-4 The Number of Healthcare Facilities (0.328)	0.102
			C3-1-5 The Number of Dedicated Public Health Facilities (0.073)	0.023
	B3-2 Availability of Medical Equipment or Facilities (0.198)	0.016	C3-2-1 The Number of Special Vehicles such as Negative Pressure Ambulances (0.339)	0.067
			C3-2-2 The Number of Infectious Disease Wards and Beds (0.099)	0.020
			C3-2-3 The Number of Infectious Disease Wards and Beds (0.066)	0.013
			C3-2-4 The Number of Fever Clinics (0.497)	0.098
	B3-3 Availability of Emergency Response Equipment (0.491)	0.010	C3-3-1 Provision of Equipment for On-site Epidemiological Investigations, On-site Sampling, and Other Emergency Response Equipment (0.164)	0.081
			C3-3-2 Emergency Medical Equipment (0.297)	0.146
			C3-3-3 Communication Equipment (0.539)	0.265
A4 Social Resilience (0.084)	B4-1 Publicity and Health Education (0.491)	0.025	C4-1-1 Formulating a Health Promotion Plan (0.359)	0.176
			C4-1-2 Conducting Regular Health Education and Publicity Activities (0.564)	0.277
			C4-1-3 Diversification of the Ways to Promote Health Education (0.077)	0.038
	B4-2 Management of Grassroots Efforts (0.198)	0.025	C4-2-1 Creating a Mechanism of Social Mobilization (0.497)	0.098
			C4-2-2 Creating a System to Manage Volunteer Teams (0.066)	0.013
			C4-2-3 Training of Grassroots Staff and Volunteers (0.339)	0.067
			C4-2-4 Creating a Mechanism for Coordination with the Village (Community) Public Health Committee (0.099)	0.020
	B4-3 The Public's Response (0.312)	0.041	C4-3-1 Monitoring Public Opinion (0.55)	0.173
			C4-3-2 Release of Information by the Government (0.090)	0.028
			C4-3-3 Media Communication and Shaping of Public Opinion (0.354)	0.110
A5 Career Resilience (0.207)	B5-1 Disease Prevention and Control (0.346)	0.017	C5-1-1 Epidemiological Investigations of and the On-site Capacity to Handle Confirmed Cases (0.115)	0.040
			C5-1-2 The Ability to Manage Suspected Cases and Close Contacts (0.050)	0.017
			C5-1-3 Disinfection Capacity On-site (0.440)	0.152
			C5-1-4 Laboratory Testing and Diagnostic Capabilities (0.318)	0.110
			C5-1-5 Building Capacity for Emergency Vaccination (0.077)	0.027
	B5-2 Medical Assistance (0.110)	0.026	C5-2-1 Hospitals that Meet the Admission Criteria (0.246)	0.027

Table 3. Indices and weights of the emergency resilience of urban public health management (continued)

Primary indicator (weight)	Secondary indicator (weight)	Combined (weight)	Tertiary indicator (weight)	Combined (weight)
			C5-2-2 Hospital Capacity (0.049)	0.005
			C5-2-3 Capacity of Relevant Hospital Departments (0.390)	0.043
			C5-2-4 Capacity for Infection Prevention and Control in Hospitals (0.068)	0.007
			C5-2-5 The Ability to Transport Patients with Infectious Diseases (0.246)	0.027
	B5-3 Command Coordination and Communication (0.544)	0.072	C5-3-1 Coordination and Communication between the Command Center and On-site Commander (0.484)	0.053
			C5-3-2 The Ability to Coordinate and Communicate with the Local Garrison and Armed Police (0.071)	0.008
			C5-3-3 The Ability to Coordinate and Communicate across Departments (0.344)	0.038
			C5-3-4 The Ability of the Yangtze River Delta Region to Coordinate and Communicate with other Regional Provinces and Cities (0.101)	0.011
A6 Technical Resilience (0.068)	B6-1 Emergency Information Technology (0.703)	0.023	C6-1-1 Constructing a Platform for the Reporting of Information on Infectious Diseases (0.095)	0.067
			C6-1-2 The Use of New Technologies in the Early Warning System (0.642)	0.451
			C6-1-3 Monitoring the Capacity to Collect Information (0.095)	0.067
			C6-1-4 Standardizing Public Health Emergency Information (0.168)	0.118
	B6-2 Translation of Research (0.182)	0.113	C6-2-1 Creating a Mechanism for Cooperation between the CDC, Universities and Research Institutes (0.564)	0.103
			C6-2-2 Constructing and Implementing a Platform to Connect Industry and Universities (0.359)	0.065
			C6-2-3 Applied Emergency Research (0.077)	0.014
	B6-3 Medicines and Vaccines (0.115)	0.048	C6-3-1 Emergency Research and Development of Targeted Drugs and Vaccines (0.101)	0.012
			C6-3-2 Emergency Use of Drugs and Vaccines (0.739)	0.085
			C6-3-3 Supervision of Drug and Vaccine Safety (0.160)	0.018

Table 4. Score table for comprehensive evaluation of Shanghai public health "emergency resilience" governance system

Target Layer	Score	Criterion Layer	Score	Sub Criteria Layer	Score
Shanghai public health "emergency resilience" governance system	82	A1 Organizational Resilience	79	B1-1 Emergency Command System	80
				B1-2 Monitoring and Early Warning System	77
				B1-3 Medical Treatment System	84
				B1-4 Organizational Support System	77
		A2 Institutional Resilience	81	B2-1 System for Forming and Managing Emergency Teams	88
				B2-2 Emergency Training and Drill System	82
				B2-3 Emergency Supplies and Fund Management System	78
				B2-4 Mechanism to Integrate Activities During Normal Times and Emergencies	80
				B2-5 Joint Prevention and Control Mechanism	81
				B2-6 System of Post-incident Recovery and Assessment	76
		A3 Facility Resilience	87	B3-1 Construction of Infrastructure	85
				B3-2 Availability of Medical Equipment or Facilities	87
				B3-3 Availability of Emergency Response Equipment	87
		A4 Social esilience	86	B4-1 Publicity and Health Education	89
				B4-2 Management of Grassroots Efforts	80
				B4-3 The Public's Response	86
		A5 Career Resilience	85	B5-1 Disease Prevention and Control	86
				B5-2 Medical Assistance	85
				B5-3 Command Coordination and Communication	85
		A6 Technical Resilience	82	B6-1 Emergency Information Technology	82
				B6-2 Translation of Research	79
				B6-3 Medicines and Vaccines	82

management. In addition, large-scale exercises can easily disrupt social order and require stress testing to expose potential vulnerabilities, balancing the contradiction between "practicality" and "controllability".

The second issue is the lack of diversification of reserves of emergency supplies. At present, reserves of emergency supplies in Shanghai mainly in the form of the government's physical reserves, and participation by companies is insufficient. The lack of both long-term and short-term planning for emergency supply reserves hampers relevant departments in responding quickly and effectively to crises after major emergencies occur, and may even result in missing the optimal window for an early response.

The third issue is a low degree of sharing emergency information and collaboration. When building their own emergency information systems, various entities in Shanghai lack unified construction standards and reasonable system planning, resulting in chaotic emergency information management and difficulty in sharing emergency information, thus causing the phenomenon of "information islands".

The fourth issue is that the advantages of traditional Chinese medicine have not been effectively capitalized upon. When a healthcare system is responding to a major public health emergency, traditional Chinese medicine has displayed certain limitations in terms of being at disparate locations, being in different stages, and differences in regional availability, and there is still a lack of systematic and institutional support for its use. During the initial stage of the COVID-19 pandemic, Shanghai did not fully understand the assistance traditional Chinese medicine could provide and failed to capitalize on the advantages of traditional Chinese medicine, and especially in terms of assisting patients.

The fifth issue is the lack of personnel in community public health. Most local community workers have not received relevant professional education and when faced with sudden public health emergencies, they can only rely on instructions from superiors to take action. Most training is only conducted in the immediate aftermath of a public health emergency, hampering the effective enhancement of the emergency management capabilities of personnel. At the same time, community volunteer teams are relatively older people, with most of them being elderly who are retired or about to retire. And due to the lack of sound laws and regulations, the legitimacy of volunteers in emergency management is often questioned, which also restricts the forming of volunteer teams.

Perspectives on the index of management of emergency resilience

China has proposed the establishment of a "big security and big emergency" framework and revised and released a new version of the Emergency Response Law of the People's Republic of China and the National Emergency Plan in 2024. Over the past few years, the national and local governments have also issued a series of policy documents to guide localities to accelerate the development of disease control systems, enhance the monitoring of infectious diseases, enhance early warning and response capabilities, and enhance the construction of resilient cities. Creation of this index is based on a review of the relevant literature on management of public health emergencies, infectious disease prevention and control policies, and evaluation of emergency capacity. It has a solid theoretical foundation and

follows the principles of implementability, systematicity, comparability, and a scientific basis to select indicators to ensure the index's reliability. Therefore, this index can serve as a reference for the creation of a urban system to manage public health emergencies in China and to improve the emergency resilience of the urban public health system.

Use of this index revealed that Shanghai's public health emergency management has insufficient specificity and implementability of emergency plans, insufficient diversification of the reserves of emergency supplies, a low level of sharing emergency information and cooperation, insufficient capitalization on the advantages of traditional Chinese medicine, and a shortage of local community public health personnel, which are hidden dangers when creating a safe and resilient city. Important factors such as local economic conditions, geographic conditions, cultural characteristics, susceptibility to disasters, the state of medical and health care, and functional organizational structures should be carefully considered when revising emergency plans. Reserves of supplies should be classified and varied for multiple levels such as the city level, district level, and neighborhood level, and the different departments and agencies at different levels should clarify who will store those reserves, what they will store, and how much they will store. A system linking public health disease prevention and control that combines traditional Chinese medicine and Western medicine should be created, ensuring close integration and collaboration between traditional Chinese medical care and other forms of medical care. Unified standards on coding information should be established to facilitate the exchange of data between different departments. Emergency response capabilities at the grassroots level should be enhanced, community health emergency teams and volunteer teams should be forming, emergency training should be conducted regularly, and the expertise of the grassroots emergency teams should be increased.

This article has focused on cities, and the indicators may not be generalizable to rural and remote areas. This study only evaluated the current status of public health emergency management in Shanghai and did not involve surveys of or comparisons to other cities. Therefore, the next step will be to compare Shanghai to other cities in China and to adjust the index to improve its utility and practicality, thus providing a reference to enhance the emergency resilience of urban public health.

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REVIEW
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The silkworm: A promising invertebrate diabetes model for natural drug discovery

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Abstract: As an economically important insect, the silkworm (*Bombyx mori*) occupies a central position in the silk industry. Its unique physiological characteristics make it a potential model animal for research on disease modeling and drug screening. The aim of this review was to explore the feasibility of the silkworm as a model animal for diabetes and to evaluate the potential application of this model in new drug discovery. Through high-glucose feeding and chemical induction, researchers successfully constructed silkworm models with diabetic phenotypes, which exhibited features such as hyperglycemia and insulin resistance similar to human diabetes. Subsequently, the researchers screened a variety of natural medicines and found that certain natural medicinal components were able to significantly reduce blood glucose levels and improve insulin sensitivity in the model silkworms. This review not only provides a new model animal for the pathophysiological study of diabetes, but also provides an experimental basis for the application of natural medicines in diabetes treatment, opens up a new way for the discovery of the active sub-ingredients of natural medicines, and is expected to provide a new strategy and source of medicines for the treatment of diabetes.

***Keywords*:** silkworm model, diabetes, natural medicine

Introduction

Diabetes is a global metabolic disease with a growing epidemic. According to the 10th edition of the IDF Diabetes Atlas, released by the International Diabetes Federation (IDF) on December 6, 2021, the number of adults aged 20-79 years with diabetes reached 537 million worldwide in 2021, which is equivalent to 1 in 10 people. Epidemiologic projections indicate that the number of people with the disease will climb to 643 million by 2030 and further to 783 million by 2045. Notably, between 2021 and 2045, the world population is expected to grow by 20%, while the number of people with diabetes will increase by 46% (*1*), significantly faster than the population growth rate. China, as the country with the largest number of diabetic patients in the world, has reached an epidemiologic level of prevalence in its adult population. Diabetes is characterized by persistent hyperglycemia and defective or impaired insulin secretion. Its typical clinical manifestations can be summarized as the "three more and one less" syndrome, *i.e.*, polydipsia, polyuria, polyphagia with progressive weight loss. As the disease progresses, patients may develop multi-system complications, including chronic progressive damage to target organs such as eyes, kidneys, nerves, heart and cardiovascular organs, which ultimately leads to organ failure. In addition, patients are at risk for serious complications such as acute metabolic disorders (*2*).

However, the current clinical application of antidiabetic drugs still has obvious limitations in disease management, and their adverse reactions not only affect the therapeutic effect, but also seriously threaten the health and quality of life of patients (*3*). Taking the commonly used drugs for type 2 diabetes treatment as an example: empagliflozin may trigger adverse reactions such as blood glucose fluctuation, nausea and dizziness; dagliflozin may lead to abnormal weight loss; and the use of cagliflozin has been associated with a variety of serious complications, including diabetic ketoacidosis, lower limb amputation, acute kidney injury, fungal infections, and osteomyelitis, among others. In addition, dulaglutide and somatostatin, which are glucagon-like peptide-1 receptor agonists, have good glucose-lowering effects, but their high incidence of gastrointestinal adverse reactions limits clinical application. The safety issues raised by these drugs not only aggravate the disease burden of patients, but also bring additional economic burden. Therefore, the development of new safe, economical, and efficient therapeutic drugs has become an urgent need in the current field of diabetes treatment.

In the process of searching for safe and effective therapeutic drugs, natural medicines have gradually emerged as a hotspot of research by virtue of their many advantages such as multi-target regulation and fewer side effects. Natural medicines not only have rich chemical diversity, complex structure and variety, which provide a large amount of material basis for drug screening, but also have a certain degree of biological adaptability and safety due to their natural screening. In addition, natural medicines contain the wisdom of traditional medicine as well as the treasures of ethnomedicine, which provide abundant clues and experiences for modern drug screening. These natural products originated from plants, animals and microorganisms are opening up completely new pathways for diabetes treatment with the help of modern scientific validation. For example, artemisinin and its derivatives can improve insulin resistance by inhibiting the inflammatory response. Many studies have shown that artemisinin is able to target the NF-κB signalling pathway and reduce the release of inflammatory factors, thereby alleviating insulin resistance (*4,5*): diazoxide (Catalpol) improves insulin resistance by activating the hepatic PI3K/Akt pathway (*6*); and curcumin attenuates diabetic myocardial fibrosis by regulating the MAPK/NF-κB signalling axis ($p < 0.05$) (*7*); baicalein stimulates insulin secretion in β-cell lines and human pancreatic islets (*8*); and berberine slows down glucose uptake by inhibiting α-glucosidase activity (*9*).

Animal model construction has become an irreplaceable experimental paradigm in the study of pathological mechanisms of diabetes and its complications. According to the evolutionary status of species and research needs, three main types of experimental systems are currently used:

Classical mammalian models: rodents (*e.g.*, rats and mice) (*10*) are widely used by virtue of their clear genetic backgrounds and short reproductive cycles; rabbits (*11*) occupy an important position in diabetes research by virtue of their unique metabolic characteristics; and pigs (*12*) have become an ideal large-animal model of diabetes because of the high degree of similarity between their physiological structures and those of humans.

Novel model organism system: With the development of histological technology, lower biological models show unique value: drosophila (*13*) provides a new perspective for diabetes research with its simple genome and short life cycle; nematode (*14*) becomes an ideal model for studying metabolic regulation mechanism with its complete insulin signalling pathway; zebrafish (*15*) plays an important role in diabetes research with its advantages of embryonic transparency and easy genetic manipulation for diabetes research.

Breakthroughs in characteristic resource organisms: as a model organism originated in China, the silkworm (*Bombyx mori*) (*16*) has attracted attention from academics for its unique regulatory mechanism of glucose metabolism and its advantages in large-scale rearing. Studies have shown that the hemolymph glucose homeostatic regulatory system of the silkworm is highly homologous to that of humans, which, coupled with its short life cycle (about 50 days) and well-defined developmental stages, provides a novel platform for the study of diabetes dynamics. Systematic comparisons show that the silkworm exhibits significant advantages in terms of the cost of glucose tolerance experiments (90% lower than that of mammals) and the convenience of phenotypic observation.

Advantages of the silkworm as a model animal

The silkworm, also known as the silkworm moth, is an economically important insect in the Lepidoptera family of silkworm moths. By virtue of its unique biological characteristics, the silkworm has developed into a valuable model organism in the field of life science research, showing broad application prospects in several research directions. Currently, researchers have successfully constructed a variety of disease models (*e.g.*, gout model (*17*), microbial infection model (*18,19*), Parkinson's mode (*16*), diabetes model, virus infection model (*20*), *etc.*). In addition, the silkworm also plays an important role in toxicology studies (*21,22*), environmental monitoring (*23,24*), and drug screening (*19,25*), providing an ideal experimental platform for related research (Table 1).

Physiological characteristics suitable for research

As a model organism, the silkworm exhibits unique advantages in experimental manipulation. Compared with mammals (*e.g.*, mice, rabbits), the silkworm does not require complex fixation devices, which significantly improves the efficiency of experiments. Compared with other insect models (*e.g.*, drosophila), the silkworm is moderately active and not easy to escape, which facilitates experimental manipulation and continuous observation, and this characteristic greatly improves the controllability and reproducibility of the experiments. Compared with invertebrates (*e.g.*, nematodes), the domestic silkworm has a moderate body size, and its organs and tissues are clearly recognizable, which facilitates precise anatomical isolation and sample collection, providing ideal conditions for in-depth mechanistic studies. These unique physiological characteristics make the silkworm a valuable model organism for metabolic disease research.

Low feeding cost and short cycle time

The silkworm has a unique developmental biology, its life cycle goes through four developmental stages: egg, larva, pupa and adult, and it only takes 23-29 days from hatching to 5th instar larvae (Figure 1). This short life

Table 1. Application of silkworm disease model in newdrug discovery

Silkworm model types	Characterization	Mechanism exploration	Success case
Diabetes (*26*)	Blood sugar levels rise markedly, resulting in the emergence of impaired glucose tolerance, which can be mitigated by hypoglycemic medications.	Increased JNK phosphorylation levels lead to insulin resistance.	1. YM0831 (*25*) 2. Extract of *Salacia reticulata* (*49*) 3. Jasmine crude polysaccharide (*27*) 4.Total flavonoids of *Paederia scandend* (*27*) 5.Total flavonoids of hibiscus flowers (*27*) 6.Total flavonoids of chamomile (*27*)
Bacteria			
Staphylococcus aureus (*28*)	After injecting bacteria, the hemolymph of silkworm resulted in a significant decrease in their survival within 24-48 h. Glycopeptide antibiotics were non-toxic to larvae and cured *S. aureus* infection.	The silkworm is infected by a variety of pathogenic bacteria, but can be effectively treated with clinical antibiotics (which have similar ED_{50} values). In addition, parameters such as drug half-life and volume of distribution in the silkworm are consistent with mammalian models (*29*).	Lysocin E (*19*)
Pseudomonas aeruginosa (*18*) *Vibrio cholerae* (*18*)	When injected into the bloodstream of 5th instar silkworm larvae, more than 90% of the larvae died within 2 days.		Silkworms could be used in anti-bacterial drug development.
Fungus			
Candida albicans (*31*) *Candida tropicalis* (*31*) *Candida glabrata* (*31*) *Cryptococcus neoformans* (*31*) *Aspergillus fu*migatus (*31*)	After injecting fungi, silkworms died.	Antifungal drugs exhibit a high protein binding capacity in the hemolymph of the silkworm, similar to that of mammalian serum, which can lead to reduced therapeutic efficacy. The silkworm recognizes not only bacterial peptidoglycans and lipopolysaccharides, but also the fungal cell wall component β-glucan, which activates the innate immune system (30, 31).	Silkworm have potential for antifungal drug discovery. ASP2397 (*32*)
Virus			
Bombyx mori nucleopolyhedrovirus	Antiviral drugs inhibit the proliferation of baculoviruses in the body fluids of the silkworm, and have a therapeutic effect.	Cinnzeylanine inhibits the proliferation of herpes simplex virus in Vero cells.	Cinnzeylanine (*20*)
Innate immunity	Upon injecting peanut oil into the body of a silkworm, melanin is generated within its system, causing the blood to turn black and the muscles to contract.	After chemical treatment (saponification reaction) to destroy the structure of TAGs, their immune activation effect is significantly weakened.	Triacylglycerol (*33*)
Toxicology (*34*)	The half-life of the drug is similar in both silkworms and mice.	The lethal dose of cytotoxic chemicals for silkworms is consistent with that for mammals, and the metabolic pathways of drugs in silkworms and mice are consistent.	Silkworms have potential for assessing drug toxicity and studying metabolic mechanisms.
Parkinson's disease (*16*)	Motor dysfunction, dopaminergic neuron degeneration, and decreased dopamine levels.	50 proteins were severely downregulated, and mechanical damage was observed in silkworm tissues	Silkworms have potential for Parkinson's disease mechanism research and drug discovery.
Gout (*17*)	Elevated uric acid Levels.	When *Bm5'N* mutation occurs in silkworms, the level of uric acid in the epidermis significantly increases.	Silkworms may be a suitable model for studying uric acid metabolism pathways associated with human diseases.

cycle combined with its strong reproductive ability can rapidly obtain a large number of offspring, significantly shortening the experimental cycle and improving research efficiency. In terms of feeding conditions, the silkworm only needs mulberry leaves or mulberry leaf-based artificial diets to meet its nutritional needs, and feeding management is simple. Compared with mammalian models, the requirements of laboratory rearing facilities for silkworms are simple, without need for complex incubators and specialized animal rooms, and a single incubator for silkworms can accommodate hundreds to thousands of individuals at the same time, which greatly saves experimental space. These advantages make establishment and maintenance costs of silkworm models significantly lower than those of traditional mammalian models, providing an economically feasible option for large-scale experimental research.

The main stages of laboratory silkworm rearing are shown in Figure 1 above. The number of days required for each stage: eggs 7–10 days, 1st instar larvae 3–4 days, 2nd instar larvae 3–4 days, 3rd instar larvae 4–5 days, 4th instar larvae 6–7 days, 5th instar larvae 7–9 days.

Pathophysiological similarities with human diabetic disease

The silkworm, has unique molecular biological advantages as a model for diabetes research. Studies have shown that the primary structure of the silkworm is significantly homologous to human insulin, and its A and B chains are highly conserved with human insulin (*35*), which makes it an ideal model for studying the pathogenesis of diabetes mellitus, its complications, and the screening of hypoglycemic drugs. In addition, the silkworm can exhibit typical diabetes-like symptoms such as metabolic disorders due to hyperglycemia under pathological conditions. It is noteworthy that a special peptide hormone, bombyxin, exists in the silkworm, and its three-dimensional structure is highly similar to that of human insulin (*36*), which provides an important molecular basis for study of the insulin signaling pathway and related metabolic regulation mechanisms.

Genetic similarity

The silkworm exhibits significant evolutionary conservation of genetic mechanisms with humans, and its genome structure is highly homologous to the human genome in several functional regions. This conservatism enables certain mutants of the silkworm to mimic the phenotypic characteristics of human genetic diseases (*37*). It provides a unique model organism platform for human research on genetic diseases. Through the silkworm model, researchers can systematically analyze the functional network of related genes, mutation mechanisms and their pathogenesis, which not only deepens our understanding of the molecular basis of genetic diseases, but also provides important theoretical support for early diagnosis of diseases and development of targeted therapies and preventive strategies, as well as potential intervention targets. Therefore, as a model organism for study of human genetic diseases, the silkworm has an irreplaceable value in both basic research and translational medicine (*38*).

Figure 1. Standardized laboratory feed system for silkworms.

Metabolic relevance

The silkworm shows remarkable similarity with mammals in terms of toxicity response and drug metabolism. On the one hand, the lethal dose levels of cytotoxic chemicals in silkworms are basically the same as those in mammals; on the other hand, the half-life of 4-methylumbelliferone in the hemolymph of silkworm larvae is 7.0 ± 0.1 min, which is similar to that in the blood of mice, according to a study using 4-methylumbelliferone as a model drug. More interestingly, at the level of metabolic mechanisms, silkworms and mammals share commonalities: both can metabolise chemicals by reacting with cytochrome P450 enzymes, binding to hydroxylated compounds, and ultimately excreting them (*34*).

Fewer ethical issues, in line with the 3R principle of animal experimentation

The ethical review of experimental animals is an important mechanism to ensure the scientific and ethical nature of animal experiments, the core of which lies in the strict adherence to the "3R" principle (Replacement, Reduction, Refinement) (*39*). According to internationally accepted ethical guidelines for animal experiments, researchers should preferentially select lower animals as experimental subjects, minimize the number of animals used by optimizing the experimental design, and improve the experimental methods to minimize animal suffering (*40*). In this context, the silkworm, as an invertebrate model organism, has obvious ethical advantages over higher mammals: its nervous system is relatively simple and its perceptual ability is limited, so there are fewer ethical controversies involved in the experimental process, and the restrictions on ethical review are relatively loose, which provides convenient conditions for carrying out large-scale experimental research.

Methods for modeling diabetes in the silkworm

The construction of the silkworm diabetes model is an important experimental platform to study the pathogenesis of diabetes and drug screening. At present, commonly used model construction methods mainly include the high sugar feed induction method and chemical drug induction method. These two methods, their principles of operation, and their advantages and disadvantages will be introduced separately in the following.

High-sugar diets induction

High sugar feed induction refers to the induction of a pathological state similar to diabetes or other metabolic disorders in experimental animals or biological models by feeding high-sugar diets for a long or short period of time, which causes a sustained increase in blood glucose levels. The human diabetic state is mimicked by feeding silkworms a mulberry leaf or artificial diets containing high concentrations of glucose, sucrose, fructose, or other sugars to elevate their blood glucose levels (*26,41-42*). A model of type 2 diabetes was successfully established after rearing 5th instar larvae for 18 h on a diet containing 10% glucose (high-glucose diet), and the silkworms showed typical diabetic characteristics: the total sugar level in the hemolymph of silkworms on the high-glucose diets was 2.4-fold higher than that of normal silkworms, their glycaemic content was significantly elevated ($p < 0.01$) and a glucose tolerance test showed impaired glucose clearance capacity. Phosphorylated JNK levels were found to be significantly increased in the fat bodies of hyperlipidemic silkworms fed a high-sugar diet for 18 h as compared to a normal-diet silkworms by Western blot analysis (*26*).

In terms of sugar selection, there were significant differences in the regulation of blood glucose in the model animals using different sugars. Glucose, as a monosaccharide, can be directly absorbed into the blood circulation, leading to a rapid increase in blood glucose; sucrose, as a disaccharide, needs to be decomposed into glucose and fructose in the body before being absorbed and utilized (*43*), so its rate of glucose increase is relatively slow; and fructose, although the same as other monosaccharides, is converted into glucose mainly through hepatic metabolism, so its glucose-raising effect is not as significant as that of glucose.

However, the method faces challenges in its implementation. There is an obvious seasonal limitation of mulberry leaves, the traditional food of silkworms, especially in the winter when the supply is insufficient, which may affect the continuity and reproducibility of the experiments. To overcome this limitation, researchers have developed artificial diets for the silkworm, among which Japanese scholars were the first to realize the breakthrough of an artificial diet feeding the 3rd instar (*44*), and the technology of feeding silkworms at the 5th instar on artificial diets is now very mature.

Chemical induction

Chemically induced models are modelling approaches in which specific chemicals are given to experimental animals to induce changes in the target disease or pathophysiology. In the field of diabetes modelling in mammals (*e.g.*, rats, mice), tetroxine (Alloxan) and streptozotocin (STZ) are two classical chemoinducers (*45*). Similarly, some researchers have used a co-injection technique in silkworm experiments, where silkworms were synchronously injected with a 40% glucose-containing solution (0.5 mL) and an 80 mg/kg solution of streptozotocin (0.5 mL), and it was found that

the glucose content of the experimental subjects showed a significant trend of glucose elevation. Streptozotocin, as an aminoglucose-nitrosourea derivative, is able to enter cells through glucose transporter protein 2 (Glut2), leading to the necrosis of insulin-producing cells (pancreatic islet β-cells). In the silkworm, glucose levels in the hemolymph are regulated mainly by a neurosecretory hormone, bombyxin, which is associated with the insulin signalling pathway. All streptozotocin may affect glucose regulation mechanisms in the silkworm by interfering with the secretion of homeoboxin or its signalling pathway, which in turn affects glucose regulation mechanisms in the silkworm (*46*).

Application of the silkworm in diabetes research

Drug screening and efficacy evaluation

Japanese researchers have found that silkworms share a conserved blood glucose regulation mechanism with mammals, and that the AMP-activated protein kinase (AMPK) and insulin signalling pathways in their hemolymph are involved in the regulation of glucose metabolism. The study demonstrated that 5-aminoimidazole-4-carboxamide-1-b-D-ribofuranoside (AICAR), an AMPK activator, and human insulin could effectively correct the growth phenotype of hyperglycemic silkworms by down-regulating the total glucose level in the hemolymph (*47,48*). This finding provides a theoretical basis for the use of silkworm models to screen for antidiabetic drugs targeting the AMPK/insulin signalling pathway. In addition, the Japanese team found that *Enterococcus faecalis* YM0831 significantly inhibited the sucrose-induced hyperglycaemic effect. When it was combined with the extract of the Traditional Chinese medicine *Kothala himbutu* (*Salacia reticulata*), it exhibited synergistic hypoglycaemic effects in the system of the silkworm (*25,49*), which provides a new idea for the development of novel complex hypoglycaemic agents. In addition, in studies using the silkworm as a model animal, a variety of herbs have been found to have hypoglycemic effects, such as jasmine crude polysaccharides, total flavonoids of *Paederia scandend*, total flavonoids of hibiscus flowers and total flavonoids of chamomile, all of which have been demonstrated to exert significant hypoglycemic efficacy by inhibiting the activity of α-glucosidase (*27*).

In terms of pharmacodynamic evaluation, the researchers successfully induced a type 2 diabetes model in silkworms by feeding them high glucose diets for 18 hours. The clinically used hypoglycaemic drugs pioglitazone and metformin both showed significant improvement in glucose tolerance in this model, which verified the reliability of this model for the evaluation of drugs used in the treatment of type 2 diabetes (*26*).

Study on the diabetes model of the silkworm, and the pathogenesis of its complications

The high glucose diet induced silkworm model (20 g of artificial diets with 10% glucose, fed continuously for 72 hours) mimics the following pathological features of diabetic reproductive system complications (*50*):

Oxidative stress markers: hemolymph malondialdehyde (MDA) levels were significantly elevated ($p < 0.01$) and superoxide dismutase (SOD) activity was significantly reduced ($p < 0.05$), suggesting systemic oxidative damage.

Reproductive system lesions: Testicular histopathology showed retarded testicular development, necrosis of spermatogonia and seminal vesicles, and obvious pathological changes, with pathological similarities to human diabetic hypogonadism.

Functional analysis of glucose metabolism-related genes in the silkworm

As an invertebrate model organism, the unique glucose metabolism regulation genes of the silkworm provide a new perspective for diabetes research:

BBX-B8 gene: a member of clade B in the gene family of insulin-like peptides in the silkworm, which affects organ development, alginate metabolism, reproduction, stress and antioxidant enzyme activities in the silkworm, whereas overexpression of the gene leads to alginate accumulation (*51*).

BmSuc1 gene: the first β-fructofuranase identified in the silkworm, and knockout of this gene decreased midgut glucose content accompanied by abnormally elevated maltase and alginase activities and impaired glycogen synthesis (*52*).

BmTre gene: *BmERR* (estrogen receptor) overexpression promotes expression of *BmTreh* in the midgut, which then accelerates conversion of alginate to glucose and increases the glucose content of hemolymph in the silkworm, suggesting that it affects energy metabolism through regulation of glycolytic genes (*53*).

Study of antidiabetic active ingredients of silkworm origin

Deoxynojirimycin (1-Deoxynojirimycin, DNJ)

DNJ is a natural polyhydroxypiperidine alkaloid, mainly enriched in the branches, leaves, roots of Moraceae (*Morus*) plants and the hemolymph of silkworms. Its hypoglycemic mechanism is mainly through competitive inhibition of α-glucosidase, which delays hydrolysis and absorption of intestinal carbohydrates (*54*). Studies have shown that male larvae of the 5th instar day 3 of the silkworm, fed with high DNJ mulberry leaves (DNJ content ≥ 0.125%), have a hemolymph DNJ concentration of up to 0.465%, which is significantly

higher than that of other developmental stages, suggesting that this period is the optimal window for obtaining DNJ on a large scale (*55,56*). Miglitol, which was developed based on the structural modification of DNJ, has been successfully used in clinical applications, and its blood glucose lowering effect was stronger than that of DNJ ($p < 0.01$) (*57*).

In addition, DNJ has multi-target therapeutic potential:

i) Improvement of metabolic disorders: it enhances insulin sensitivity by activating the PI3K/AKT pathway with elevated phosphorylation levels ($p < 0.01$) (*58,59*), and also has an effect on adipocyte metabolism *via* intestinal flora, which improves adipose metabolism-associated disease states (*60*);

ii) Nephroprotective effects: in a diabetic nephropathy model, DNJ intervention reduced the urinary protein excretion rate and inhibited glomerular thylakoid matrix expansion (*61,62*);

iii) Cardioprotective potential: *in vitro* experiments confirmed that DNJ concentration up to 30 μM could reverse mitochondrial membrane potential attenuation ($p < 0.001$), providing new ideas for the treatment of hypertrophic cardiomyopathy (*63*).

Bombyxin

Bombyxin is the first insulin-like heterodimeric peptide (molecular weight ~5 kDa) found in insects, and its A and B chains share 50% and 30% sequence homology with human insulin, respectively (*35,64*). Functional studies have shown that neck ligation of homeopathic silkworm larvae injected with homeopathin reduced hemolymph alginate concentration and elevated alginase activity (*65,66*); and *in vitro* cellular experiments confirmed that Homeopathy regulates glucose uptake and glycogen synthesis in HepG2 cells *via* the PI3K/Akt pathway, which in turn affects energy storage and utilization homeostasis (*67*).

Core regulatory pathway of silkworm diabetes model

Diabetes is a chronic metabolic disease with multifactorial interactions, and its pathogenesis involves complex factors such as genetic susceptibility (*68*), obesity, dietary imbalance (*69*), circadian rhythm disruption, viral infections (*70*), and drug side effects (*71*). In recent years, through the analysis of key signaling pathways and their application in silkworm models, researchers have further revealed the molecular mechanism of diabetes and accelerated development of new hypoglycemic drugs (Figure 2).

AMPK signaling pathway

AMPK is a central regulator of energy metabolism that is activated by sensing changes in the intracellular AMP/ATP ratio. It regulates metabolic homeostasis

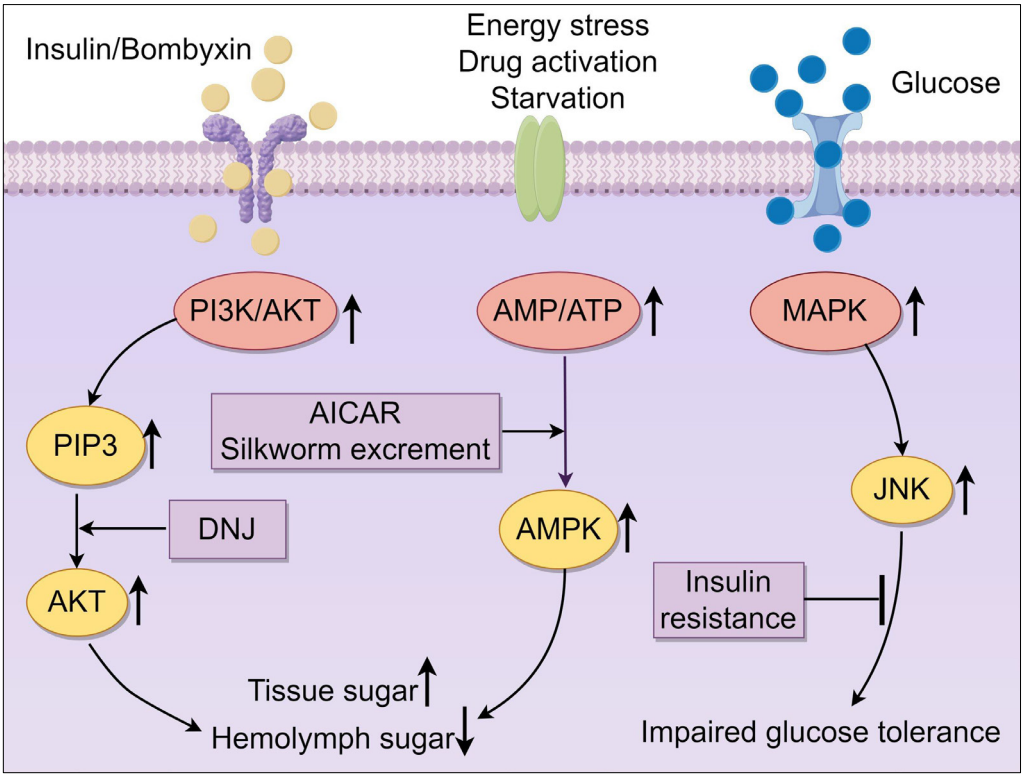

Figure 2. Key signaling pathways in the silkworm diabetes model. The figure shows the interactions between the insulin signaling pathway, PI3K/Akt pathway, AMPK pathway, and MAPK pathway in the silkworm diabetes model. These pathways are activated through molecular cascades and jointly regulate sugar levels in tissues and hemolymph, revealing the mechanism of insulin resistance.

through a dual action: inhibiting glycolipid synthesis (*e.g.*, inhibition of acetyl coenzyme A carboxylase) and promoting catabolism (*e.g.*, enhancing fatty acid oxidation) (*72-74*). In diabetic silkworms, activation of AMPK in response to energetic stress, drug (*e.g.*, AICAR) stimulation results in an increase in tissue glucose levels and a decrease in hemolymph glucose levels (*47*). Notably, extracts of silkworm excrement (*i.e.*, a kind of Tradition Chinese Medicine) have also been shown to exert hypoglycemic effects by upregulating AMPK phosphorylation levels (*75*).

PI3K/Akt signaling pathway

As the core pathway of insulin signaling, homeopathins and insulin activate phosphatidylinositol 3-kinase (PI3K), which catalyzes the generation of phosphatidylinositol 3-phosphate (PIP3), which then phosphorylates and activates Akt (protein kinase B). Activated Akt enhances glucose uptake and hepatic glycogen synthesis in peripheral tissues (*48,76*).

MAPK signaling pathway

The MAPK (mitogen-activated protein kinase) pathway is generally involved in insulin resistance by regulating chronic inflammatory responses. Activation of the MAPK pathway, followed by enhanced phosphorylation of JNK in the silkworm, usually in a high glucose environment, leads to impaired glucose tolerance and insulin resistance in the silkworm (*26,48*).

Natural drug development paradigm based on silkworm modeling

Our research team proposes a stepwise development strategy that integrates the silkworm model with histological techniques:

Initial screening phase (*i.e.*, screening *in vivo*): Referring to the data obtained by previous researchers (*42,50*), we used 10% high-glucose diets to induce the modeling for 18 h. Modeling was initially considered successful with a blood glucose value > 11.1 mmol/L, and then the candidate compounds were screened by *in vivo* efficacy evaluations (*e.g.*, blood glucose value determination, glucose tolerance test, glucose-lowering rate, *etc.*).

Validation phase (*i.e.*, validation *in vitro*): In order to deeply investigate the glucose-lowering potential of the candidate compounds in the *in vitro* environment, a model of insulin resistance can be constructed by using human hepatocellular carcinoma cells (HepG2 cells). Co-cultivating the HepG2 cells with insulin and high glucose concentration to establish an *in vitro* insulin-resistant cell model, and then performing glucose consumption and glycogen synthesis assays (*77,78*) and then assessing whether candidate compounds are able to effectively improve insulin resistance or not, and whether the candidate compounds could effectively improve glucose uptake and metabolism in insulin-resistant cells.

Separation and purification of target chemical monomers and spectral analysis: separation and purification of target chemical monomers is to precisely separate and purify the target monomers based on the difference in physicochemical properties between monomers and impurities by using chromatography, extraction and other techniques. Afterwards, the structural information of the target monomer, such as functional groups, chemical bonding, molecular weight and spatial configuration, can be analyzed by ultraviolet (UV), infrared (IR), nuclear magnetic resonance (NMR), mass spectrometry (MS), high-speed countercurrent chromatography (HSCCC) and other spectroscopic means (*79*). Structural identification of the active ingredients can also be accomplished by UPLC/Q-TOF-MS/conjugated NMR (*80*). Secondary validation of hypoglycemic activity: after obtaining the monomer compounds, confirmatory experiments for hypoglycemic activity were again performed *in vivo* (silkworms) and *in vitro* (HepG2 cells).

Glucose-lowering mechanism studies: glucose uptake assay, glycogen synthesis assay, protein expression analysis related to insulin signaling pathway (*e.g.*, protein expression and phosphorylation levels can be detected by protein immunoblotting (Western blot) (*81*) and also by detecting the expression level of insulin genes by using real-time quantitative polymerase chain reaction (qPCR), *etc.* (*82*).

Cross-species validation: efficacy confirmation in mammals, including glucose tolerance test, pharmacokinetic parameters ($t_{1/2}$, CL, V_{ss}) (*83*), dose-response curves, protein expression analyses, toxicity assessment (LD_{50}), AUC analyses, and correlation analyses comparing sensitivities and differences between silkworms and mammals to the drug.

Conclusion

Despite the unique advantages of the silkworm model in diabetes research, its biological limitations need to be recognized objectively: the silkworm lacks the adaptive immune system (*e.g.*, T/B lymphocyte network) and the complex endocrine regulatory axes (*e.g.*, hypothalamus-pituitary-adrenal axis) that are unique to mammals, and its diabetes pathology is difficult to completely mimic the chronic complications in humans (*e.g.*, diabetic nephropathy with microvascular pathology). In addition, issues such as stability of model building and the damaging nature of the model animals caused by the chemicals when induced need to be further improved and adapted.

In the future, we can strive to further optimize the diabetes model of the silkworm, so as to enhance reliability and applicability of the model. For example,

gene editing technology can be used in 2004, a genome-wide test led by Southwest University of China revealed the functional annotations of about 18,510 genes in the silkworm (*84*), a landmark study that not only provided key data for invertebrate developmental biology, but also made the silkworm an ideal model organism for gene editing. Based on this technology platform, researchers have been able to accurately mimic the pathological process of diabetes by targeting the editing of genes related to pancreatic β-cell function (*e.g.*, *HNF4A, HNF1A, PTPN22R620W, INS*, *etc.*) or key nodes of the insulin signalling pathway (*e.g.*, PI3K-Akt, cAMP).

It is worth noting that the insulin signaling pathway is highly conserved between silkworms and humans, which makes the results of related studies in model organisms widely applicable and of important reference value. In terms of experimental strategy, the researchers constructed a dual-track technology system. On the one hand, CRISPR-Cas9-mediated gene editing technology was used to precisely target the key nodes in the insulin signaling pathway and edit the related genes; and on the other hand, the key links in the insulin signaling pathway were focused on, and the regulatory mechanism was explored in depth. This combination of technologies can flexibly realize the precise regulation and in-depth analysis of the insulin signaling pathway (*85,86*).

Although gene editing technology can accurately reproduce single-gene diabetes subtypes such as neonatal diabetes (*87*), its application still faces multiple challenges: firstly, gene editing technology is difficult to operate, requiring a professional technical team and sophisticated experimental equipment to ensure the accuracy of the operation, secondly, gene editing experiments are extremely demanding on the environment and conditions, which need to be carried out in highly sterile and stable environments, and furthermore, the cost of gene editing is high, including the acquisition of equipment, reagents and consumables, as well as the cost of labor, and finally, if editing errors occur during the gene editing process, it may lead to unpredictable consequences and even irreversible damage to the genome of the experimental organisms (*88*).

However, gene editing technology still has a broad application prospect in the study of diabetes modeling in the silkworm. Through gene editing, specific genes can be precisely modified to accurately model the pathogenesis of human monogenic diabetes. This not only contributes to an in-depth understanding of the pathophysiological process of diabetes, but also provides strong support for the development of new therapeutic approaches.

At the same time, the similarities and differences between the silkworm and human diabetes should be explored in depth, so as to explore new ideas and methods for the treatment of diabetes. In addition, the application of the silkworm to the field of diabetes personalized medicine should be strengthened to provide a strong basis for the realization of precise treatment.

In conclusion, the use of the silkworm as a model animal for diabetes research has great potential in the study of diabetes disease pathogenesis, screening of diabetes drugs, evaluation of pharmacological efficacy, and toxicological studies. And as a valuable research resource, natural medicines are rich in medicinal potential and provide a source of innovation for modern medicine. The silkworm may be expected to become a key model animal for the development of new natural drugs for the treatment of diabetes, bringing new breakthroughs in the treatment of diabetes.

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Reversal of global health inequality in pancreatitis burden from 1990 to 2021: A cross-national GBD 2021 analysis with forecast to 2030

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Abstract: Pancreatitis is a rapidly expanding global non-communicable disease, marked by substantial disparities across populations. However, comprehensive long-term assessments of global health inequalities remain scarce. This study examined inequality in the pancreatitis burden from 1990 to 2021, identified principal determinants, and forecasted future trends across countries with varying Socio-demographic Index (SDI) levels. Using data from the Global Burden of Disease 2021, we assessed inequalities in the prevalence, incidence, and disability-adjusted life years of pancreatitis *via* the Slope Index of Inequality (SII) and Concentration Index (CI). Decomposition analysis was used to identify drivers of change, and a Bayesian age-period-cohort model projected trends to 2030. Between 1990 and 2019, the SII decreased from 13.83 to 8.61, signaling a reduction in absolute health inequality. Nevertheless, beginning in 2020, the SII turned negative, reaching –10.79 in 2021, indicating a structural reversal in disease burden distribution from high- to low-SDI countries. Concurrently, the CI declined from –0.04 to –0.10, suggesting worsening relative inequality. Decomposition revealed population growth and aging as primary drivers of the rising burden, while epidemiological improvements contributed minimally, particularly in low-SDI regions. Projections suggest that while global age-standardized rates may continue to decrease through 2030, the proportional burden in low-SDI countries is expected to rise steadily. The global socioeconomic distribution of pancreatitis burden is experiencing a profound shift, with inequalities increasingly concentrated in low-SDI areas. Driven by demographic trends, this shift underscores the necessity for targeted global strategies to mitigate disparities and bolster health system resilience.

***Keywords*:** global burden of disease, slope index of inequality, concentration index

Introduction

Pancreatitis is a sterile inflammatory disorder that now ranks among the most pressing global public-health challenges (*1*). In the Global Burden of Disease (GBD) framework, it is recorded as a single cause, yet clinically it encompasses two distinct syndromes: acute pancreatitis, a sudden inflammatory attack with high early mortality, and chronic pancreatitis, a progressive fibroinflammatory disease that causes long-term disability (*2-4*). Together, these conditions generated an estimated 2.7 million incident cases, 5.9 million prevalent cases, and 122,000 deaths worldwide in 2021 (*5*). Increasing evidence shows that this burden is distributed unevenly across geographic regions and socioeconomic strata, placing equity — not simple disease control — at the center of contemporary pancreatitis epidemiology and motivating the focused analysis of health inequalities.

Investigations into health inequalities are vital for both clinical medicine and public health (*6*). Such analyses underscore disparities in disease burden among socioeconomic groups, facilitating the identification of vulnerable populations and guiding targeted interventions and resource distribution (*7,8*). The GBD database delivers critical datasets for evaluating disease burden (*9,10*). Previous research has predominantly examined the pancreatitis burden at global, regional, and national scales, typically relying on cross-sectional data on

incidence, mortality, and disability-adjusted life years (DALYs), with limited methodological diversity (*5,11*). Although these studies offer valuable insights, they frequently lack a dedicated analysis of health inequalities and seldom investigate their temporal trends.

This study utilized data from GBD 2021 to systematically evaluate shifts in the pancreatitis burden across countries and regions from 1990 to 2021, with particular emphasis on the temporal dynamics of health inequalities and their socioeconomic and public health determinants. Additionally, the study projected the global and regional burden of pancreatitis through 2030, intending to support evidence-based public health policies and resource distribution strategies.

Materials and Methods

Data sources

Data for this study were retrieved from the Global Health Data Exchange *via* its official website (*https://vizhub.healthdata.org/gbd-results/*). All data used in this study were directly extracted from the latest GBD 2021 database. Pancreatitis was classified following the International Classification of Diseases, Tenth Revision, using codes K85.0–K85.9, K86.0, and K86.1. To comprehensively evaluate the disease burden, key indicators, namely prevalence, incidence, and DALYs, were included. All indicators underwent age-standardization to facilitate comparability across populations. Data were stratified further by geographic region, Socio-demographic Index (SDI), age group, and sex to provide a comprehensive evaluation of the pancreatitis burden across diverse population subgroups. Because the GBD database comprises publicly available, anonymized data, no ethical approval was required. All methods conformed to the GBD 2021 modeling protocol and adhered to the Guidelines for Accurate and Transparent Health Estimates Reporting (*12*), thereby ensuring methodological rigor and transparency.

Statistical analysis

The estimated annual percentage change (EAPC) was applied to evaluate temporal trends in age-standardized rates (ASRs) (*13*). EAPCs and their 95% confidence intervals (CIs) were calculated using linear regression models. A positive EAPC whose lower CI bound exceeds zero signifies an upward trend, whereas a negative EAPC whose upper CI bound is below zero indicates a downward trend. All disease burden metrics were presented as point estimates with corresponding 95% uncertainty intervals (UIs), derived from 1,000 random draws from the posterior distribution. The 2.5th and 97.5th percentiles served as the lower and upper bounds, respectively, to convey the credibility of the estimates.

Temporal trends in pancreatitis burden indicators and ASRs from 1990 to 2021 were analyzed both globally and across SDI regions. Joinpoint regression analysis (version 5.3.0) was used to identify statistically significant shifts in trend directions (*14*), and annual percentage changes were calculated for each segment. Furthermore, age- and sex-specific differences in the disease burden were evaluated. To explore regional disparities, a Bayesian meta-regression-based linear mixed-effects model was applied to assess associations between burden indicators and national SDI levels (*10*).

To elucidate the factors driving changes in disease burden, the Das Gupta decomposition method was utilized to separate total variations into three components: population growth, aging, and epidemiological shifts (*15,16*). This approach quantifies each factor's relative contribution.

Crude DALY rates served as the metric for evaluating health inequalities associated with pancreatitis. Disparities among countries and regions were measured *via* the slope index of inequality (SII) and the concentration index (CI) (*17,18*). The SII was determined by regressing DALY rates on country-level SDI, thereby quantifying absolute inequality across nations. The CI was derived from fitting a Lorenz curve to the cumulative share of DALYs against the cumulative population share. CI values range from –1 to 1, with negative values representing higher burden in low-SDI regions and positive values in high-SDI regions. Finally, a Bayesian age-period-cohort (BAPC) model (*19*) was employed to forecast future trends in the global and regional pancreatitis burden through 2030, drawing on historical data from 1990 to 2021. All analyses were performed in R software (version 4.4.1), considering p-values < 0.05 to be statistically significant.

Results

Temporal trends in the global burden of pancreatitis

From 1990 to 2021, the absolute global burden of pancreatitis exhibited a consistent rise. The prevalent cases increased from 4.15 million to 5.90 million, incident cases from 1.73 million to 2.75 million, and DALYs from 2.58 million to 4.10 million, which corresponded to rises of 42.17%, 58.96%, and 58.91%, respectively. Conversely, the ASRs declined: the age-standardized prevalence rate (ASPR) decreased from 93.74 to 68.99 per 100,000 (EAPC = –1.09); the age-standardized incidence rate (ASIR) dropped from 37.62 to 32.81 per 100,000 (EAPC = –0.49); and the age-standardized disability-adjusted life years rate (ASDR) fell from 57.39 to 48.43 per 100,000 (EAPC = –0.61) (Tables 1-3, Figures 1-2).

Age and sex distribution characteristics

In 2021, the numbers of prevalent cases, incident

cases, and total DALYs linked to pancreatitis rose with advancing age, peaking among middle-aged and older adults before declining (Figure 3A). Males consistently demonstrated higher prevalence, incidence, and DALY rates than females, especially in the 30–59 age group. This gender disparity attenuated among individuals aged 70 years and older (Figure 3B).

Regional variations in disease burden

In 2021, considerable regional variation in the pancreatitis burden was observed across GBD regions and countries (Tables 1-3, Figures 4-6). Eastern Europe, Central Asia, and South Asia experienced the highest burdens, with DALYs rising significantly since 1990. In Eastern Europe, DALYs increased from 371,000 to 675,000, and ASDR rose from 141.99 to 240.99 per 100,000 (EAPC = +1.41), positioning it as one of the few regions globally with an upward age-standardized trend. In contrast, High-income Asia Pacific, East Asia, and Western Europe showed declining trends in age-standardized metrics. For instance, in High-income Asia Pacific, ASDR decreased from 31.00 to 16.87 per 100,000 (EAPC = –2.19), marking one of the fastest declines globally. Similarly, ASDR in East Asia dropped from 29.96 to 18.53 per 100,000 (EAPC = –1.58), accompanied by simultaneous declines in prevalence and incidence.

Decomposition analysis of changes in disease burden

The changes in crude pancreatitis rates from 1990 to 2021 were decomposed into three contributing factors: population growth, aging, and epidemiological shifts. For prevalence, population growth contributed 139.03%, aging accounted for 51.08%, and epidemiological changes contributed –90.11%. For incidence, contributions were 160.46% from population growth, –20.14% from aging, and –40.32% from epidemiological shifts. For DALYs, the contributions were 104.90% from population growth, 31.70% from aging, and –36.60% from epidemiological shifts. The relative influence of these factors differed across SDI levels. In general, population growth was the primary driver in low- and middle-SDI countries, whereas aging played a dominant role in high-SDI countries. The direction and magnitude of epidemiological shifts varied across SDI groups (Figure 7).

Evolution of global health inequality and the reversal phenomenon

SII monitoring showed a reduction in absolute income-related health inequality across SDI levels from 1990 to 2019, with the SII for crude DALY rates falling from 13.83 to 8.61 (Figures 8, A and B). However, beginning in 2020, the SII became negative (–3.62) for the first time and decreased further to –10.79 in 2021. The CI for DALYs decreased from –0.04 in 1990 to –0.10 in 2021, with the curve further diverging from the equality line (Figure 8C).

Forecast of future burden trends

Projections suggest that global ASPR, ASIR, and ASDR will continue to decrease through 2030 (Figure 9). In high-SDI countries, the burden is anticipated to plateau or decline, while low-SDI countries will bear an increasing proportion of the global pancreatitis burden (Supplemental Figures S1-2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=103*).

Discussion

This study employs data from GBD 2021 to provide a comprehensive assessment of global trends in pancreatitis burden and related health inequalities from 1990 to 2021. Despite the decline in ASRs, the absolute burden has risen, reinforcing the growing impact of pancreatitis on global public health. The burden remained unequally distributed by sex, age, and region, reflecting enduring structural disparities. Further analysis revealed that population growth and aging were the main drivers of the rising burden, while improvements in epidemiological factors played a mitigating role. Notably, health inequalities exhibited minimal improvement over time. Although absolute inequality decreased in earlier years, relative inequality progressively worsened. Since 2020, a noticeable reversal has occurred, with the burden shifting from high- to low-SDI countries, revealing socioeconomic reconcentration rather than an actual reduction in inequality. This shift highlights the entrenched and worsening nature of global health disparities. Projections suggest that although global ASRs for pancreatitis may decline by 2030, low-SDI countries are projected to experience an increasing burden, which may exacerbate global health inequalities.

Previous GBD 2019 and 2021 studies documented persistent declines in age-standardized prevalence, incidence, and mortality of pancreatitis, while global numbers of prevalent cases, incident cases, and DALYs continued to increase, demonstrating the coexistence of declining rates and a rising absolute burden (*5,11*). Building on these findings, this study applied decomposition analysis to prevalence, incidence, and DALYs, quantifying the relative contributions of population growth, aging, and epidemiological shifts. Results indicated that population growth was the dominant contributor across all indicators, particularly in low- and middle-SDI countries. The effect of aging was complex: it increased prevalence and DALYs due to cumulative chronic health loss in older populations, but reduced incidence, possibly due to under-diagnosis

Table 1. Prevalence and ASPR of pancreatitis in 1990 and 2021 and the temporal trends from 1990 to 2021

Location	1990		2021		1990–2021
	Case No. (95% UI)	ASPR per 100,000 (95% UI)	Case No. (95% UI)	ASPR per 100,000 (95% UI)	EAPC in ASPR (95% CI)
Global	4148305 (3042449, 5639570)	93.74 (68.31, 127.08)	5900340 (4376043, 7838798)	68.99 (51.26, 91.29)	-1.09 (-1.15, -1.03)
High-income Asia Pacific	216094 (148598, 313085)	107.98 (74.37, 154.71)	240270 (177415, 313839)	84.25 (64.14, 108.02)	-0.49 (-0.68, -0.31)
Central Asia	105928 (78148, 144548)	193.68 (141.31, 266.08)	186359 (134695, 258449)	198.86 (144.92, 273.25)	0.08 (0.04, 0.11)
Southeast Asia	123476 (84869, 170333)	37 (25.01, 51.82)	287206 (192642, 402947)	39.91 (26.9, 55.44)	0.25 (0.23, 0.27)
East Asia	361290 (245281, 520967)	34.98 (23.56, 50.5)	505641 (356676, 718544)	24.18 (17.35, 33.34)	-1.32 (-1.79, -0.85)
Central Europe	192379 (136913, 270027)	133.34 (96.33, 188.43)	184625 (145053, 230736)	104.53 (83.68, 129.15)	-1.14 (-1.39, -0.89)
Eastern Europe	1888989 (1348790, 2635807)	707.46 (513.99,976.18)	2147275 (1499103, 2992643)	723.28 (525.24, 1003.43)	0.05 (-0.22, 0.33)
North Africa and Middle East	111863 (78197, 154573)	45.32 (31.5,62.3)	263146 (182720, 364679)	44.81 (31, 61.22)	0 (-0.01, 0)
Australasia	12120 (8577, 16490)	53.75 (37.93, 72.68)	21627 (15189, 29521)	49.71 (35.16, 67.52)	-0.15 (-0.2, -0.1)
Western Europe	221151 (164445, 287229)	45.17 (33.89, 58.53)	331644 (259348, 421579)	49.29 (38.81, 61.86)	-0.14 (-0.29, 0.01)
Andean Latin America	8412 (6246, 11053)	33.19 (24.1, 44.41)	19602 (14213, 26689)	31.21 (22.53, 42.63)	-0.1 (-0.15, -0.05)
Caribbean	14957 (10260, 20509)	51.99 (35.62, 71.95)	27788 (19017, 38350)	53.07 (36.3, 73.15)	0.07 (0.06, 0.09)
High-income North America	346881 (247220, 464413)	108.24 (77.51, 145.27)	445425 (326587, 576416)	81.39 (61.13, 103.26)	-1.16 (-1.36, -0.96)
Western Sub-Saharan Africa	41826 (28558, 56669)	32.69 (22.23, 45.18)	109504 (75059, 149631)	33.71 (22.97, 46.39)	0.08 (0.07, 0.09)
South Asia	298616 (204350, 409182)	36.34 (24.47, 49.96)	660317 (448007, 909405)	37.77 (25.59, 51.79)	0.13 (0.12, 0.15)
Oceania	1251 (869, 1760)	30.35 (20.77, 43.6)	3047 (2064, 4420)	30.49 (20.77, 44.6)	0.04 (0.02, 0.07)
Central Sub-Saharan Africa	9000 (5882, 12530)	25.45 (16.68, 35.45)	23789 (15500, 32985)	25.74 (17.04, 35.48)	0.12 (0.09, 0.15)
Central Latin America	46998 (34874, 62015)	42.44 (30.96, 57.41)	102106 (75647, 134285)	39.39 (29.26, 51.92)	-0.19 (-0.27, -0.11)
Southern Latin America	28350 (21090, 38077)	59.88 (44.51, 80.81)	41516 (33443, 50036)	52.44 (42.36, 63.15)	-0.46 (-0.52, -0.4)
Tropical Latin America	66583 (51914, 82135)	61.25 (47.91, 75.93)	181046 (141234, 225320)	69.9 (54.71, 86.42)	0.45 (0.33, 0.56)
Eastern Sub-Saharan Africa	36153 (24284, 49099)	30.35 (20.34, 41.73)	88832 (60066, 122019)	31.02 (21.02, 42.9)	0.06 (0.04, 0.08)
Southern Sub-Saharan Africa	15990 (11037, 21844)	42.03 (28.78, 57.73)	29575 (20182, 41037)	40.75 (27.66, 55.94)	-0.2 (-0.24, -0.15)

ASPR: age-standardized prevalence rate, CI: confidence interval, EAPC: estimated annual percentage changes, UI: uncertainty interval.

Table 2. Incidence and ASIR of pancreatitis in 1990 and 2021 and the temporal trends from 1990 to 2021

Location	1990		2021		1990–2021
	Case No. (95% UI)	ASPR per 100,000 (95% UI)	Case No. (95% UI)	ASPR per 100,000 (95% UI)	EAPC in ASPR (95% CI)
Global	1728141 (1495096, 1995752)	37.62 (32.57, 43.46)	2747368 (2413878, 3133076)	32.81 (28.85, 37.38)	-0.49 (-0.55, -0.43)
High-income Asia Pacific	65578 (55888, 76898)	33.76 (28.76, 39.23)	73137 (64060, 82719)	29.16 (25.57, 32.94)	-0.43 (-0.48, -0.38)
Central Asia	26598 (22702, 31290)	46.74 (40.24, 54.17)	45722 (39128, 53162)	47.94 (41.43, 55.37)	0.06 (0.03, 0.09)
Southeast Asia	89288 (74781, 105803)	24.59 (20.89, 28.84)	179146 (152380, 209528)	24.44 (20.95, 28.45)	-0.04 (-0.05, -0.02)
East Asia	377308 (311766, 447071)	35.65 (30.12, 41.71)	470652 (403601, 548056)	24.3 (20.98, 28.08)	-1.36 (-1.7, -1.02)
Central Europe	73033 (63194, 84733)	52.37 (45.48, 60.61)	70559 (64883, 76851)	43.31 (39.88, 46.92)	-0.81 (-0.9, -0.71)
Eastern Europe	237581 (195713, 287166)	92.77 (76.88, 111.19)	268392 (223074, 322226)	99.35 (82.69, 117.93)	0.19 (0.01, 0.37)
North Africa and Middle East	63035 (52688,74092)	27.08 (23.18,31.5)	146216 (125435,169956)	26.34 (22.92,30.07)	-0.03 (-0.05, -0.02)
Australasia	7820 (6696, 9079)	34.96 (30.14, 40.38)	13559 (11690, 15749)	32.78 (28.62, 37.63)	-0.21 (-0.26, -0.16)
Western Europe	132208 (118034, 148292)	27.68 (24.65, 31.11)	198887 (182278, 215736)	31.08 (28.49, 34.14)	0.08 (-0.04, 0.19)
Andean Latin America	11876 (10281, 13776)	42.12 (36.75, 48.28)	25050 (22198, 28320)	38.79 (34.56, 43.67)	-0.39 (-0.45, -0.33)
Caribbean	8784 (7430, 10257)	28.88 (24.69, 33.7)	14591 (12548, 17049)	28.47 (24.46, 33.25)	-0.03 (-0.05, -0.01)
High-income North America	203919 (179759, 231498)	63.63 (55.87, 72.08)	264132 (244466, 283649)	51.99 (48.36, 55.53)	-0.7 (-0.83, -0.56)
Western Sub-Saharan Africa	29515 (24427, 34805)	22.59 (19.15, 26.39)	77625 (63947, 91923)	23.32 (19.81, 27.2)	0.09 (0.08, 0.1)
South Asia	277106 (229054, 331366)	31.64 (26.29, 37.45)	634729 (528404, 757200)	34.97 (29.04, 41.28)	0.42 (0.38, 0.46)
Oceania	954 (789, 1129)	21.6 (18.42,2 5.17)	2225 (1853, 2647)	20.95 (17.82, 24.46)	-0.11 (-0.12, -0.11)
Central Sub-Saharan Africa	6718 (5511, 8053)	18.84 (15.81, 22)	17422 (14205, 20645)	18.69 (15.8, 21.86)	-0.02 (-0.04, -0.01)
Central Latin America	47214 (40375, 54700)	37.85 (32.67, 43.62)	102357 (89704, 117033)	39.22 (34.3, 44.74)	0.05 (0.02, 0.09)
Southern Latin America	14703 (12881, 16806)	30.92 (27.19, 35.23)	27581 (24438, 31491)	35.59 (31.52, 40.52)	0.06 (-0.08, 0.19)
Tropical Latin America	22676 (20193, 25697)	18.82 (16.81, 21.05)	42519 (37419, 48224)	16.63 (14.7, 18.83)	-0.27 (-0.36, -0.19)
Eastern Sub-Saharan Africa	23816 (19528, 28411)	19.63 (16.62, 22.97)	57435 (47012, 68537)	19.73 (16.73, 23.14)	0 (-0.02, 0.02)
Southern Sub-Saharan Africa	8412 (6970, 9971)	21.74 (18.56, 25.52)	15432 (12869, 18279)	21.22 (18.09, 24.89)	-0.12 (-0.17, -0.08)

ASPR: age-standardized prevalence rate, CI: confidence interval, EAPC: estimated annual percentage changes, UI: uncertainty interval.

Table 3. DALYs and ASDR of pancreatitis in 1990 and 2019 and the temporal trends from 1990 to 2021

Location	1990		2021		1990–2021
	DALYs No. (95% UI)	ASPR per 100,000 (95% UI)	DALYs No. (95% UI)	ASPR per 100,000 (95% UI)	EAPC in ASPR (95% CI)
Global	2583402 (2265738, 2985509)	57.39 (50.34, 66.07)	4101154 (3647631, 4684283)	48.43 (43.07, 55.35)	-0.61 (-0.73, -0.49)
High-income Asia Pacific	61138 (51955, 72205)	31 (26.33, 36.66)	56035 (46991, 67531)	16.87 (13.99, 20.8)	-2.19 (-2.33, -2.05)
Central Asia	45577 (39446, 51891)	84.58 (72.98, 96.02)	72819 (61133, 87133)	77.14 (64.95, 91.96)	-0.77 (-1.04, -0.5)
Southeast Asia	189737 (142679, 256438)	57.92 (43.51, 77.54)	332855 (262388, 492344)	46.9 (37.21, 69.3)	-0.79 (-0.84, -0.73)
East Asia	307618 (251065, 375431)	29.96 (24.31, 36.61)	364563 (288981, 468429)	18.53 (14.77, 23.88)	-1.58 (-1.64, -1.53)
Central Europe	157124 (148011, 167599)	110.93 (104.63, 118.22)	156970 (143758, 169208)	91.75 (84.24, 99.2)	-0.93 (-1.14, -0.72)
Eastern Europe	370859 (314475, 452709)	141.99 (120.6, 173.32)	675000 (591617, 781577)	240.99 (211.6, 278.4)	1.41 (0.87, 1.95)
North Africa and Middle East	42821 (32610, 55536)	22.04 (16.3, 29.27)	94244 (76404, 115152)	19.47 (15.96, 23.84)	-0.28 (-0.31, -0.25)
Australasia	6215 (5690, 6814)	27.28 (24.98, 30)	9425 (8240, 10729)	20.07 (17.49, 22.94)	-0.86 (-1.09, -0.64)
Western Europe	215416 (204742, 226425)	42.56 (40.5, 44.78)	223172 (203349, 239445)	29.35 (27.27, 31.8)	-1.23 (-1.31, -1.16)
Andean Latin America	31019 (25114,38243)	110.59 (88.97,135.81)	45852 (36993,56198)	72.01 (58.39,88.31)	-1.5 (-1.61,-1.39)
Caribbean	13699 (12061, 15362)	46.6 (41.15, 52.26)	21590 (18438, 25131)	41.55 (35.44, 48.38)	-0.27 (-0.36, -0.17)
High-income North America	114419 (102882, 130220)	35.2 (31.63, 40.18)	169758 (154651, 189505)	32.64 (29.9, 36.14)	-0.36 (-0.57, -0.15)
Western Sub-Saharan Africa	120091 (88444, 177064)	105.45 (78.25, 153.13)	309900 (229727, 399293)	106.59 (79.03, 135.71)	0.05 (0, 0.1)
South Asia	621817 (470132, 853167)	77.9 (58.09, 105.99)	991510 (780478, 1238906)	57.3 (45.14, 71.84)	-0.89 (-0.97, -0.81)
Oceania	1504 (747, 2371)	31.7 (15.77, 49.26)	2729 (1571, 4237)	24.16 (13.85, 37.52)	-1.02 (-1.1, -0.94)
Central Sub-Saharan Africa	11986 (7752, 19871)	36.57 (23.56, 59.8)	31686 (20957, 51190)	35.98 (24.09, 57.3)	0.05 (-0.05, 0.15)
Central Latin America	81333 (78107, 84575)	69.09 (66.37, 71.83)	173650 (155450, 192013)	66.28 (59.33, 73.21)	-0.15 (-0.32, 0.01)
Southern Latin America	41196 (38641, 44061)	87.43 (81.94, 93.41)	44257 (41033, 47795)	54.4 (50.55,58.84)	-1.22 (-1.42, -1.02)
Tropical Latin America	97559 (93262, 102039)	81.32 (77.77,85.06)	199347 (187796, 212703)	76.98 (72.49, 82.14)	0.06 (-0.13, 0.24)
Eastern Sub-Saharan Africa	39130 (25451, 58303)	37.45 (23.93,56.74)	99334 (61289, 143914)	37.88 (23.34, 55.32)	0.05 (-0.01, 0.1)
Southern Sub-Saharan Africa	13147 (9380, 17495)	35.73 (25.15, 48.28)	26458 (20649, 32801)	36.35 (28.1, 44.2)	0.19 (-0.03, 0.41)

ASDR: age-standardized DALY rate, CI: confidence interval, DALYs: disability-adjusted life years, EAPC: estimated annual percentage changes, UI: uncertainty interval.

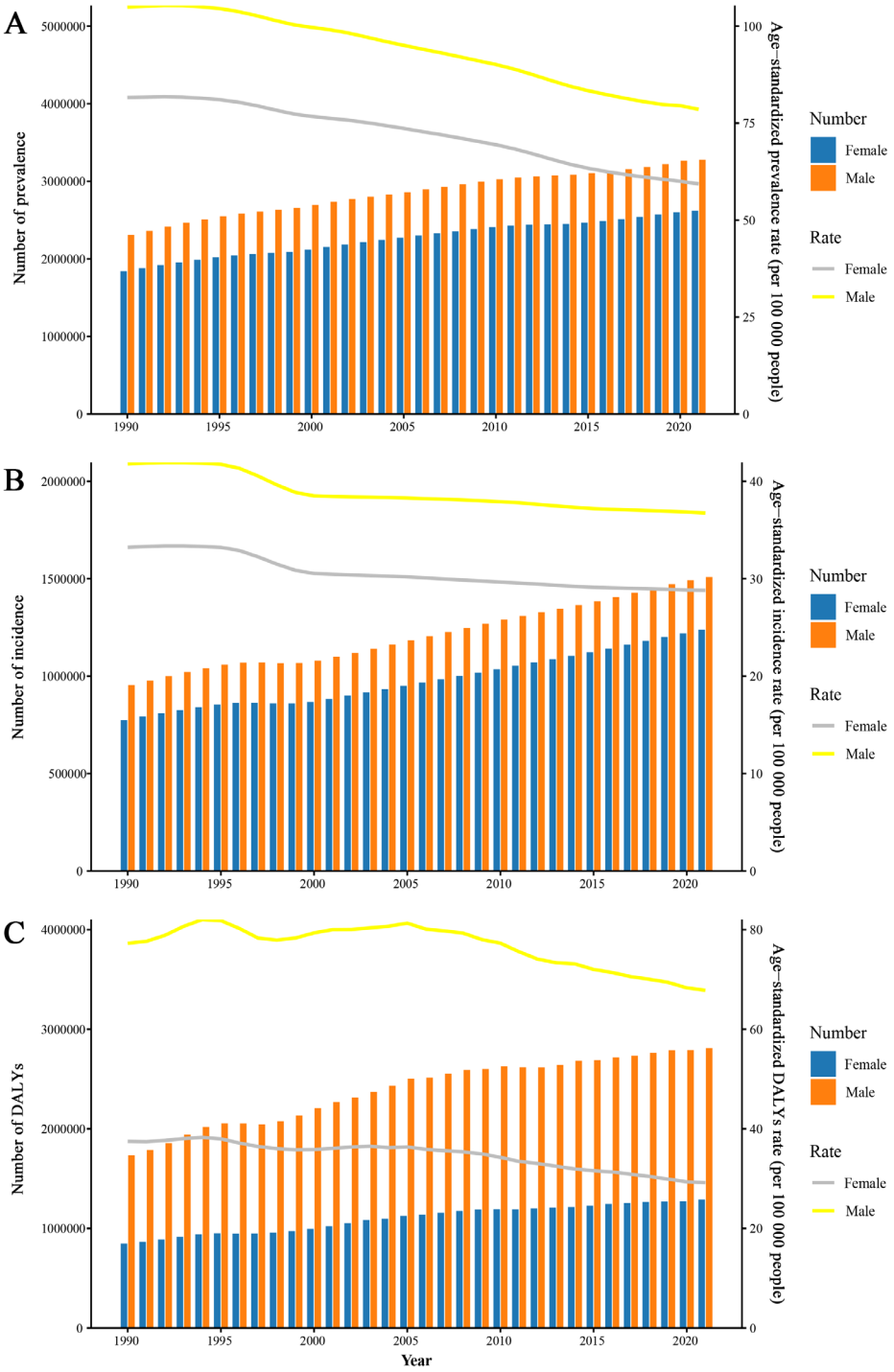

Figure 1. Global trends in pancreatitis prevalence, incidence, and DALYs, 1990–2021, shown as absolute numbers and age-standardized rates. DALYs: disability-adjusted life years.

of acute episodes in older adults, caused by delays or atypical symptoms. Epidemiological shifts generally had a beneficial effect, especially in high- and upper-middle-SDI countries, while only marginal improvements were observed in low-SDI regions, emphasizing inequities in prevention and control capabilities.

The study further revealed significant disparities across demographic and geographic groups, reflecting entrenched structural inequities. Males consistently demonstrated higher prevalence, incidence, and DALY rates than females, with the largest differences observed in individuals aged 30–59 years. The burden also increased with age, with middle-aged and older adults shouldering the largest proportion of health losses. This dual sensitivity to sex and age may be attributed to gender-specific risk factors (*e.g.*, alcohol use, smoking, obesity) (*20*), occupational exposures (*21*), and heightened physiological vulnerability in older adults (*22*). Geographically, DALYs continued to increase in low-SDI regions, including Eastern Europe, Central Asia,

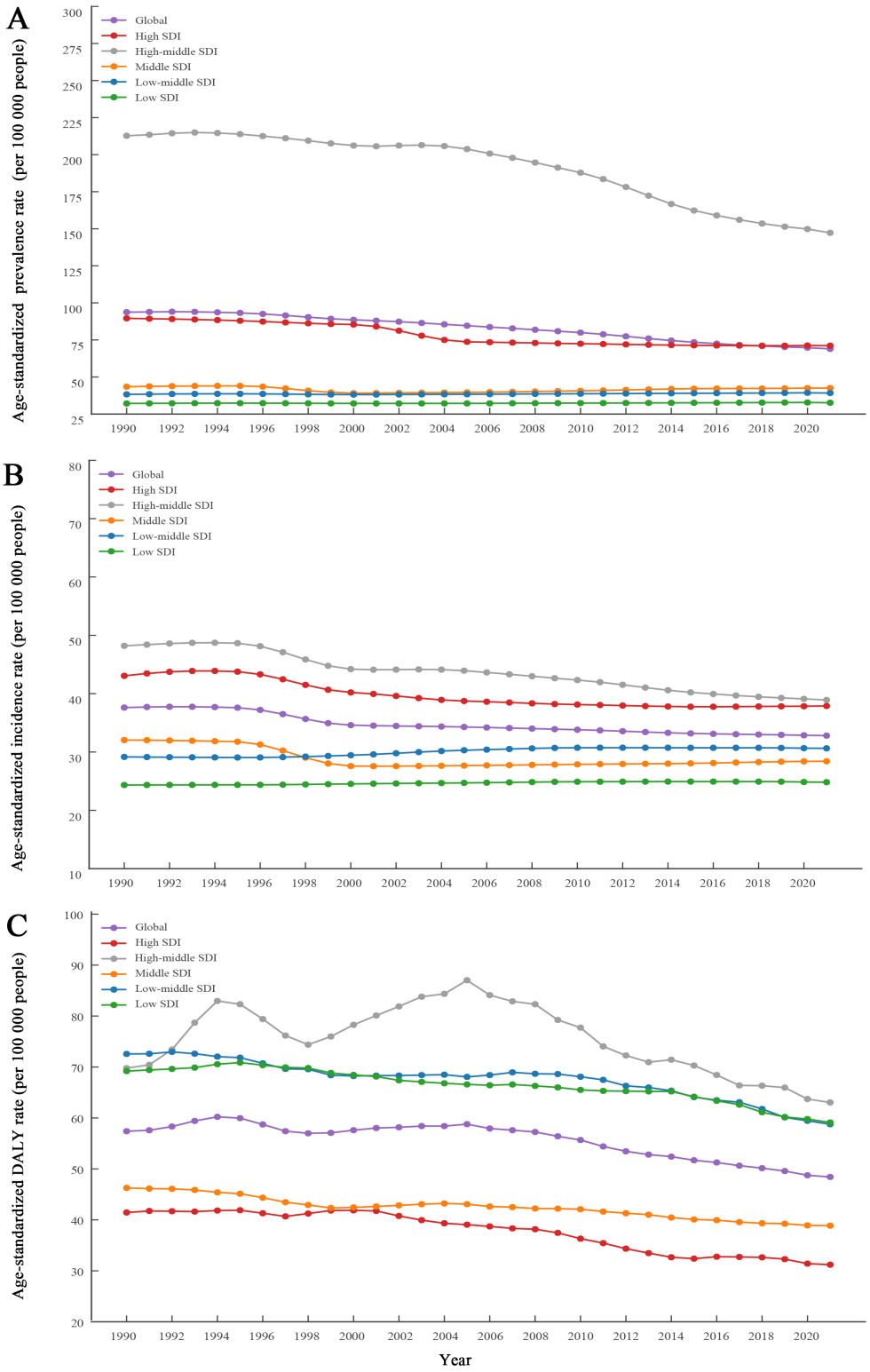

Figure 2. Trends in age-standardized prevalence, incidence, and DALY rates of pancreatitis globally and by SDI region, 1990–2021. DALYs: disability-adjusted life years; SDI: Socio-demographic Index.

and South Asia. In opposition, high-SDI regions, such as High-income Asia Pacific, East Asia, and Western Europe, consistently demonstrated declines in ASRs. These findings align with previous GBD reports (*5*). The persistence of intersecting inequalities illustrates the importance of identifying high-risk populations and strategically allocating resources to ensure equitable and effective prevention.

While stratified analyses by region and SDI level revealed distinct geographic and developmental patterns, descriptive comparisons alone fail to fully capture the complexity of global health inequality. To evaluate the

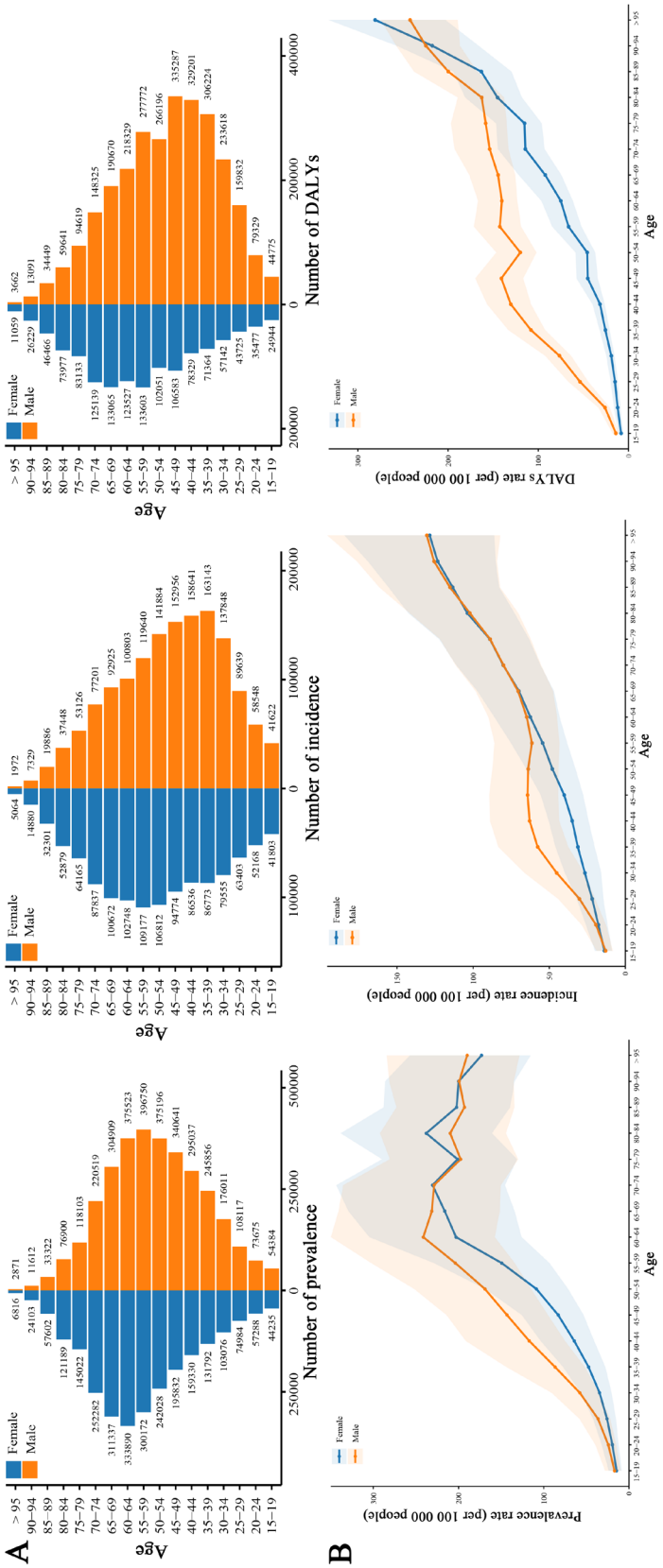

Figure 3. Age and sex distribution characteristics of pancreatitis burden in 2021. DALYs: disability-adjusted life years.

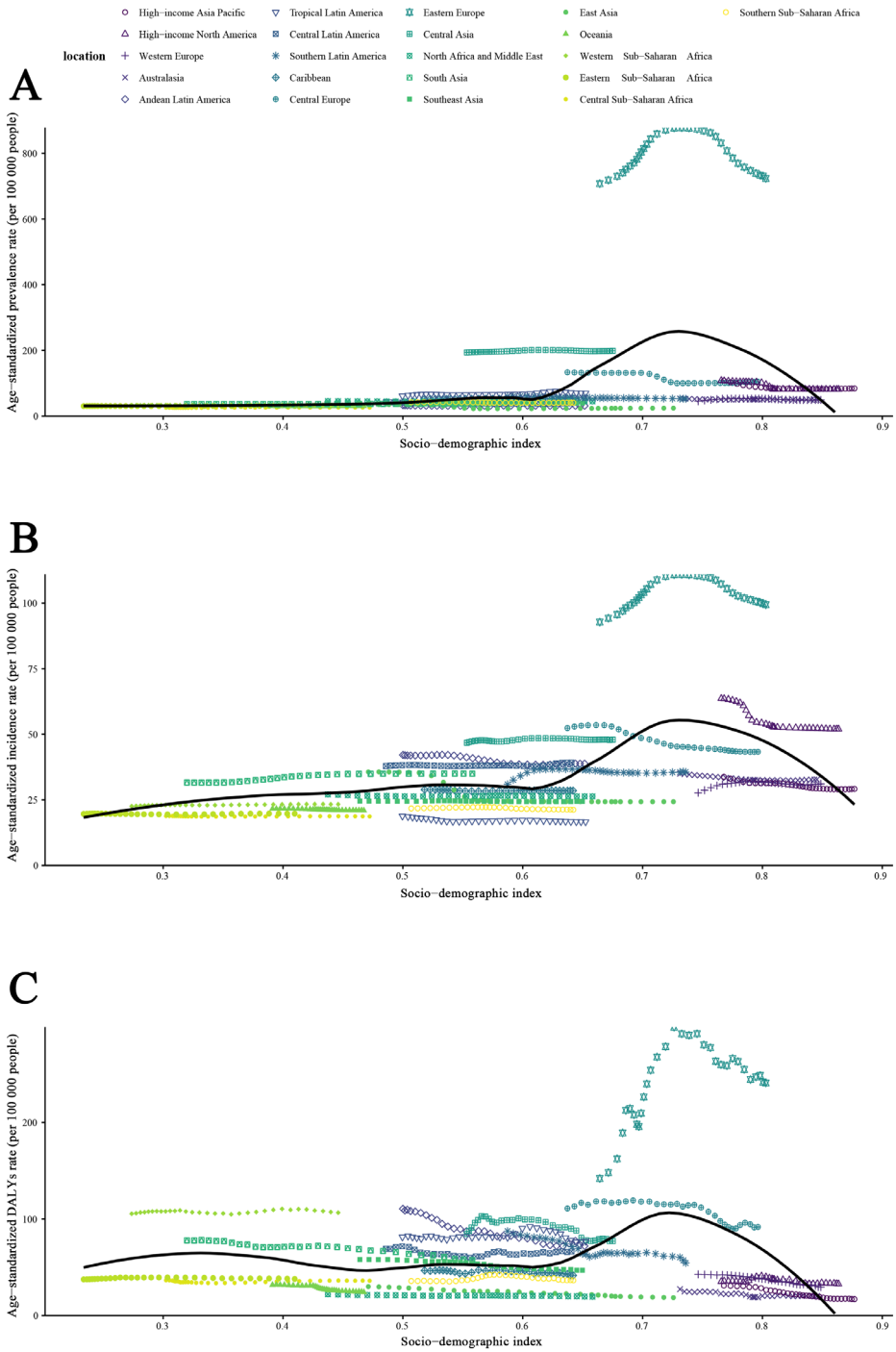

Figure 4. Changes in age-standardized prevalence, incidence, and DALY rates of pancreatitis across SDI regions. DALYs: disability-adjusted life years; SDI: Socio-demographic Index.

distribution of disease burden across socioeconomic contexts, this study employed the SII and CI (*17,18*). From 1990 to 2019, the SII decreased from 13.83 to 8.61, indicating reduced absolute disparities between high- and low-SDI countries, although the burden continued to be concentrated in more developed regions. However, in 2020, the SII shifted to a negative value of –3.62 and further dropped to –10.79 in 2021, signaling a structural shift of burden toward low-SDI countries. This shift coincided with the COVID-19 pandemic, which may have amplified low-SDI countries' vulnerability through overwhelmed health systems, disrupted chronic disease services, diverted public health resources, and reduced healthcare access, ultimately intensifying the concentration of non-communicable disease burdens such as pancreatitis (*23,24*). Despite the shift in burden epicenter, absolute health inequality has not meaningfully improved over time. Simultaneously, the CI dropped from –0.04 in 1990 to –0.10 in 2021, signifying a growing concentration of burden in low-SDI countries and worsening relative inequality driven by uneven structural resource allocation. Taken together, the

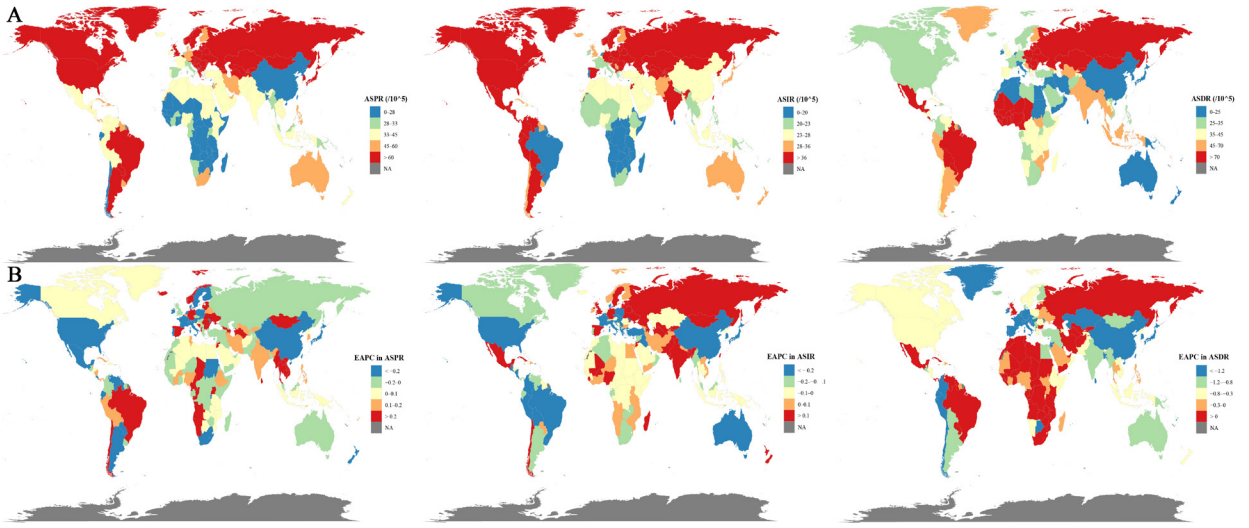

Figure 5. Global pancreatitis burden in 204 Countries and Territories: (A) age-standardized prevalence rate (ASPR), age-standardized incidence rate (ASIR), and age-standardized DALY rate (ASDR) in 2021; **(B)** EAPC of ASPR, ASIR, and ASDR from 1990 to 2021. DALYs: disability-adjusted life years; EAPC: estimated annual percentage changes.

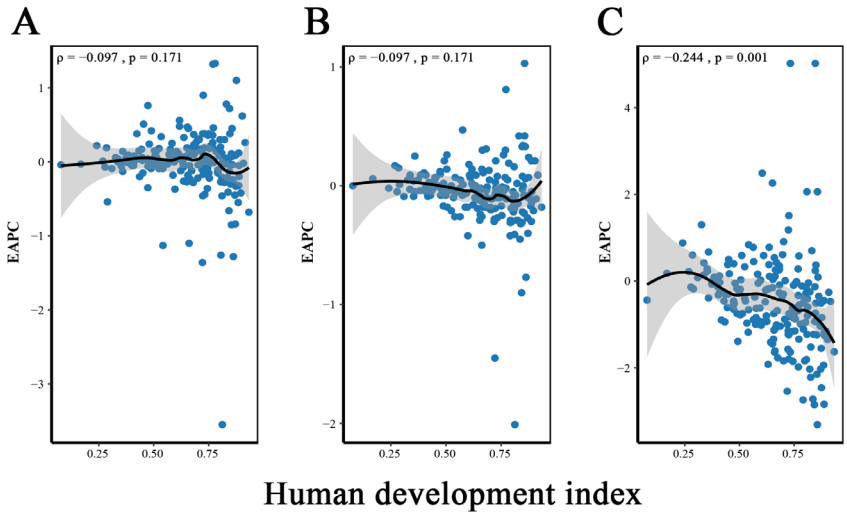

Figure 6. Global pancreatitis burden across 204 countries and territories by human development index in 2021.

SII and CI analyses reveal a shift in pancreatitis burden from development-level–driven inequality to structural reconcentration, a shift exacerbated by the COVID-19 pandemic.

Based on the identified reversal of global pancreatitis burden toward low-SDI countries and the emergence of entrenched structural inequalities, this study applied a BAPC model to project future trends. The projections suggest that while the global age-standardized burden of pancreatitis is expected to decrease by 2030, low-SDI countries will shoulder an increasing share, shifting the epicenter toward more socioeconomically disadvantaged regions and exacerbating existing inequalities. This trend suggests that inequality is not only a current concern but may persist in more systemic and less visible forms. These findings highlight the urgent need for global public health strategies to go beyond conventional disease control and address structural challenges, particularly by strengthening primary healthcare in low-SDI countries and improving chronic disease management and screening programs (*25*). Synchronously, global resource allocation should prioritize high-burden regions and vulnerable populations, enabling more targeted and equitable interventions (*26*). Strengthening international cooperation and institutional support, while integrating structural equity into global health agendas, is crucial to mitigate the shifting burden of chronic diseases and reduce global health disparities.

Several limitations should be acknowledged. First, the GBD database does not differentiate between acute and chronic pancreatitis, limiting the ability to assess their distinct etiologies and burden characteristics. Second, the reliance on national-level data restricts subnational analyses and reduces spatial resolution for

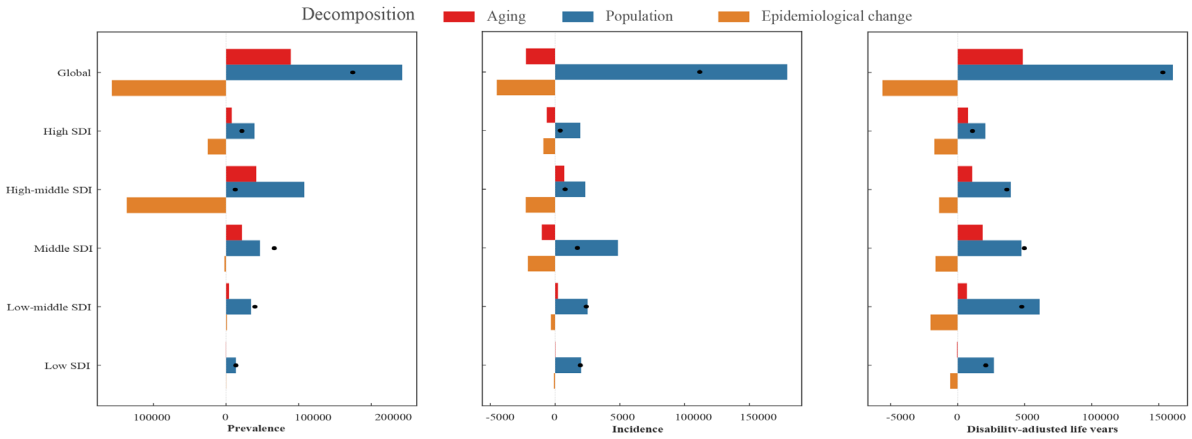

Figure 7. Decomposition analysis of pancreatitis indicators from 1990 to 2021. The black dot represents the overall change value of population growth, aging, and epidemiological change.

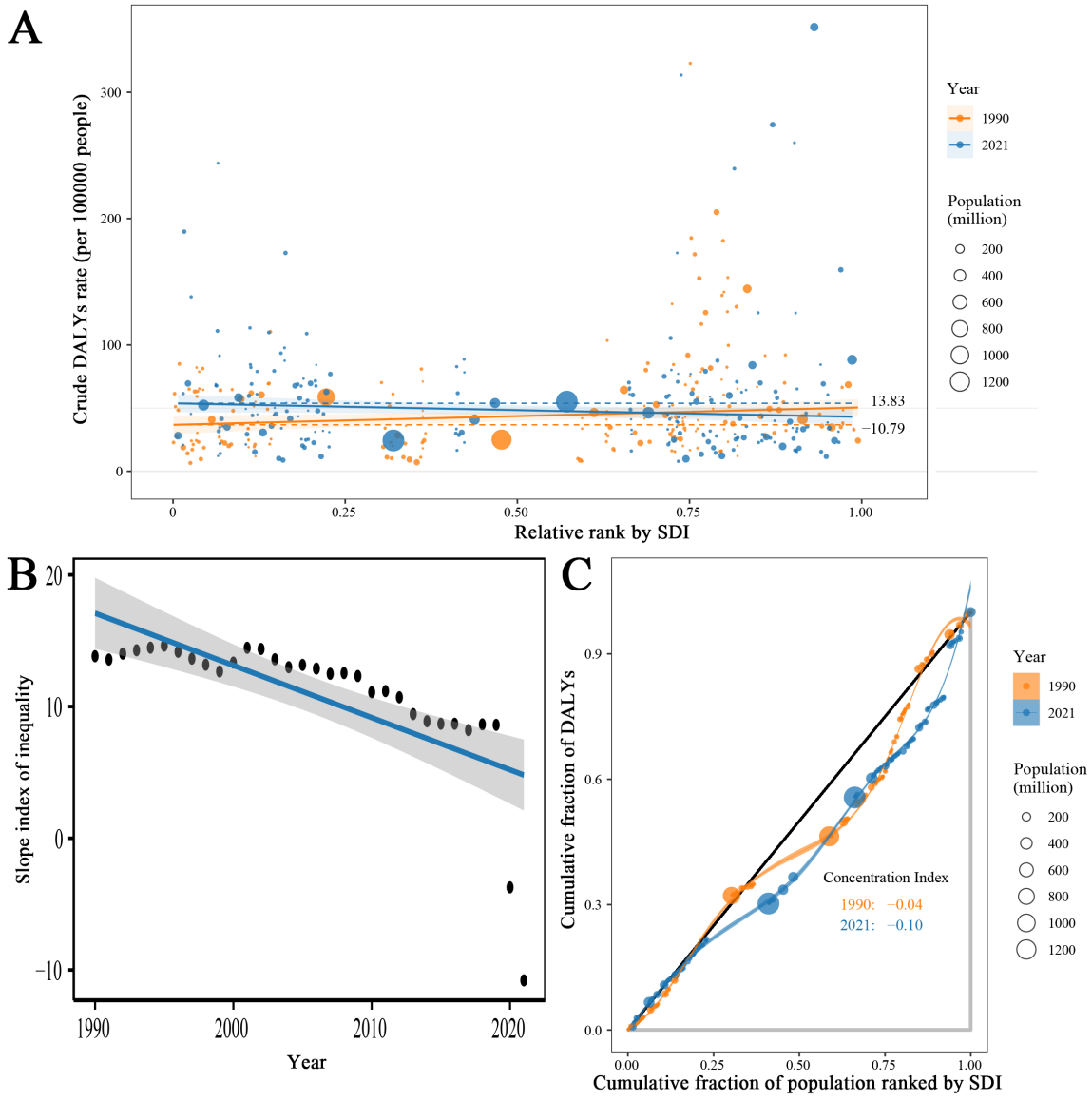

Figure 8. Trends in income-related health inequality in pancreatitis burden: slope index of inequality and concentration index analysis. DALYs: disability-adjusted life years.

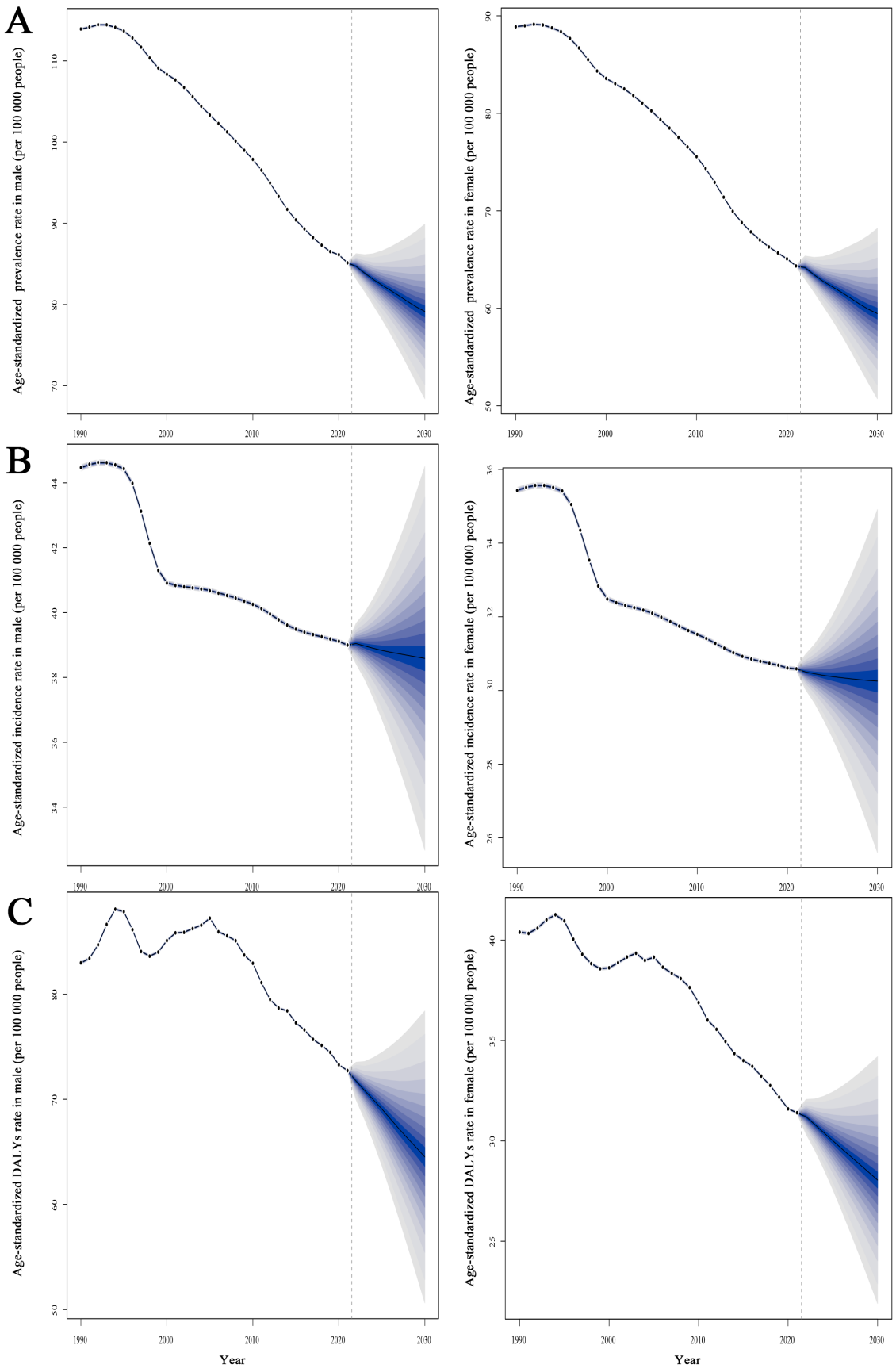

Figure 9. Projected number of new cases for all pancreatitis in 2030 according to the SDI. DALYs: disability-adjusted life years; SDI: Socio-demographic Index.

health policy planning. Third, the GBD database has limited primary data coverage in some economically disadvantaged regions. In such settings, model-based estimates may underestimate the true disease burden. Fourth, GBD data are mainly obtained from secondary sources and are not linked to clinical datasets, limiting insights into patient-level outcomes. Finally, although UIs are reported, regional variability may affect the stability and comparability of trend estimates.

In conclusion, this study provides a comprehensive assessment of the global evolution of the pancreatitis burden from 1990 to 2021, focusing on temporal trends, geographic disparities, and structural inequalities. Through decomposition analysis, we quantified the relative contributions of population growth, aging, and epidemiological changes, identifying the key drivers of the increasing global burden. Notably, the combined use of the SII and the CI showed a socioeconomic reversal in burden distribution, with the epicenter shifting from high- to low-SDI countries. This transition signals deepening structural entrenchment and worsening global health inequities. Forecasts based on the BAPC model indicate that this trend is likely to persist and may even intensify by 2030. These findings emphasize the urgent need to realign global health policies toward low-SDI countries by improving basic healthcare and implementing equity-focused interventions to alleviate the widening gaps in pancreatitis burden.

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Regional assessment is useful for identifying populations at high-risk of hepatitis B virus transmission: A nationwide analysis of population-based surveillance including the COVID-19 pandemic era

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Abstract: Prevention of new infections is important for the elimination of viral hepatitis B. Assessing the impact of the Coronavirus disease 2019 (COVID-19) pandemic on hepatitis B incidence is important for future infection control measures. A recent hospital-based questionnaire survey implied that a regional assessment in each country would be useful for establishing new preventive measures. This retrospective study examined publicly reported national data of patients diagnosed with acute hepatitis B in Japan between 2015 and 2022. The transition of total numbers, incidence, sex, and age distribution in each year were analyzed. Comparisons were made between populous and non-populous prefectures before and during the COVID-19 pandemic (2015–2019 *vs.* 2020–2022). A median of 210.0 patients with acute hepatitis B (interquartile range [IQR], 176.5–231.2 patients) were reported in each year. The number and incidence of acute hepatitis B cases significantly decreased during the pandemic, and the impact of COVID-19 was pronounced in males, especially in non-populous prefectures. Populous prefectures had significantly higher incidence in males compared with non-populous prefectures (3.55 [3.26–4.07] *vs*. 2.30 [1.78–2.64] cases per 1,000,000 people per year; $p = 0.004$), whereas those of females did not. Regarding patient age, the proportions of patients aged in their 20s, especially females, were higher in populous prefectures. These results may reflect differences in lifestyle, including sexual behaviors, in each population with the interaction of the COVID-19 pandemic. Identifying high-risk populations in each area and establishing a tailored strategy to eliminate viral hepatitis would be useful for countries worldwide.

***Keywords*:** acute hepatitis B, national data, regional assessment, COVID-19, sexually transmitted disease

Introduction

The elimination of viral hepatitis, including hepatitis B, is a major global health goal. In 2016, the World Health Organization (WHO) published a global sector strategy for viral hepatitis elimination, which aimed to reduce new hepatitis infections by 90% and deaths by 65% by 2030 worldwide, including in developing countries (*1*). Vaccination successfully prevents the vertical and horizontal transmission of hepatitis B virus (HBV) (*2*), and nucleoside/nucleotide analogs efficiently suppress HBV replication (*3,4*). Consequently, the number of active viral carriers has decreased in Japan (*5*). To achieve the remaining major focus in eliminating viral hepatitis, namely the prevention of new infections, means of identifying high-risk populations are urgently needed.

The Coronavirus disease 2019 (COVID-19) pandemic has had profound effects on global healthcare systems (*6*). Regarding infectious diseases, the number of reported cases of most infections decreased during the COVID-19 pandemic (*7*). We recently reported a questionnaire-based survey at nationwide tertiary care centers to reveal a real-world trend in the incidence of acute hepatitis B in Japan, presenting a significant decrease in the number of such cases in Japan (*8*); these results were consistent with those reported in foreign countries (*9-11*). However, the number of reported cases of sexually transmitted diseases (STDs) in Japan was relatively stable during

the COVID-19 pandemic and increased only in the later phase (*12-14*). Acute viral hepatitis has an aspect of a STD, and new measures are urgently needed to control this rebound.

The proceeding questionnaire-based survey also revealed that the sex ratio of acute viral hepatitis cases differed regionally; namely, populous prefectures, including Tokyo, the most populous capital city in Japan, had a higher proportion of male patients than non-populous prefectures (*8*). We assumed that detailed data, namely, age and incidence in each area, could provide further insights into the development of tailored strategies for the prevention of rebounding acute viral hepatitis.

In this study, we analyzed publicly reported national data concerning acute viral hepatitis B in the Infectious Diseases Weekly Report (IDWR) published by the National Institute of Infectious Diseases (NIID) in Japan (*15,16*).

Patients and Methods

Study design and data sources

This retrospective study examined publicly reported national data concerning acute hepatitis B infections in Japan between 2015 and 2022. In Japan, a doctor who diagnoses a patient with newly diagnosed acute viral hepatitis B is legally required to report and register details of the patient with the National Epidemiological Surveillance of Infectious Diseases (NESID) system, which is run jointly by the NIID, prefectural and municipal public health institutes and public health centers, and the Ministry of Health, Labour and Welfare. In the NESID system, acute hepatitis B is defined as the detection of IgM anti-HBc antibodies (excluding cases of acute exacerbation in obvious carriers). The number of cases classified according to sex or reported prefecture was obtained from the NIID website as IDWR (*15,16*). Population data were obtained from the Ministry of Health, Labour and Welfare website (*17*).

This study was conducted in accordance with the principles of the Declaration of Helsinki and complied with the ethical guidelines for medical and health research involving human subjects established by the Japanese Ministry of Education, Culture, Sports, Science, and Technology and the Ministry of Health, Labor, and Welfare. This study was approved by the Research Ethics Committee of the Faculty of Medicine, the University of Tokyo (approval number: 2024504NIe).

Regional assessments

Japan is divided into 47 prefectures that are grouped into eight regions based on geographical and historical factors. These regions are: Hokkaido, Tohoku (including Aomori, Iwate, Miyagi, Akita, Yamagata, and Fukushima); Kanto-Shinetsu (including Ibaraki, Tochigi, Gunma, Saitama, Chiba, Tokyo, Kanagawa, Niigata, Yamanashi, and Nagano); Tokai-Hokuriku (including Toyama, Ishikawa, Gifu, Shizuoka, Aichi, and Mie); Kinki (including Fukui, Shiga, Kyoto, Osaka, Hyogo, Nara, and Wakayama); Chugoku (Tottori, Shimane, Okayama, Hiroshima, and Yamaguchi); Shikoku (including Tokushima, Kagawa, Ehime, and Kochi); and Kyushu (including Fukuoka, Saga, Nagasaki, Kumamoto, Oita, Miyazaki, Kagoshima, and Okinawa).

We selected Tokyo (the most populous city and one of the centers of Kanto-Shinetsu region: 13,443,000 persons in 2022), Kanagawa (the second-most populous city and one of the centers of Kanto-Shinetsu region: 8,991,000 persons), Osaka (the third-most populous city and the center of the Kinki region: 8,524,000 persons), Aichi (the fourth populous city and the center of the Tokai region: 7,228,000 persons), and Fukuoka (the nineth-most populous city and the center of Kyushu region: 5,030,000 persons), as populous prefectures based on their population density and regional characteristics.

Statistical analysis

Data are presented as medians and interquartile ranges (IQRs) for quantitative variables, and numbers and percentages for qualitative variables. For comparisons between two categories, namely before and during the COVID-19 pandemic (2015–2019 *vs.* 2020–2022), and populous prefectures and non-populous prefectures, Welch's *t*-test was used to assess statistical significance. The proportion of 20s in each group is presented with 95% confidential intervals (CIs) calculated using the Wilson method, and the Chi-squared test was used to assess statistical significance. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using R software v.4.3 and later (R Foundation, Vienna, Austria, *http://www.r-project.org*).

Results

Trends in national incidence of acute hepatitis B infection

In total, a median of 210.0 patients with acute hepatitis B (interquartile range [IQR], 176.5–231.2 patients) were reported in each year, with the proportion of males remaining relatively constant throughout the period at a median of 81.7% (IQR, 78.5%–84.4%) (Figure 1A). During the COVID-19 pandemic, the number of patients significantly decreased during 2020–2022 compared to that during 2015–2019 (median [IQR] = 148.0 [142.0–167.0] patients *vs.* 228.0 [214.0–241.0] patients; $p = 0.02$).

The median incidences were 1.68 (IQR, 1.43–1.85), 2.79 (IQR, 2.29–3.08), and 0.62 (IQR, 0.50–0.73) cases per 1,000,000 people per year for total, males, and females, respectively (Figure 1B). During the COVID-19

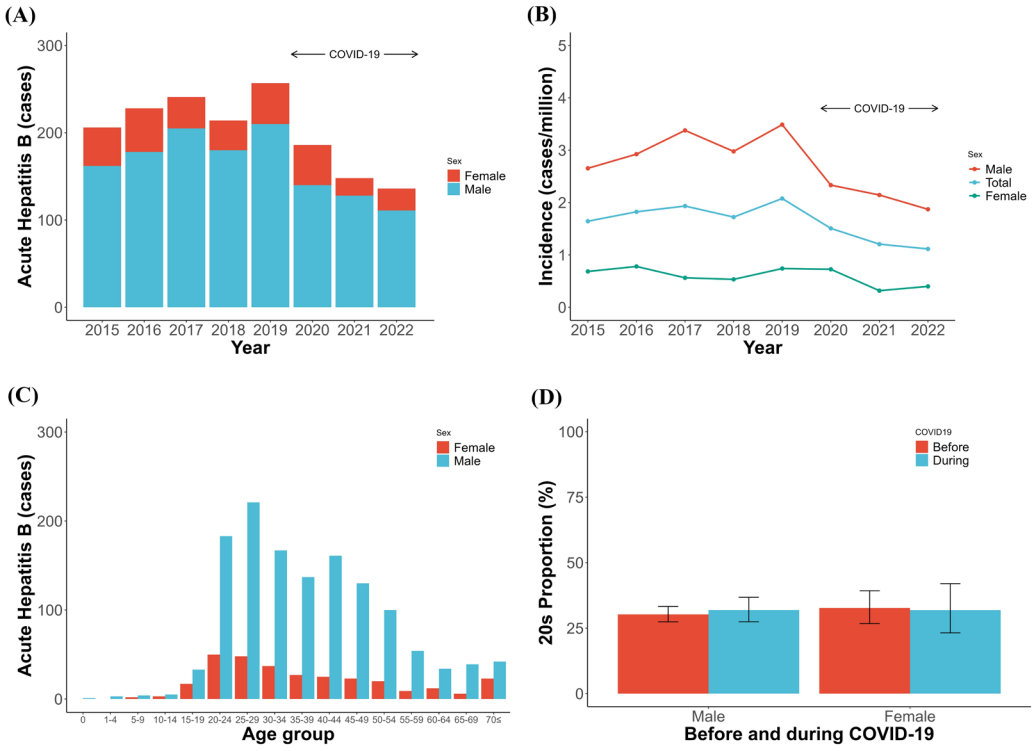

Figure 1. Impact of the COVID-19 pandemic on the transition of total number, incidence, and age range of acute hepatitis B in Japan. (A) Number of acute hepatitis B cases in each year; **(B)** Incidence of acute hepatitis B in each year; **(C)** Age range of acute hepatitis B cases in an entire period; **(D)** Proportion of 20s in the eras before and during the COVID pandemic. The proportion of 20s and 95% confidence intervals (Wilson method) in each group are shown.

pandemic, the incidences of total and male patients significantly decreased during 2020–2022 compared with that of 2015–2019 (median [IQR] = 1.21 [1.16–1.36] *vs.* 1.82 [1.72–1.93] cases per 1,000,000 people per year; $p = 0.02$, and 2.15 [2.01–2.24 *vs.* 2.98 [2.92–3.38] cases per 1,000,000 people per year; $p = 0.004$), whereas those of females did not (median [IQR] = 0.40 [0.36–0.56] *vs.* 0.68 [0.56–0.74] cases per 1,000,000 people per year; $p = 0.28$).

In terms of age at diagnosis, there was a peak in the number of patients in their 20s for both sexes (Figure 1C). The proportion of patients in their 20s was consistent before and during the COVID-19 pandemic (30.3% [95% CI 27.4–33.3] *vs.* 31.9% [27.4–36.8]; $p = 0.60$ in males and 32.7% [26.7–39.3] *vs.* 31.9% [23.2–42.0]; $p = 0.99$ in females, respectively, Figures 1D).

Regional assessment of incidence of acute hepatitis B

We evaluated the total number and incidence of acute hepatitis B infections in each prefecture (Supplemental Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=101*). Tokyo, the capital and the most populous city, had both the highest number of patients (in total 394 patients per eight years) and the highest annual incidence (median [IQR] = 3.79 [3.09–4.37] cases per 1,000,000 people per year). Choropleth maps of the population in 2022 and the total number of acute hepatitis B cases per eight years in each prefecture were described in Figure 2A and 2B, respectively.

To highlight the impact of population, we selected populous prefectures (Tokyo, Kanagawa, Osaka, Aichi, and Fukuoka) and compared them with other prefectures. The number of patients with acute hepatitis B were decreased both in the populous and non-populous prefectures during 2020–2022 compared with that of 2015–2019 (median [IQR] = 70.0 [61.0–81.0] patients *vs.* 100.0 [94.0–109.0] patients; $p = 0.09$ in the populous prefectures, and 84.0 [81.0–89.0] patients *vs.* 120.0 [119.0–131.0] patients; $p = 0.001$ in the non-populous prefectures, respectively, Figure 3A and 3B). Similar to our previous report, the proportion of males was relatively higher in populous prefectures than in non-populous prefectures (median [IQR] = 81.3% [80.6%–85.1%] *vs.* 80.8% [77.3%–83.1%], respectively; $p = 0.16$).

The populous prefectures had significantly higher infection incidence in the total and male populations compared with non-populous prefectures (median [IQR] = 2.14 [1.93–2.36] *vs.* 1.45 [1.15–1.52] cases per 1,000,000 people per year in total population; $p = 0.005$, and 3.55 [3.26–4.07] *vs.* 2.30 [1.78–2.64] cases per 1,000,000 people per year in male population; $p = 0.004$), whereas those of females did not (median [IQR] = 0.77

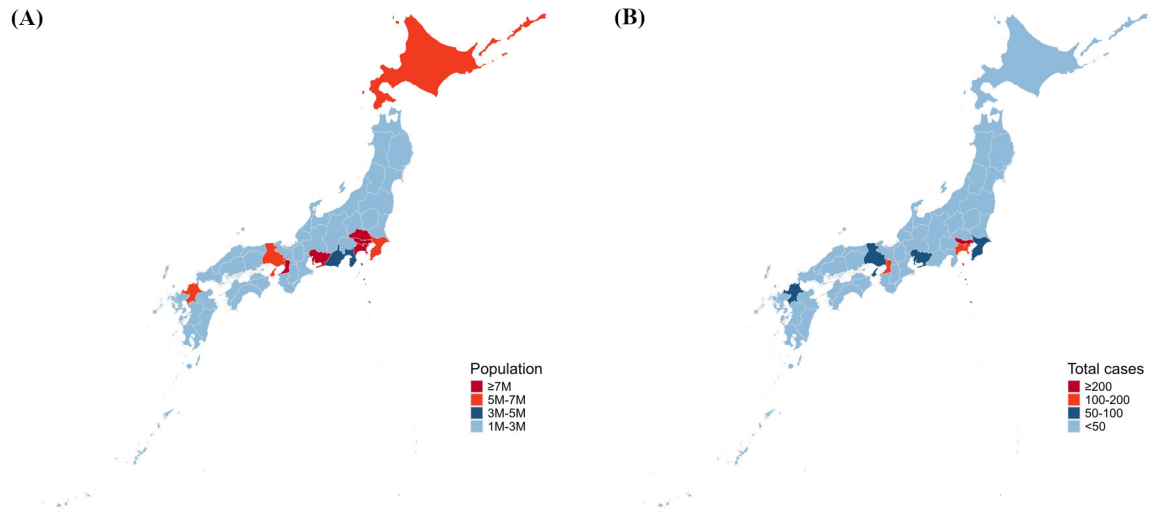

Figure 2. Choropleth maps of population and total number of acute hepatitis B cases in each prefecture in Japan. (A) Choropleth map of population in 2022 in each prefecture; **(B)** Choropleth map of total number of acute hepatitis B per eight years in each prefecture.

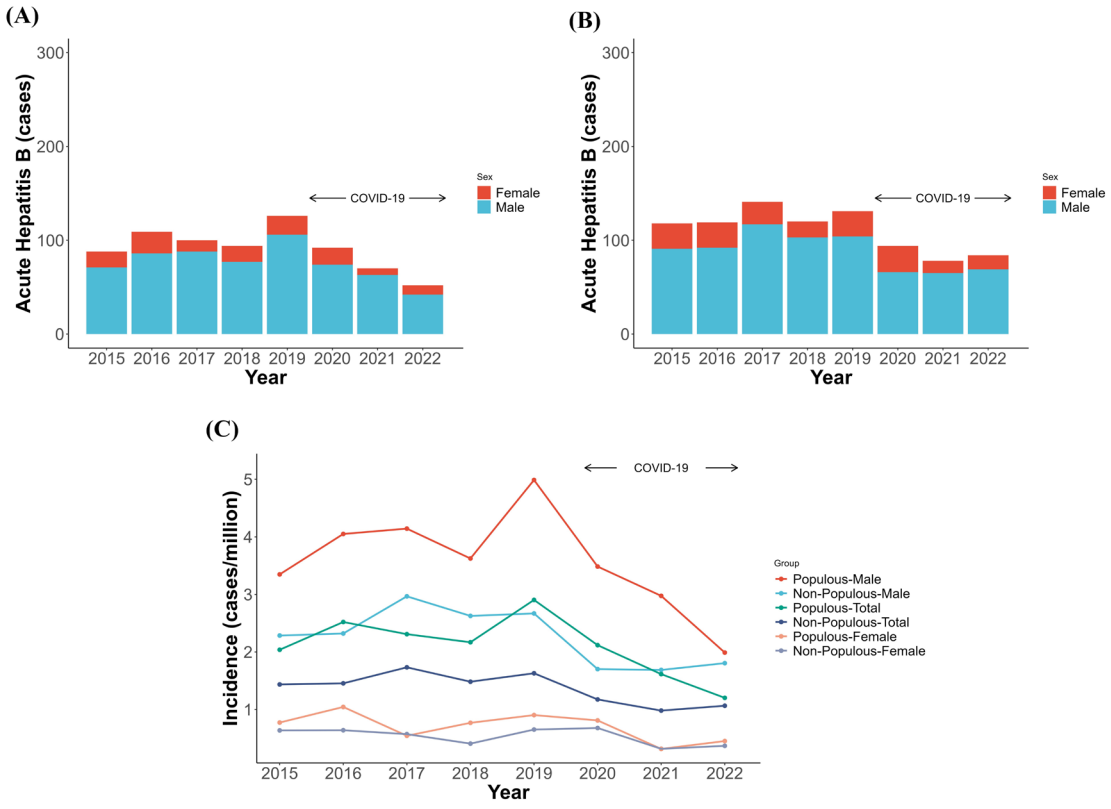

Figure 3. Transition of total number and incidence of acute hepatitis B in populous and non-populous prefectures in Japan. (A) Number of acute hepatitis B cases in populous prefectures; **(B)** Number of acute hepatitis B cases in non-populous prefectures; **(C)** Incidence of acute hepatitis B in populous and non-populous prefectures.

[0.52–0.83] *vs.* 0.61 [0.40–0.64] cases per 1,000,000 people per year; $p = 0.12$, Figure 3C). Interestingly, regarding the impact of the COVID-19 pandemic on changes in incidence, the incidence of males in the non-populous prefectures was significantly decreased (median [IQR] = 2.63 [2.32–2.67] and 1.70 [1.70–1.75] cases per 1,000,000 people per year in 2015-2019 and 2020–2022, respectively; $p = 0.002$), and that in the populous prefectures was relatively decreased (median [IQR] = 4.05 [3.62–4.14] and 2.98 [2.48–3.23] cases per 1,000,000 people per year in 2015–2019 and 2020–2022, respectively; $p = 0.09$), whereas those of females did not.

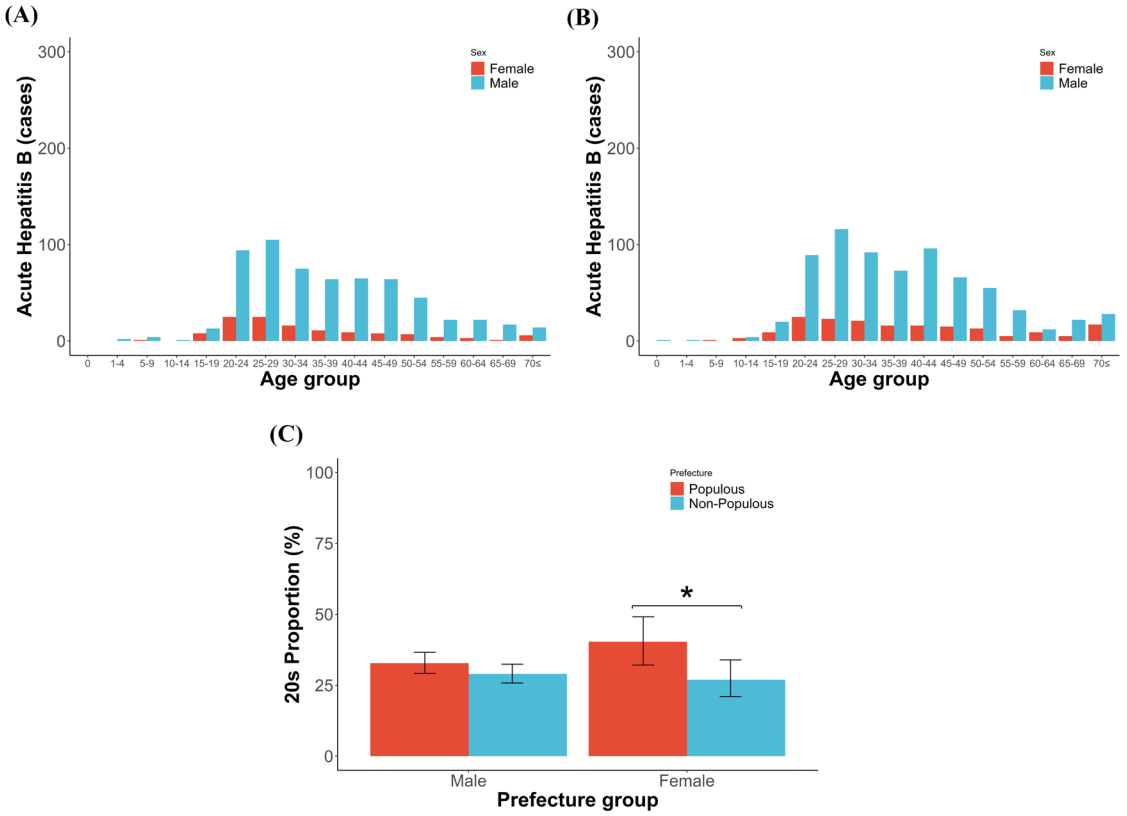

Figure 4. Age range of acute hepatitis B cases in populous and non-populous prefectures in Japan. (A) Age range of the acute hepatitis B cases in populous prefectures; **(B)** Age range of the acute hepatitis B cases in non-populous prefectures; **(C)** Proportion of 20s in populous and non-populous prefectures. The proportion of 20s and 95% confidence intervals (Wilson method) in each group are shown. *$p < 0.05$.

The distributions of patients' ages were described in Figure 4A for populous prefectures and Figure 4B for the non-populous prefectures. Interestingly, the proportions of 20s patients were higher in the populous prefectures than those in the non-populous prefectures, especially in females (32.8% [95% CI: 29.2–36.6] *vs.* 29.0 [25.8–32.4]; $p = 0.15$ in males and 40.3% [32.1–49.1] *vs.* 27.0% [21.0–33.9]; $p = 0.02$ for females, Figures 4C).

Discussion

We analyzed national data surrounding the characteristics of patients with acute hepatitis B in Japan, focusing on the impact of the COVID-19 pandemic and regional differences. The number and incidence of acute hepatitis B cases significantly decreased during the COVID-19 pandemic, and the impact of COVID-19 was pronounced in males, especially in non-populous prefectures. The incidence of males in populous prefectures was significantly higher than that in non-populous prefectures, whereas that of females was similar between the groups. In populous prefectures, the proportion of younger patients, especially females, was higher than that in non-populous prefectures.

Employing the number of patients reported from each prefecture and the population each year, we calculated the annual incidence in addition to the numbers of patients in each prefecture. The incidence of acute hepatitis B cases significantly decreased during the COVID-19 pandemic, similar to previous reports from other countries (*9,10*). Interestingly, although the incidence in males was significantly decreased during the COVID-19 pandemic, that in females did not. In general, COVID-19 restrictions were associated with a reduction in sexual activity including in Japan (*18-20*). Focusing on the practice of sexual behaviors, Li *et al.* reported that the number of sexual partners and risky sexual behaviors – defined as inconsistent condom use, casual sexual partnerships, or multiple sexual partnerships – decreased more in men than in women (*21*). In this context, a higher incidence of acute hepatitis B infections is noted among men who have sex with men (MSM) (*22*). It has also been reported that MSM reduced their risky sexual behavior during the COVID-19 pandemic (*23*). Although we had no data regarding sexuality in this study, it is suspected that the decreased incidence in males might be partly caused by MSM. Overall, the sex differences in incidence transition in our study might be due to differences in sexual behavior between males and females.

We also focused on regional differences between populous and non-populous prefectures in terms of incidence, sex ratio, and age distribution of patients with acute hepatitis B. In populous prefectures, a significantly higher incidence of males, a relatively higher male ratio, and a significantly higher proportion of people in their 20s, especially females, was observed compared with non-populous prefectures. Regarding the male population, we previously reported that hepatitis C virus/human immunodeficiency virus-coinfected patients are more likely to be male, have other STDs, and live in Tokyo, the most populous city in Japan (*24*). The higher incidence of male in populous prefectures might reflect a population of sexually active patients, including MSM. Interestingly, the decline in male incidence was more pronounced in non-populous than in populous prefectures when the effects of the COVID-19 pandemic and regional differences were considered together. These time series and regional differences could be caused not only by differences in the population at risk, but also by changes in lifestyle, including inter-prefectural travel, in each area during the COVID-19 pandemic period, especially when behavioral restrictions were prominent (*25-28*), although the changes in sexual behavior have not been sufficiently assessed. Regarding females, the difference in the proportion of ages between populous and non-populous prefectures represents a novel finding. In populous prefectures, females in their 20s should be considered as a high-risk population. In contrast, in non-populous prefectures, HBV infections occurred evenly across a wide range of age groups, including those aged > 70 years. These results indicate the potential of targeted and specific population-based approaches for the prevention and screening of infected persons depending on the characteristics of a given region. These results may have implications for the establishment of individual measures, including vaccinations in populous and non-populous areas, not only in Japan, but also in many other countries.

Our study had certain limitations. First, although information concerning transmission routes is registered in the NESID system, the raw data are not publicly available owing to regulations in Japan. However, a recent public summary reported that sexual contact is an abundant transmission route (*16*). Second, although case reporting is legally required, some cases may be missing because surveillance data are on a reported basis.

In conclusion, national data regarding acute hepatitis B infection in Japan clearly revealed the impact of the COVID-19 pandemic and of epidemiological differences, such as a higher incidence of males and a higher proportion of people in their 20s, especially females, in populous prefectures. Identifying high-risk populations is necessary to establish tailored strategies for eliminating viral hepatitis in each area. This research suggests that to develop rapid and effective measures for hepatitis prevention, it would be useful to translate global and national goals into targets for specific populations, including regions and age groups.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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Association between procedure volume and 30-day mortality in stroke patients treated with EVT or IV rt-PA during the introduction period of EVT in Japan

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Abstract: This study aimed to determine whether procedure volume is associated with 30-day mortality following endovascular thrombectomy (EVT) or intravenous recombinant tissue plasminogen activator (IV rt-PA) for stroke during the introduction period of EVT in Japan. Using nationwide claims records, we investigated data from 8,227 patients undergoing EVT and 13,406 and 6,035 patients undergoing rt-PA monotherapy in hospitals with and without EVT capability, respectively, between April 2014 and February 2016 in Japan. Procedure volume was categorized into three groups according to tertiles of the annual number of EVTs or IV rt-PA injections performed in the hospitals. Hierarchical logistic regression demonstrated that the odds ratio (95% confidence interval) of 30-day mortality following EVT was significantly lower in middle- (0.77 [0.62–0.96]) and high- (0.69 [0.53–0.89]) volume hospitals than that in low-volume hospitals even after adjusting for potential confounding factors. The generalized additive mixed models revealed no obvious threshold volume of EVT to reduce the mortality risk. By contrast, mortality risk following IV rt-PA monotherapy did not decrease in hospitals without EVT capability but did with increasing IV rt-PA volume in hospitals with EVT capability (P for heterogeneity 0.003). The risk of 30-day mortality after EVT for acute ischemic stroke decreased linearly according to EVT procedure volume in each hospital. However, the association between IV rt-PA volume and mortality risk was modified by the hospital's EVT capability. Further research is warranted to determine whether the volume-outcome relationship we observed is a temporary phenomenon following EVT or a consistent trend over time.

***Keywords*:** outcome, endovascular thrombectomy, intravenous recombinant tissue plasminogen activator

Introduction

Stroke remains a major cause of death worldwide (*1*). However, recent advances in reperfusion therapy have significantly reduced case-fatality rates following acute ischemic stroke (AIS) (*2,3*). The therapeutic windows for intravenous recombinant tissue plasminogen activator (IV rt-PA) and endovascular thrombectomy (EVT) are limited, with their efficacy and safety being highly time-dependent (*4-7*). Therefore, patients with stroke who may benefit from reperfusion therapy must be transported as early as possible to the nearest stroke center for timely intervention. To ensure access to IV rt-PA and EVT for every patient in need, stroke centers must be strategically located with sufficient experience and technical expertise to achieve prompt and effective recanalization (*8*).

Hospital volume has been linked to stroke outcomes, though results are sometimes inconsistent (*9-14*). Specifically, higher procedure volumes may be associated with better outcomes following reperfusion therapy for AIS. However, whether outcomes following AIS are influenced by the volume of EVT, IV rt-PA, or both remains to be determined (*15-21*). Furthermore, it remains unclear whether the volume-outcome relationship for IV rt-PA administration remains consistent between hospitals with and without EVT capability following the introduction of EVT.

This study aimed to determine whether procedure volume is associated with 30-day mortality risk following EVT or IV rt-PA in patients with AIS and whether the relationship between IV rt-PA volume and post-procedure mortality varies based on a hospital's EVT capability in the post-EVT era. To this end, we collected nationwide claims data for all patients with AIS

who underwent EVT or IV rt-PA across Japan when EVT was being integrated into stroke care systems.

Materials and Methods

Study design, setting, and data source

We obtained nationwide data of consecutive patients with AIS who underwent reperfusion therapy in Japan through the National Database (NDB) of Health Insurance Claims and Specific Health Checkups, one of the largest healthcare claims databases in the world, covering the entire Japanese population. The NDB includes the claims data for over 95% of hospitalized patients in Japan. Anonymized claims data from the NDB were provided for this study by the Ministry of Health, Labour, and Welfare following a review of our study protocol by a government advisory committee (No. 0326–26). The Institutional Review Board of Kyushu University approved this study (No. 28–70), and the requirement for informed consent was waived since all data were anonymized prior to access. Using the NDB, we analyzed data from patients with AIS hospitalized and treated with EVT or IV rt-PA across Japan.

Study patients

This study included patients with AIS who were hospitalized and received reperfusion therapy in Japan from April 2014 to February 2016. During this study, the number of IV rt-PA therapies administered in Japan stabilized, while EVT usage significantly increased (*22*). Patients were categorized into two groups: those who underwent EVT with or without IV rt-PA (EVT group) and those treated with IV rt-PA alone (IV rt-PA group). Meanwhile, hospitals were classified based on their EVT capability, determined by whether they performed EVT during the study period (Supplemental Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=102*).

Procedure volume

Procedure volume was defined as the annual number of patients treated with EVT or IV rt-PA at each hospital during the study period. We categorized procedure volume into three groups based on the tertile of the annual number of therapies performed at each hospital.

Clinical outcome

The clinical outcome was the 30-day mortality rate following reperfusion therapy for AIS, defined as death from any cause within 30 days of the therapy for the index stroke (*22,23*).

Covariates

We collected patient-level variables, including age, sex, and stroke severity, to adjust for the risk of death in individual patients. Stroke severity was assessed using a claims-based severity index previously developed and validated for hospitalized patients with AIS (*19,24,25*). This index comprised seven variables from the claims database: airway suctioning, bacterial sensitivity test, general ward stay, intensive care unit stay, nasogastric tube use, osmotherapy use, and urinary catheterization. These variables were assessed within one day of admission and used as covariates.

Hospitals were categorized into three levels of stroke care: stroke centers (high level of care), tertiary hospitals (middle level of care), and other types (low level of care). Definitions for these care levels are provided in the Supplemental Methods (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=102*). Using administrative data, we collected information on the density of hospitals across the three-stroke care levels, the density of neuroendovascular specialists, population density, the proportion of rural residents, annual wage levels, and rates of delayed ambulance transport. We also gathered administrative data on regional population demographics, socioeconomic status, and healthcare system. Definitions of these factors and their data sources are detailed in the Supplemental Methods (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=102*).

Statistical analysis

We compared differences in baseline characteristics among hospitals with varying stroke volumes using the χ^2 test. Logistic regression analysis was used to test trends in characteristics according to stroke volume. The Cochran–Armitage test assessed trends in crude mortality rates by procedure volume. To investigate the association between categorized procedure volume and 30-day mortality, we employed a hierarchical logistic model that accounted for clustering effects within the hospitals. A random intercept model was utilized, assuming the random intercept follows a normal distribution (*26*).

We constructed two multivariable models in addition to adjusting for age and sex. Multivariable model 1 included age, sex, and stroke severity index variables for each patient. Multivariable model 2 included hospital factors (low, middle, or high level of stroke care) and regional factors (demographics: population density and proportion of rural residents; medical services: density of hospitals across the three-stroke care levels, density of neuroendovascular specialists, and rate of delayed ambulance transport; socioeconomic status: annual wage level).

To confirm the association between the number of procedures and 30-day mortality, we conducted an additional analysis using a generalized additive mixed

model with a smoothing spline function applied to procedure volume (*27*). Heterogeneity between hospitals with and without EVT capability was assessed by including an interaction term for procedure volume × subgroup. All statistical analyses were conducted using the R statistical package (*http://www.r-project.org*, version 4.2.0). Further analysis details using the R statistical package are presented in the Supplemental Methods (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=102*). A two-sided P value of < 0.05 was considered statistically significant.

Results

Baseline characteristics

During the study period, a total of 8,227 patients underwent EVT, while IV rt-PA monotherapy was administered in 13,406 in hospitals with EVT capability and 6,035 patients in hospitals without EVT capability (Supplemental Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=102*). We compared the baseline characteristics of these patients as well as the stroke care levels in the hospitals where they received reperfusion therapy based on the annual volume of each procedure. Stroke severity was assessed using a claims-based severity index composed of six factors.

The proportions of older patients, females, and those requiring intensive care unit stay and nasogastric intubation tended to increase with higher EVT volume, whereas the proportion of patients requiring osmotherapy decreased as EVT volume increased (Table 1). Additionally, the proportion of stroke centers increased with higher EVT volumes (Table 1).

In patients treated with IV rt-PA monotherapy, the proportion of cases requiring intensive care unit stay, bacterial sensitivity testing, and nasogastric intubation increased, while the proportions of cases requiring airway suctioning, osmotherapy, and urinary catheterization decreased as IV rt-PA volume increased (Table 2). Similar to EVT, the level of stroke care improved with increasing IV rt-PA volumes (Table 2). Regional characteristics varied according to EVT (Supplemental Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=102*) and IV rt-PA volumes (Supplemental Table S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=102*).

Procedure volume and 30-day mortality

During the study period, as EVT was introduced and increasingly utilized across the country, EVT procedure volumes were low in most hospitals across Japan (Supplemental Figure S2A, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=102*). For IV rt-PA monotherapy, the highest number of treatments administered in a single hospital with EVT capability ranged from 6 to 10 per year (Supplemental Figure S2B, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=102*), while in hospitals without EVT capacity, it was ≤ 5 per year (Supplemental Figure S2C, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=102*). The mortality rates following EVT or IV rt-PA administration varied among individual hospitals depending on their procedure volumes for EVT (Supplemental Figure S3A, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=102*) and for IV rt-PA in EVT-capable (Supplemental Figure S3B, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=102*) or -incapable hospitals (Supplemental Figure S3C, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=102*).

Table 1. Baseline characteristics of patients undergoing EVT

	G1, *n* = 2,682	G2, *n* = 2,832	G3, *n* = 2,713	*P*	P_{trend}
Patient factors					
Age, y, mean (SD)	74.5 (12.1)	74.8 (12.9)	75.1 (12.2)	< 0.001	< 0.001
Women, *n* (%)	1,104 (41.2)	1,196 (42.2)	1,191 (43.9)	0.12	0.04
Stroke severity, *n* (%)					
Airway suctioning	766 (28.6)	807 (28.5)	829 (30.6)	0.16	0.11
Bacterial sensitivity test	119 (4.4)	94 (3.3)	122 (4.5)	0.04	0.91
Intensive care unit stay	1,899 (70.8)	2141 (75.6)	2216 (81.7)	< 0.001	< 0.001
Nasogastric intubation	299 (11.1)	313 (11.1)	355 (13.1)	0.03	0.03
Osmotherapy	423 (15.8)	384 (13.6)	265 (9.8)	< 0.001	< 0.001
Urinary catheterization	1,023 (38.1)	1,021 (36.1)	1,073 (39.6)	0.03	0.28
Hospital factors, *n* (%)					
Stroke centers	2,085 (77.7)	2,456 (86.7)	2,463 (90.8)	< 0.001	< 0.001
Non-stroke centers					
Tertiary hospitals	514 (19.2)	360 (12.7)	250 (9.2)		
Other hospitals	83 (3.1)	16 (0.6)	0 (0.0)		

Procedure volume was classified into three groups based on the annual number of patients undergoing EVT: G1 (1–7 pts/y), G2 (8–16 pts/y), and G3 (17–64 pts/y). EVT: endovascular thrombectomy, pts: patients, P_{trend}: P for trend.

Association between procedure volume and 30-day mortality after EVT

The crude 30-day mortality rate following EVT tended to decrease as the number of EVTs performed increased (Table 3). The age- and sex-adjusted odds ratios for 30-day mortality following EVT were significantly lower in middle- and high-volume hospitals than in low-volume hospitals (Table 3). These associations remained significant even after adjusting for various patient, hospital, and regional covariates.

Association between procedure volume and 30-day mortality following IV rt-PA monotherapy

We examined the trend for mortality rates following IV rt-PA administration. In hospitals with EVT capability, there was a significant decrease in the 30-day mortality rate following IV rt-PA monotherapy, whereas no such trend was observed in hospitals without EVT capability (Table 4). In EVT-capable hospitals, the age- and sex-adjusted odds ratios of 30-day mortality were lower in high-volume hospitals than in low-volume hospitals. Conversely, in hospitals without EVT capability, the mortality risk following IV rt-PA administration did not decrease with higher IV rt-PA volumes. Furthermore, EVT capability significantly modified the association between IV rt-PA volume and post-administration mortality, even after adjusting for multiple confounding factors.

Volume-outcome relationship between procedure volume and 30-day mortality following EVT or IV rt-PA monotherapy

We examined the volume-outcome relationship between EVT or IV rt-PA volumes and post-procedure mortality using a generalized additive mixed model. The results indicated that the mortality risk decreased as EVT volume increased (Figure 1A). In contrast, the relationship between IV rt-PA volume and mortality risk significantly varied based on the hospital's EVT capability. Specifically, in hospitals with EVT capability, the risk of 30-day mortality following IV rt-PA administration decreased as IV rt-PA volume increased (Figure 1B). However, in hospitals without

Table 2. Baseline characteristics of patients undergoing IV rt-PA monotherapy

	G1, *n* = 6,595	G2, *n* = 6,319	G3, *n* = 6,527	*P*	P_{trend}
Patient factors					
Age, y, mean (SD)	75.1 (11.9)	75.3 (12.0)	75.3 (12.4)	< 0.001	0.12
Women, *n* (%)	2,729 (41.4)	2,622 (41.5)	2,744 (42.0)	0.72	0.44
Stroke severity, *n* (%)					
Airway suctioning	1,299 (19.7)	1,231 (19.5)	1,139 (17.5)	0.001	0.001
Bacterial sensitivity test	171 (2.6)	123 (1.9)	233 (3.6)	< 0.001	< 0.001
Intensive care unit stay	3,107 (47.1)	4,681 (74.1)	4,777 (73.2)	< 0.001	< 0.001
Nasogastric intubation	278 (4.2)	305 (4.8)	440 (6.7)	< 0.001	< 0.001
Osmotherapy	718 (10.9)	548 (8.7)	501 (7.7)	< 0.001	< 0.001
Urinary catheterization	3,330 (50.5)	2,911 (46.1)	2,756 (42.2)	< 0.001	< 0.001
Hospital factors, *n* (%)					
Stroke centers	3,798 (57.6)	5,258 (83.2)	5,751 (88.1)	< 0.001	< 0.001
Non-stroke centers					
Tertiary hospitals	2,420 (36.7)	991 (15.7)	776 (11.9)		
Other hospitals	377 (5.7)	70 (1.1)	0 (0.0)		

Procedure volume was classified into three groups based on the annual number of patients undergoing IV rt-PA monotherapy: G1 (1–10 pts/y), G2 (11–20 pts/y), and G3 (21–101 pts/y). IV rt-PA: intravenous recombinant tissue plasminogen activator, pts: patients, P_{trend}: P for trend.

Table 3. Association between procedure volume and 30-day mortality following EVT

	Event (%)	Age- and sex- adjusted		Multivariable model 1		Multivariable model 2	
		OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
G1, *n* = 2,682	310 (11.6)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
G2, *n* = 2,832	262 (9.3)	0.78 (0.63–0.95)	0.02	0.82 (0.66–1.02)	0.07	0.77 (0.62–0.96)	0.02
G3, *n* = 2,713	221 (8.1)	0.68 (0.53–0.86)	0.001	0.76 (0.59–0.98)	0.04	0.69 (0.53–0.89)	0.005
P for trend	0.002		< 0.001		0.02		0.002

Multivariable model 1 included variables for stroke severity (airway suctioning, bacterial sensitivity test, intensive care unit stay, nasogastric intubation, osmotherapy, and urinary catheterization), as well as patient age and sex. Multivariable model 2 included regional factors (hospital density, EVT specialist density, population density, rural population, wage level, and delayed ambulance transport) and hospital factors (stroke centers, tertiary hospitals except stroke centers, and other hospitals), as well as patient variables in Model 1. EVT: endovascular thrombectomy, OR: odds ratio, CI: confidence interval, pts: patients. Procedure volume was classified into three groups based on the annual number of patients undergoing EVT: G1 (1–7 pts/y), G2 (8–16 pts/y), and G3 (17–64 pts/y).

Table 4. Association between procedure volume and 30-day mortality following IV rt-PA monotherapy

	Event (%)	Age- and sex- adjusted		Multivariable model 1		Multivariable model 2	
		OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
EVT capable hospitals							
G1, *n* = 3042	208 (6.8)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
G2, *n* = 4759	335 (7.0)	1.02 (0.83–1.25)	0.85	1.03 (0.83–1.27)	0.82	0.94 (0.76–1.17)	0.59
G3, *n* = 5605	302 (5.4)	0.76 (0.61–0.94)	0.01	0.78 (0.62–0.97)	0.03	0.70 (0.56–0.88)	0.002
P for trend	0.01		0.01		0.02		0.002
EVT incapable hospitals							
G1, *n* = 3553	257 (7.2)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
G2, *n* = 1560	141 (9.0)	1.26 (0.99–1.62)	0.06	1.43 (1.09–1.88)	0.010	1.31 (1.00–1.72)	0.047
G3, *n* = 922	67 (7.3)	0.99 (0.69–1.42)	0.95	1.29 (0.86–1.93)	0.22	1.19 (0.81–1.75)	0.38
P for trend	0.34		0.40		0.03		0.12
P for interaction	0.03		0.04		0.002		0.003

Procedure volume was classified into three groups based on the annual number of patients undergoing IV rt-PA monotherapy: G1 (1–10 pts/y), G2 (11–20 pts/y), and G3 (21–101 pts/y). Multivariable model 1 included variables for stroke severity (airway suctioning, bacterial sensitivity test, intensive care unit stay, nasogastric intubation, osmotherapy, and urinary catheterization) as well as patient age and sex. Multivariable model 2 included regional factors (hospital density, EVT specialist density, population density, rural population, wage level, and delayed ambulance transport) and hospital factors (stroke centers, tertiary hospitals except stroke centers, and other hospitals), as well as patient variables in model 1. IV rt-PA: intravenous recombinant tissue plasminogen activator, OR: odds ratio, CI: confidence interval, EVT: endovascular thrombectomy, pts: patients.

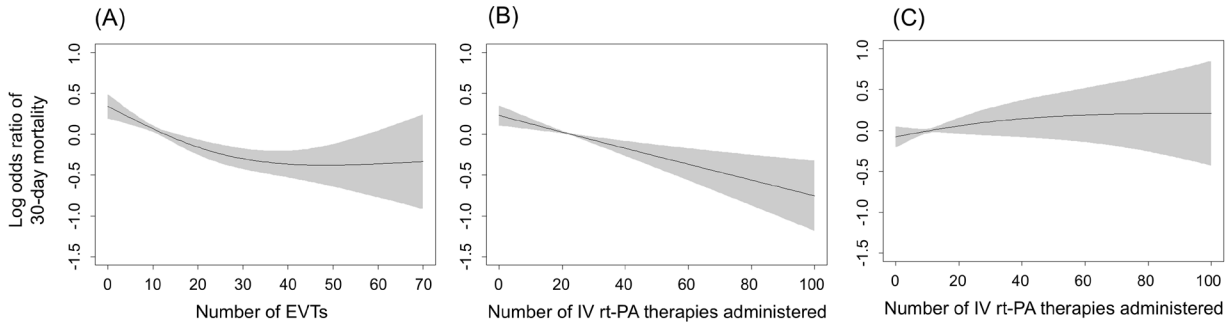

Figure 1. Relationship between procedure volume and 30-day mortality following EVT or IV rt-PA monotherapy. The relationship between procedure volume and 30-day mortality following EVT **(A)** or IV rt-PA therapy in hospitals with **(B)** or without **(C)** EVT capability is shown. The vertical axis represents the log odds ratio of the 30-day mortality, and the horizontal axis shows the annual number of EVTs (A) or IV rt-PA therapies in hospitals with (B) or without (C) EVT capability. The multivariable-adjusted odds ratio was calculated using a generalized additive mixed model. The solid line shows the point estimate, and the dotted lines represent the 95% confidence interval. IV rt-PA: intravenous recombinant tissue plasminogen activator, EVT: endovascular thrombectomy.

EVT capability, the mortality risk remained unchanged or tended to increase as IV rt-PA volume increased (Figure 1C).

Discussion

The major findings of this study are as follows: During the initial period of EVT adoption in Japan, a higher procedure volume was associated with a lower risk of 30-day mortality following EVT for AIS. However, no specific volume threshold was identified in the relationship between EVT volume and mortality risk. In contrast, the association between the IV rt-PA volume and 30-day mortality risk significantly varied based on the hospital's EVT capability. While hospitals with EVT capability showed a trend of decreasing mortality risk with increasing IV rt-PA volume, this volume-outcome relationship was not observed for IV rt-PA in hospitals without EVT capacity. These findings suggest a volume-outcome relationship for EVT volume in relation to post-procedure mortality during the initial EVT adoption period in Japan, while the volume-outcome relationship for IV rt-PA appears to be influenced by the presence of EVT capability at the hospital during this period.

Procedure volume and outcome after EVT

As endovascular experience accumulates, technical proficiency likely improves, which may explain the improved outcomes observed with higher EVT volumes. Although recent studies have explored the volume-outcome relationship for EVT, their findings remain inconclusive. Higher EVT volumes are associated with lower mortality in Korea (*19*) and the United States (*15,17,20,21*), while one study in the United States found no significant association between intra-arterial procedure volume and in-hospital mortality (*18*). Our findings support a volume-outcome relationship,

indicating that higher EVT volumes are associated with reduced mortality risk when EVT was increasingly adopted across Japan.

Operator experience contributes to safer, more effective endovascular techniques, ultimately increasing procedural success rates and improving EVT outcomes. In this study, while no specific EVT volume threshold for reduced post-procedural mortality was identified, there remains a need for comprehensive education and training programs to increase the number and proficiency of neuro-interventional specialists. From a hospital perspective, improved post-procedural outcomes stem more from efficient processes than structural elements, as the volume-outcome relationship persisted even when controlling for stroke care levels. Higher volumes may foster high-quality care by enhancing more sophisticated, interdisciplinary coordination.

Procedure volume and outcome following IV rt-PA administration

The relationship between procedure volume and mortality risk following IV rt-PA administration for AIS remains inadequately understood. A previous Japanese study conducted between 2010 and 2012 reported no clear volume-outcome relationship for IV rt-PA administration (*16*). However, our findings suggest that this relationship may be influenced by the availability of EVT. Among patients treated with EVT at EVT-capable hospitals, we observed similar trends of decreasing mortality risk with higher EVT volumes, regardless of whether patients were pretreated with IV rt-PA (data not shown). In contrast, the volume-outcome relationship for IV rt-PA administration varied based on whether hospitals were equipped to provide additional EVT.

Although the exact reasons for this shift remain to be determined, several plausible explanations have been proposed. In high-volume hospitals for IV rt-PA with EVT capability, high-risk patients might have been more frequently excluded from the IV rt-PA-only cohort due to subsequent EVT treatment compared with low-volume hospitals. Conversely, high-volume IV rt-PA hospitals without EVT capability might have faced higher mortality risks as they are limited to administering IV rt-PA alone, even for patients who would otherwise be candidates for EVT. In terms of stroke care quality, high-volume hospitals that adopted EVT during the study period were likely early adopters of advanced treatments, with organizational structures and processes that positively impacted patient outcomes. Conversely, high-volume IV rt-PA hospitals without EVT capability might have lagged behind advancements in stroke treatment, continuing to rely on IV rt-PA monotherapy. These differences in practice and capability likely contributed to the observed changes in the volume-outcome relationship based on EVT availability. A detailed investigation into hospital-specific stroke care practices is essential to identify the factors driving this shift in the volume-outcome relationship for IV rt-PA. Such insights could guide improvements in stroke care delivery and patient outcomes.

Clinical implications

This study analyzed the use of EVT during its introductory phase in Japan, a period characterized by limited procedural volume, minimal operator experience, and evolving technical approaches (*22*). It is important to consider that the observed volume-outcome relationship may reflect only the early stage of EVT implementation. Therefore, future studies should determine whether this relationship changes across different phases of EVT adoption — initial, widespread, and mature — or persists when experienced mentors and practitioners are available.

In Japan, the healthcare system, characterized by a large number of hospitals and beds but relatively few EVT cases per specialist, likely influences per-facility EVT volumes. The Japanese guidelines for IV rt-PA administration recommend monitoring in stroke care units or similar settings for at least 24 h post-treatment due to the bleeding risks associated with IV rt-PA. Patients are typically closely monitored in stroke care units or high-care units equipped with advanced acute stroke systems. During the early real-world application of EVT, geographic and institutional differences might have contributed to variability in treatment quality. These therapeutic environments for reperfusion therapy may vary significantly between countries. Therefore, it is essential to determine whether the volume-outcome relationship differs internationally.

Study strengths and limitations

This study has several notable strengths. First, the administrative dataset included nearly all patients receiving reperfusion therapy in Japan, reducing selection bias. Second, the volume-outcome relationship was analyzed based on reperfusion therapy type while considering patient, hospital, and regional characteristics.

This study has some limitations. First, due to the claims database, some clinical data relevant to mortality risks, such as baseline neurological severity and recanalization rate, were unavailable. Instead, surrogate variables were used to gauge stroke severity, which have been validated in previous studies (*19,24,25*). Second, patients treated with the "drip and ship" approach were included, although they represented < 3% of the total. Third, EVT volumes in high-volume hospitals were lower than the global standard, and the volume-outcome relationship in other healthcare systems warrants further assessment. Fourth, hospital care quality could not be directly controlled, despite using a hierarchical logistic regression model. Finally, the study was limited to a

specific period in Japan, affecting the generalizability of its findings. Validation studies are needed to confirm the volume-outcome relationship for reperfusion therapy in other contexts.

In conclusion, this study underscores the volume-outcome relationship between EVT or IV rt-PA administration and mortality in patients with ischemic stroke. The linear relationship between EVT volume and post-procedural mortality aligns with the "practice-makes-perfect" hypothesis. Conversely, the volume-outcome relationship for IV rt-PA administration varies based on the hospital's EVT capabilities. Further investigation is needed to determine whether these volume-outcome relationships for EVT and IV rt-PA hold true across different EVT implementation stages and international healthcare systems.

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Depressive symptoms and chronic disease trajectories and predictors in middle-aged and older adults in China: An eight-year multi-trajectory analysis

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Abstract: This study aims to identify and predict latent trajectories of depression and chronic disease among middle-aged and older adults in China using data-driven and interpretable machine learning methods, and to explore key factors that promote healthy aging. To achieve this, we analyzed longitudinal data from 13,073 middle-aged and older adults in the China Health and Retirement Longitudinal Study (CHARLS). Group-based multi-trajectory modeling (GBMTM) was applied to identify latent trajectory groups for depression and chronic disease statuses. Predictive factors included sociodemographic characteristics, health conditions, and lifestyle factors. Machine learning models and dynamic nomograms were used to predict trajectory groups, and model performance was evaluated using the area under the receiver operating characteristic curve (AUROC) and decision curve analysis (DCA). As a result, three main trajectory groups were identified: a normal healthy trajectory group (26.9%), a potential depression and disease increase trajectory group (55.6%), and a high depression and disease burden trajectory group (17.5%). Additionally, the study found that older age, disability, shorter sleep duration, and poor self-reported health status were associated with a higher likelihood of belonging to the latent depression and disease increase trajectory group or the high disease burden trajectory group, particularly among urban women. In conclusion, this study demonstrates that the GBMTM and machine learning models can effectively identify and predict depression and chronic disease trajectories. The identified predictors are crucial for developing targeted interventions to promote healthy aging among the middle-aged and older adults.

***Keywords*:** group-based multi-trajectory modeling, successful aging, depression, chronic disease, predictive models

Introduction

As global population aging accelerates, China is facing severe social and health challenges (*1*). The country's older adult population now exceeds that of all European nations combined, making aging a major public health concern (*2*). Chronic diseases are among the most serious consequences of aging, contributing to a substantial societal burden and imposing significant psychological and economic stress on both patients and their families (*3*). In China, 75.8% of older adults have at least one chronic condition (*4*), and the risk of multimorbidity increases with age (*5*).

Depression, characterized by low mood and anhedonia, is also common in older adults (*6,7*). It is strongly associated with chronic illness, with individuals experiencing multiple conditions exhibiting a higher risk of depression (*8,9*). Furthermore, studies have shown that the incidence of depression exhibits clear temporal dynamics, with the risk of chronic diseases increases progressively with age (*10*). Despite the increasing prevalence of depression and chronic diseases, research on the developmental trajectory patterns between depression and chronic diseases remains relatively limited. Therefore, investigating the joint development trajectories of depression and chronic diseases is crucial for formulating effective prevention and intervention strategies.

Although prior studies have investigated the trajectories of depression or chronic disease separately, few have integrated both to assess the heterogeneity and interrelation in their progression (*11,12*). Traditional statistical models, such as multiple regression, often fail to capture nonlinear trends and higher-order interactions (*13*). Machine learning methods address these limitations by modeling complex, nonlinear relationships and improving predictive accuracy (*14*). However, the application of machine learning to chronic disease

trajectories remains limited (*15*).

This study aims to address the following key scientific questions: First, using group-based multi-trajectory modeling (GBMTM), we will analyze the dynamic changes in depression and chronic disease trajectories over eight years among adults aged 45 and older in the China Health and Retirement Longitudinal Study (CHARLS). Second, based on feature selection techniques including Least Absolute Shrinkage and Selection Operator (LASSO) and Recursive Feature Elimination (RFE), we will construct and evaluate nine machine learning algorithms —Logistic Regression (LR), Multi-Layer Perceptron (MLP), LightGBM, Elastic Net (Enet), Decision Tree (DT), Support Vector Machine (SVM), k-Nearest Neighbors (KNN), Random Forest (RF), and Extreme Gradient Boosting (XGB) — to systematically classify and predict trajectory groups of depression and chronic disease. The performance of each algorithm will be assessed in terms of predictive accuracy. Third, we will use SHAP (SHapley Additive exPlanations), logistic regression, and nomograms to identify and visualize the most influential predictors of the identified trajectories.

Materials and Methods

Data source

This study is based on data from the CHARLS conducted in 2011, 2013, 2015, and 2018. CHARLS is a nationally representative cohort study, with the baseline survey conducted in 2011 through a multistage probability sampling method. The survey covers 28 provinces, 150 counties, and 450 villages or urban communities across China. Follow-up surveys were conducted in 2013, 2015, and 2018, aiming to comprehensively collect data on the health status and related factors of older adults in China. CHARLS was approved by the Biomedical Ethics Committee of Peking University (IRB00001052-11015), and all participants provided written informed consent (*16*). The present analysis adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (*17*).

In this study, the exclusion criteria were as follows: participants who were younger than 45 years of age at baseline (n = 2,547), those missing baseline depression scores or chronic disease data (n = 1,606), or those lacking key information (*e.g.*, education level, marital status, smoking habits, drinking habits, self-reported health status, and related diseases) (n = 24,565). Additionally, 4,569 participants were excluded due to missing follow-up data on depression and chronic disease. To ensure the robustness of the results, 6,691 individuals who had data from only one measurement were also excluded. Ultimately, a total of 13,073 participants with complete data from at least two time points were included in the final analysis (Supplemental Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=104*).

Assessment of depression and chronic disease count

Depressive symptoms were assessed using the 10-item version of the Center for Epidemiologic Studies Depression Scale (CESD-10), which has demonstrated validity for evaluating depression among Chinese adults (*18*). The scale consists of 10 items, each with four response options referring to the frequency of symptoms over the past week: *i*) rarely or none of the time (< 1 day), *ii*) some or a little of the time (1–2 days), *iii*) occasionally or a moderate amount of time (3–4 days), and *iv*) most or all of the time (5–7 days). The total score ranges from 0 to 30, with higher scores indicating more severe depressive symptoms. In the study, a CESD-10 score of ≥ 10 was used to define the presence of depressive symptoms (*19*).

The number of chronic diseases was assessed using a standardized questionnaire, which asked participants whether they had ever been diagnosed by a physician with any of the following conditions: hypertension, dyslipidemia, diabetes, cancer, chronic pulmonary disease, liver disease, heart disease, stroke, kidney disease, digestive system diseases, emotional or psychiatric disorders, memory-related diseases, arthritis or rheumatic diseases, or asthma. The total number of chronic diseases was then calculated (ranging from 0 to 14). Participants were classified into four groups: 0 (no chronic diseases), 1 (one chronic disease), 2 (two chronic diseases), and ≥ 3 (three or more chronic diseases) (*20*).

Heterogeneous trajectory grouping

This study utilized the GBMTM to identify groups of individuals with similar trajectories of depressive symptoms and chronic disease count. GBMTM is primarily used to analyze longitudinal data, aiming to cluster individuals with comparable developmental patterns and to identify distinct trajectory subgroups (*21*). Detailed information on the implementation of the trajectory model is provided in Supplemental Method 1 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=104*).

The selection of the trajectory model was based on several criteria, including the Bayesian Information Criterion (BIC), Akaike's Information Criterion (AIC), log-likelihood (LL), and entropy. Additionally, to further validate the model's robustness, we used Average Posterior Probability (AvePP, requiring a value above 0.7) and the Predicted Probability of Group Membership (PPGM, requiring a value above 5%) as supplementary statistical indicators (*22*).

Predictive variables

To predict the trajectory groups of depression, this study initially screened 14 variables based on previous research (*20,23*). These variables were consistently recorded across all four waves of data and were considered relevant to depression status. The specific descriptions and definitions of the variables can be found in Supplemental Method 2 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=104*), with detailed information provided in Supplemental Table S1 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=104*).

The predictive variables in the study were divided into three major categories: sociodemographic characteristics, health status, and health behaviors.

i) Sociodemographic Characteristics: This category includes basic information such as age, gender, education level, marital status, and place of residence.

ii) Health Status: This category encompasses various factors closely related to both physical and mental health, including average daily sleep duration, self-reported health status (compared to the previous year), Activities of Daily Living (ADL), Instrumental Activities of Daily Living (IADL), cognitive status (MMSE), and the presence of any disability.

iii) Health Behaviors: This includes smoking status, drinking status, participation in exercise, and involvement in leisure activities.

To minimize the impact of missing data on model prediction performance, missing values were imputed using the missForest algorithm, which is based on the assumption of randomness for the missing values. This algorithm performs well with mixed-type data, and its implementation is described in Supplemental Method 3 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=104*).

Analysis methods

Feature selection

Simplicity is one of the core principles in building predictive models to prevent overfitting, which can be achieved through feature selection (*24*). Thus, this study employed a two-stage selection approach, including LASSO and RFE. In RFE, RF, DT, and Naive Bayes (NB) were compared as base models. A detailed description of the feature selection process is provided in Supplemental Method 4 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=104*).

Initially, LASSO and RFE were used separately to perform feature selection on the initial set of variables. The LASSO model applies L1 regularization to select a sparse subset of features that are significantly associated with the target variable. LASSO has a notable advantage in handling multicollinearity among features and generates models with high interpretability (*25*). During the RFE phase, recursive feature selection was conducted based on DT, LR, and NB base models to leverage the ability of different models to assess feature importance.

Ultimately, considering both the LASSO and RFE selection results, six key variables were identified (Supplemental Figure S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=104*). This multi-method feature selection strategy not only effectively improved the predictive performance of the model but also significantly reduced redundant features, further enhancing the model's simplicity and generalizability.

Development and validation of trajectory group prediction models

The development and validation of predictive models followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement (*26*). Although a single algorithm may suffice for prediction in practical applications, to avoid model selection bias, we tested multiple algorithms, including LR, Enet, KNN, LightGBM, DT, MLP, RF, SVM, and XGBoost (*27-29*). A detailed description of the methods is provided in Supplemental Method S5 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=104*).

The data was randomly divided into a training set (70%) and a testing set (30%). Given the imbalanced distribution of depression symptoms and sleep duration trajectory groups, Synthetic Minority Over-sampling Technique (SMOTE) was applied to resample the training set to reduce predictive bias caused by data imbalance (*30*).

To avoid data leakage and result bias, data preprocessing, including missing value imputation, feature selection, standardization, one-hot encoding, and resampling, was first completed on the training set after the testing data was separated (*31*). Hyperparameters for the training set were optimized using 10-fold cross-validation and grid search, with the best hyperparameters selected based on predictive accuracy. Finally, internal validation was conducted on the testing set using 1,000 bootstrap resamples to assess the model's generalizability (*32,33*).

We performed a comprehensive comparison of the nine machine learning models' performances, using various evaluation metrics to assess model performance, including area under the receiver operating characteristic curve (AUROC), accuracy, Kappa coefficient, sensitivity, specificity, Matthews correlation coefficient (MCC), Youden index, balanced accuracy, precision, recall, F1 score, and Brier score (Supplemental Method 6, (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=104*). These metrics allowed for a multi-dimensional assessment of the models' classification capabilities.

Furthermore, to evaluate the practical effectiveness of the models, we introduced decision curve analysis

(DCA) to compare the net benefits of the models. This comprehensive evaluation helps to better understand the advantages and limitations of each model and provides a scientific basis for model selection in practical applications.

Additionally, based on the results of the LR model, we created a forest plot to display the key factors influencing the trajectory groups of depression and chronic disease count. We also developed a nomogram based on the LR model for practical application. Finally, a dynamic nomogram was constructed for the dynamic prediction of depression status and chronic disease trajectory groups (*33*). The overall workflow for model development and validation is shown in Figure 1.

Sensitivity analysis

A sensitivity analysis was performed to evaluate the robustness of the primary findings. Given that trajectory analysis yields more stable results for individuals with more frequent assessments, we included 8,241 participants who completed at least three waves of the CES-D 10 and chronic disease questionnaires. The results of the trajectory analysis were consistent with the main analysis (Supplemental Figure S3, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=104*).

Statistical analysis

Statistical analyses were performed using R software (version 4.4.1) and Stata (version 18.0). Continuous variables are presented as Mean ± SD and were compared using the Student's *t*-test or the Mann-Whitney test; categorical variables are described as frequencies (percentages) and were compared using chi-square tests or Fisher's exact test.

The development of machine learning models was conducted using the "tidymodels" package in R. Static and dynamic nomograms were constructed using the "rms", "regplot", "DynNom", and "shiny" packages. A two-sided P-value < 0.05 was considered statistically significant.

Results

Depression symptoms and chronic disease count trajectory groups

Based on depression status and chronic disease count, three trajectory groups were identified as the best-fitting model (BIC = –232,734.10, AIC = –232,629.40, log-likelihood: –232,601.40, Entropy = 0.927) (Figure 2). The single trajectory analysis of depression status and sleep duration, along with their estimated parameters, is provided in Supplemental Table S2 and S3 and Supplemental Figure S4 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=104*).

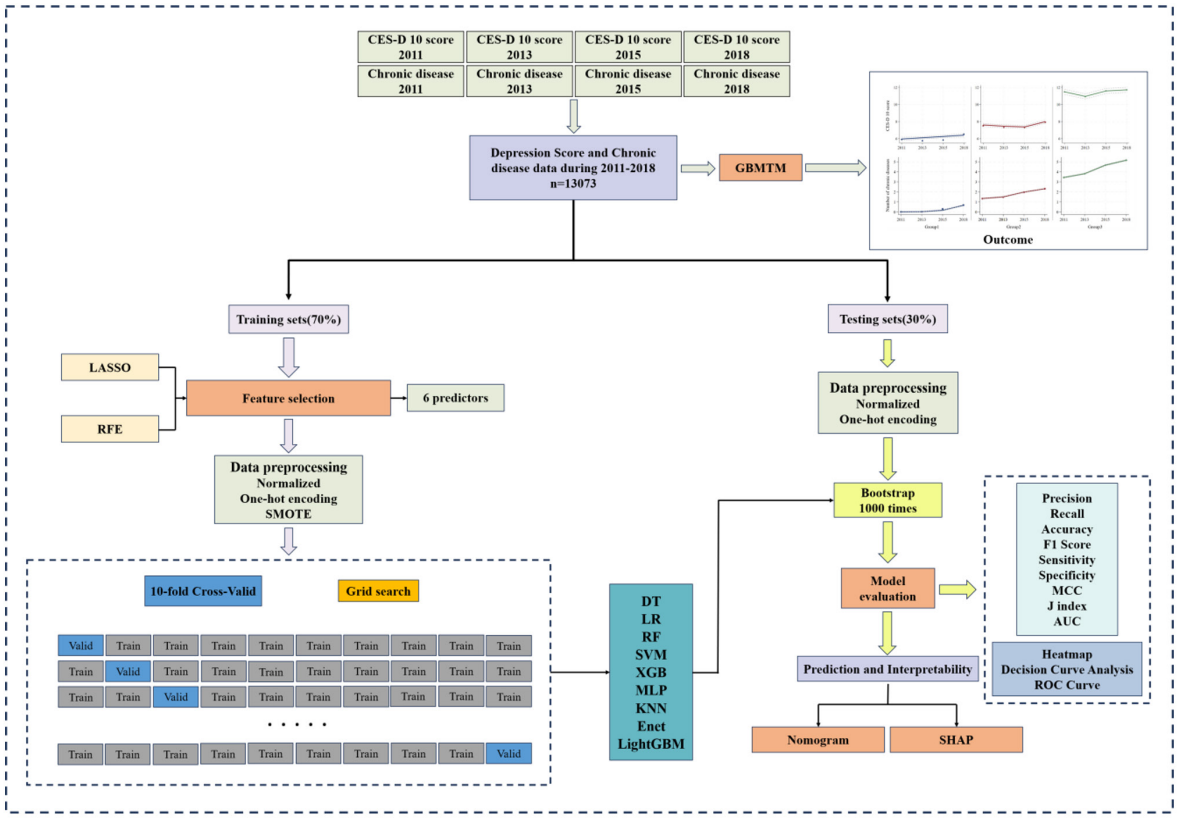

Figure 1. Workflow of model development and validation.

As shown in Figure 2, 26.9% of individuals exhibited a relatively stable and low level of both CES-D 10 scores (indicating depression status) and chronic disease count, which was defined as the "normal healthy" trajectory group (Group 1). In addition, 55.6% of individuals showed an increasing trend in depression status and chronic disease count over time, with depression levels at a threshold that suggested potential depression; this group was defined as the "potential depression and disease increase" trajectory group (Group 2). On the other hand, 17.5% of individuals exhibited more severe depression and an increased chronic disease burden, with a rising trend in both factors during the follow-up period, which was defined as the "high depression and disease burden" trajectory group (Group 3).

Baseline characteristics of participants

At baseline, the mean age of participants was 57.31 ± 8.64 years, with 49.3% of participants being female. The average CES-D 10 score was 7.68 ± 5.99, and the average sleep duration was 6.40 ± 1.76 hours. Additionally, comparisons of other participant characteristics and baseline features across different trajectory groups are provided in Supplemental Table S4 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=104*).

Predictors of depression and chronic disease count trajectory groups

This study utilized both LASSO regression and RFE methods to optimize the selection of predictors for the depression trajectory groups. LASSO regression analysis identified 6 key predictive variables from an initial set of 14 candidate variables. After considering both the simplicity and accuracy of the predictive model, and integrating the results from LASSO and RFE, a final set of 6 core predictive features was determined. These features included baseline age, gender, disability status, place of residence, self-reported health status, and average sleep duration. The related analysis results are detailed in Supplemental Figure S2 and Supplemental Table S5 and S6 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=104*).

Performance evaluation of trajectory prediction models

The performance evaluation results of the machine learning models based on the test set are shown in Figure 3 and Supplemental Table S7 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=104*). Figure 3 illustrates the performance of various models across recall, sensitivity, specificity, F1 score, accuracy, balanced accuracy, AUROC, precision, and Brier score. The predictive models constructed using the 6 key features identified by LASSO regression and RFE achieved AUROCs of 0.65 or higher on the test set. Among these models, SVM demonstrated the highest performance, with an AUROC of 0.72. In contrast, other models, including LR and XGBoost, also exhibited AUROCs exceeding 0.7. Specificity remained consistently high across all models, around 0.70, indicating reliable identification of negative cases. XGBoost achieved the highest precision (0.54), while the F1 score and balanced accuracy remained stable

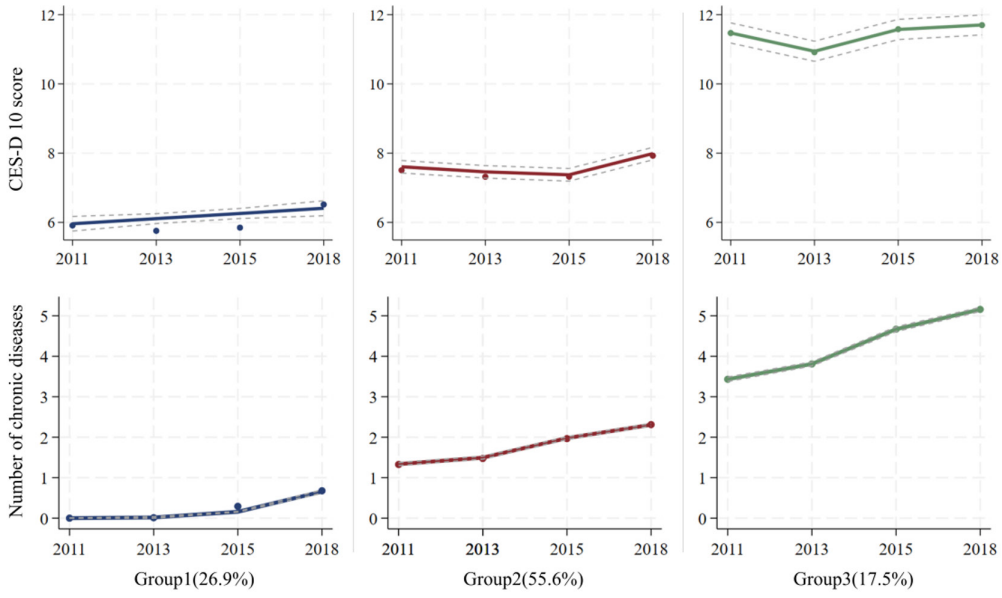

Figure 2. Trend for the single outcome within (reading down) and between (reading across) the two groups (at least two waves, *n* = 13,073). Group 1: normal healthy trajectory group; Group 2: potential depression and disease increase trajectory group; Group 3: high depression and disease burden trajectory group. CES-D 10, The 10-item Center for Epidemiologic Studies Depression Scale.

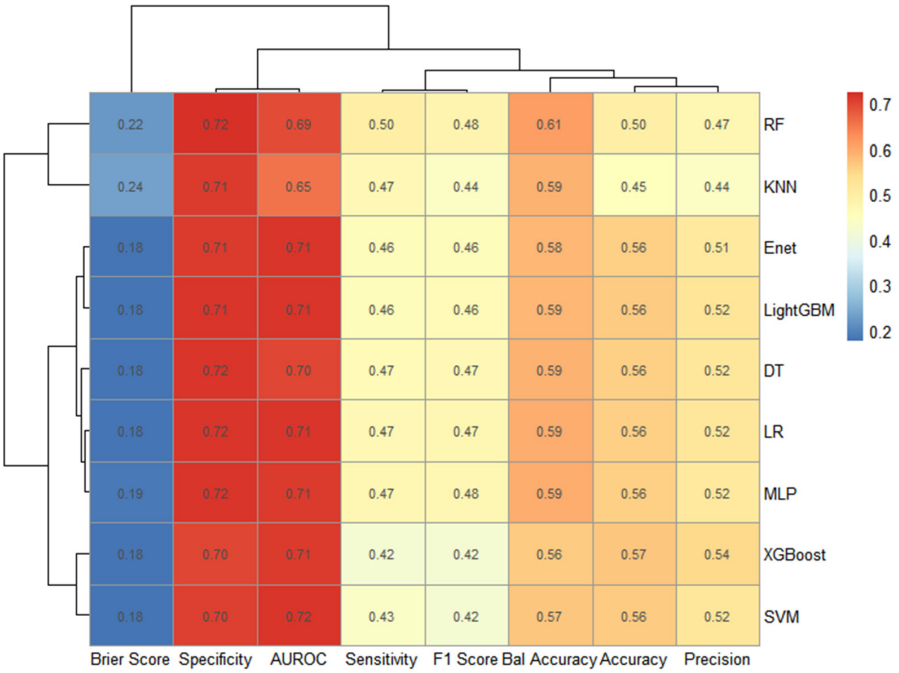

Figure 3. Heatmap for the performance of machine learning models.

across models, ranging from 0.47 to 0.50 and 0.56 to 0.59, respectively. Calibration, measured by the Brier score, revealed low predictive errors across the models, reflecting their overall reliability. While SVM exhibited the strongest discriminative power, other models showed unique advantages: XGBoost achieved the highest precision, random forest excelled in specificity, and logistic regression and ensemble methods maintained consistent calibration, highlighting the complementary strengths of different machine learning models across various performance metrics.

Figure 4 (A-C) presents the ROC curves and their corresponding AUC values for different machine learning models in predicting the three trajectory groups. Overall, the models demonstrated strong predictive performance in Group 1 and Group 3, with AUC values approaching 0.7, indicating good overall predictive accuracy. Among these models, SVM, LR, and XGBoost performed particularly well, exhibiting stable and superior predictive capabilities. However, the models performed relatively poorly in Group 2, with notably lower AUC values. This phenomenon may be attributed to class imbalance or greater heterogeneity within Group 2.

Figure 4 (D-F) further evaluates the net benefit of different models at various decision thresholds through clinical DCA. The DCA results provide insights into the potential clinical utility of these models. In Group 1 (Figure 4D), most models showed higher net benefit within a lower decision threshold range (less than 0.3), particularly LR and XGBoost, demonstrating their potential for practical application in clinical decision-making. In Group 2 (Figure 4E), the net benefit of the models was generally lower and exhibited some degree of fluctuation. For Group 3 (Figure 4F), XGBoost and SVM showed higher net benefit within the lower threshold range, further confirming their predictive advantage and clinical applicability in Group 3.

Interpretability analysis of the predictive model

In this study, the logistic regression model exhibited excellent performance. To further interpret the predictive results of the logistic regression model, we introduced SHAP values, which help to elucidate the contribution of each variable to the model's predictions. SHAP decomposes the model's predictions into the individual contributions of each input feature, allowing for a quantification of how each variable affects the model's outcome. As shown in Figure 5 (A-C), the SHAP analysis revealed that self-reported health status, age, sleep duration, and disability status were the most influential variables in predicting the trajectory groups 1, 2, and 3. These features were central to the model's output and provide valuable insights for future strategies aimed at preventing depression and chronic disease burdens.

To further explore the relationship between the core variables and the burden of depression and chronic diseases, and to simplify the analysis, we combined trajectory groups 2 and 3 into a single group representing the increased burden of depression and chronic diseases. Based on restricted cubic splines (RCS) analysis (Figure 5D, 5E), the results showed that increasing age significantly elevated the risk of depression and chronic

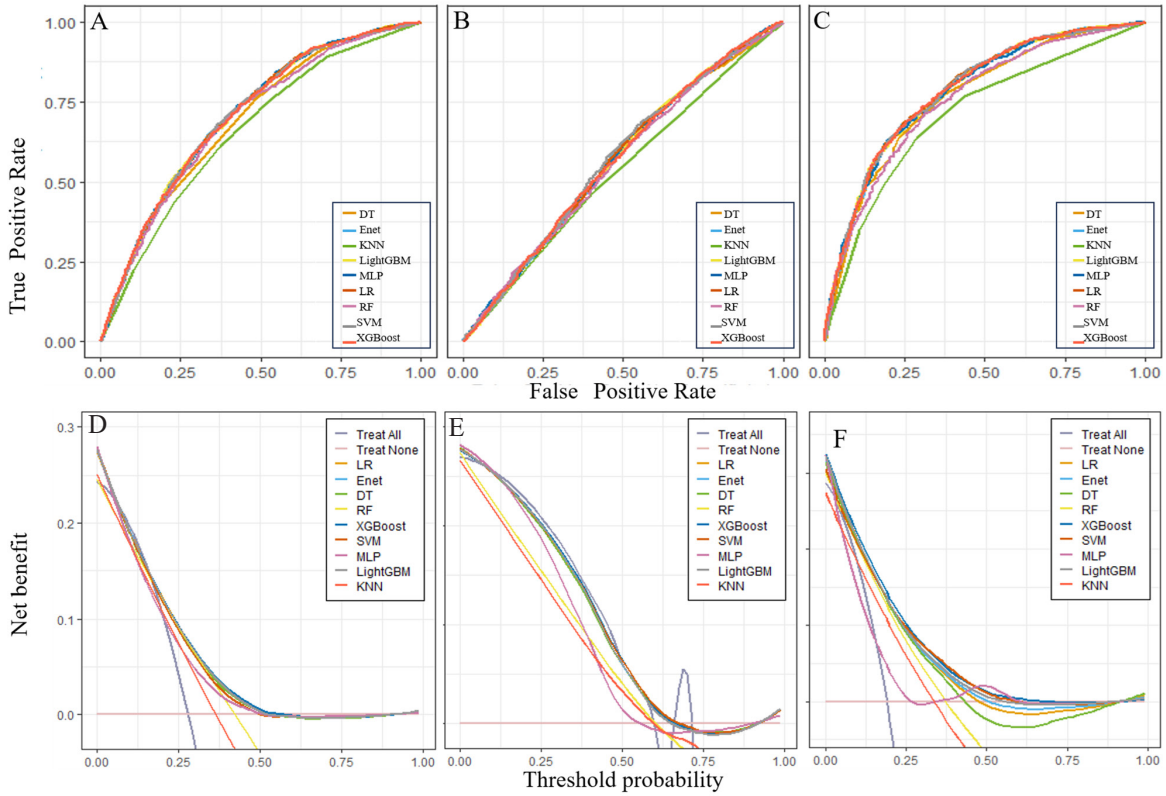

Figure 4. ROC and DCA curves for the machine learning models. ROC, receiver operating characteristics curves; DCA, decision curve analysis.

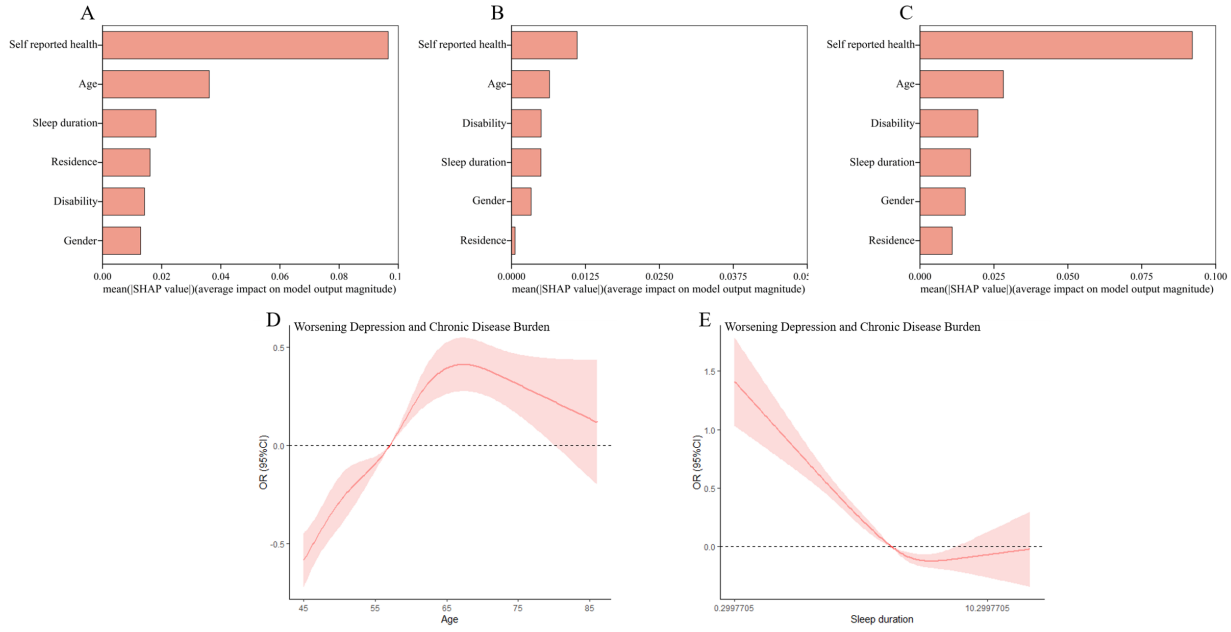

Figure 5. Interpretability analysis with SHapley Additive exPlanations and RCS based on logistic regression to analyze the relationship between important variables including age and sleep duration and depression and chronic disease trajectory. RCS, restricted cubic spline.

disease burden, whereas longer sleep duration was associated with a significantly reduced risk. This finding was further validated by logistic regression analysis. Overall, changes in age and sleep duration were found to be crucial determinants of the risk for depression and chronic disease burden, providing a scientific basis for the development of targeted intervention strategies.

To further enhance the interpretability of the model,

we incorporated the confusion matrix (Supplemental Figure S5, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=104*), which provides a more intuitive representation of the model's predictive accuracy across different trajectory groups, thereby further supporting the validity and reliability of the model's results.

Nomogram for predicting trajectory groups

As shown in Figure 6A, logistic regression analysis (Supplemental Table S8, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=104*) revealed that baseline characteristics play a significant role in predicting the trajectory groups of "potential depression and disease increase" and "high depression and disease burden". The results are presented in the form of a forest plot. Feature selection through LASSO and RFE methods identified six key factors as important predictors of these two trajectory groups. Specifically, younger age, male sex, rural residence, absence of disability, better self-reported health, and longer sleep duration were identified as protective factors, significantly reducing the likelihood of individuals entering the "potential depression and disease increase" and "high depression and disease burden" trajectory groups.

To further simplify the model and enhance its practical utility, we combined the "potential depression and disease increase" and "high depression and disease burden" trajectory groups into a single group labeled "worsening depression and chronic disease burden", as both represent poor depression status and increased chronic disease burden (*34*). Based on this, we developed a static nomogram (Figure 6B) and a dynamic nomogram (Figure 6C, link: *https://ranyandynamicnomogram.shinyapps.io/dynnomapp-2/*) to predict the probability of future increases in depression and chronic disease burden for individuals.

Discussion

This study, utilizing data from the CHARLS spanning from 2011 to 2018, is the first to explore the development trajectories of depressive symptoms and the number of chronic diseases in middle-aged and older adults in China, as well as their key predictors. Using GBMTM, we identified three major trajectories of depression and chronic diseases, finding that only 26.9% of participants exhibited stable depressive symptoms and chronic disease conditions over the study period. Additionally, by incorporating machine learning algorithms, we successfully identified the following six key predictive factors: baseline age, place of residence, disability status, average sleep duration, self-reported health status, and gender. SHAP analysis was employed to explain the importance of these factors in predicting the different trajectory groups, and RCS analysis revealed the non-linear relationships between age, sleep duration, and the trajectories of increasing depression and chronic disease burden.

The findings indicate that older age, urban residence, insufficient sleep, poorer health, and disability status in middle-aged and older women are more likely to be associated with trajectories of increasing depression and chronic disease burden. We observed a positive correlation between depressive symptoms and age, with the number of chronic diseases increasing as age progresses. Existing research supports the notion that depression may lead to further deterioration in neuropsychological functioning among older adults, and they are more susceptible to chronic diseases as they age (*35*). Notably, women have a higher risk of chronic

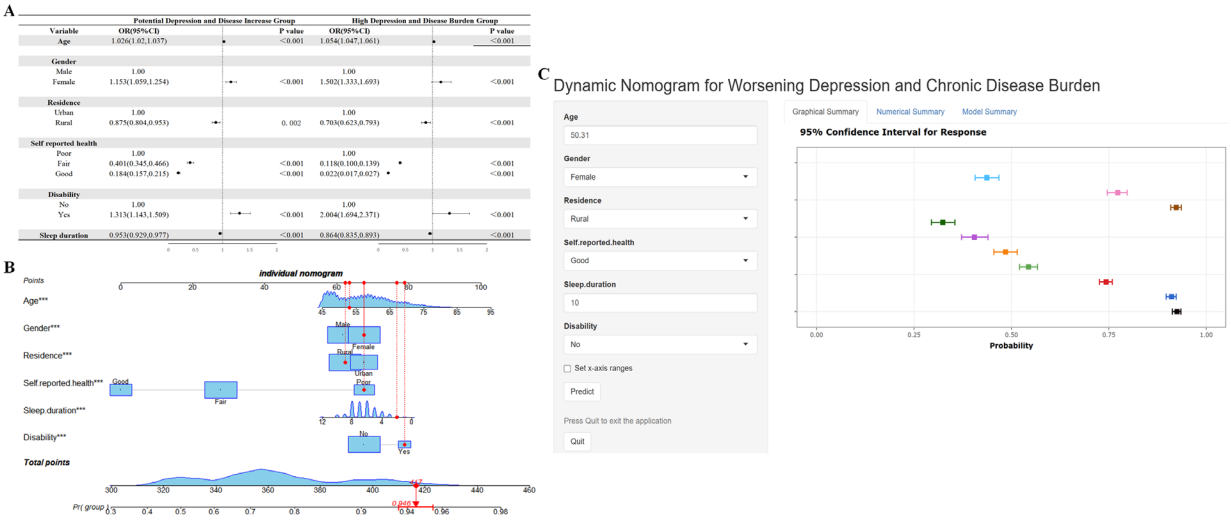

Figure 6. Forest plot, static and dynamic nomogram for the LR model. (A): Forest plot for Worsening Depression and Chronic Disease Burden based on LR; **(B)**: Static Nomogram for Worsening Depression and Chronic Disease Burden; **(C)**: Dynamic Nomogram for Worsening Depression and Chronic Disease Burden. LR: logistic Regression.

diseases such as cardiovascular disease and diabetes (*36*), and the interplay of social and physiological factors makes them more vulnerable to depression (*37,38*).

Both insufficient and excessive sleep have been linked to an elevated risk of depression and adverse physical health outcomes (*39*). Disability not only increases the prevalence of chronic diseases but is also associated with a higher incidence of depressive symptoms (*40*). Therefore, improving basic health and quality of life, along with maintaining good sleep quality, is crucial for promoting healthy aging. Individuals with poorer self-reported health status often experience more significant depression and chronic disease issues due to physical disabilities and emotional distress (*41*). Consequently, maintaining basic health and improving quality of life are essential for promoting positive aging.

This study validates the potential of integrating machine learning techniques with existing health data as an effective screening tool. This tool not only helps optimize the assessment of depression and chronic disease conditions in middle-aged and older adults but also provides guidance for the personalization and flexibility of prevention and treatment strategies. Furthermore, the study identifies low-cost and easily accessible predictive factors, such as good sleep quality and maintaining overall health, which provide a scientific basis for developing preventive strategies targeted at high-risk groups. These strategies may help delay the progression of depressive and chronic disease symptoms.

The practical value of this study is substantial. First, we used the GBMTM method to explore, for the first time, the group characteristics of depression and chronic diseases among the older population in China. Second, through LASSO and RFE feature selection methods, coupled with the further explanation provided by SHAP values, this study reveals the mechanisms through which various variables influence the trajectory categories of depression and chronic disease. Additionally, we analyzed the non-linear relationship between age, sleep duration, and the high-risk trajectory groups for depression and chronic disease using RCS curves. Finally, the static and dynamic nomogram tools designed in this study provide critical technical support for personalized risk assessment in community healthcare services, thus laying the foundation for the development of early prevention and intervention strategies.

Despite the significant progress made in this study, there are some limitations. First, while internal validation was conducted at multiple time points to assess the generalizability of the model, external validation was not performed to confirm the model's stability. Second, because the dataset includes only CES-D 10 depression assessments and chronic disease questionnaire data from up to four time points, the model's applicability to data from additional time points could not be verified. Furthermore, although existing studies have shown a significant association between cognitive decline and depressive symptoms (*42*), this study did not further investigate the potential role of cognitive status in predicting depression and chronic disease trajectories due to limitations in data resources and research design. Future research should further explore these issues and address these limitations to enhance our understanding of aging health trajectories and the reliability of predictive models.

Conclusion

This study identified three trajectory patterns of comorbid depression and chronic disease among the middle-aged and older adults in China. The results indicate that women who are older, reside in urban areas, have disabilities, self-report poor health, and have shorter sleep durations are more likely to belong to the high-risk trajectory of increasing depression and chronic disease. Additionally, the dynamic nomogram proposed in this study provides a practical tool for early risk identification, offering new insights for the development of targeted mental health screening and intervention strategies for the middle-aged and older adults.

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A pilot model of centralized anti-HIV-1 drug resistance testing with decentralized treatment in resource-limited settings

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Abstract: Vietnam is a lower-middle-income country where HIV drug resistance (DR) testing is not widely accessible, and antiretroviral therapy (ART) options remain limited. Since 2016, HIV services have gradually transitioned from international donor support to national Social Health Insurance (SHI). Under the decentralized policy of SHI, HIV treatment has been delivered at local neighborhood hospitals, where experience in managing ART failure is still lacking. This study evaluated a pilot model of centralized DR testing combined with decentralized treatment implementation in Northern Vietnam. Seven provincial hospitals and three healthcare facilities participated. Patients' viral loads (VL) were monitored every six months over a 48-month period (October 2019–September 2023). ART failure was defined as VL ≥ 1,000 copies/mL, which triggered DR testing at the National Hospital for Tropical Diseases in Hanoi. Based on DR results, tailored ART recommendations were provided to local hospitals and healthcare settings. The effectiveness of subsequent ART following DR testing was assessed by VL suppression at 90 days or later. Among 179 patients experiencing ART failure, DR testing was successful in 170 cases. DR mutations were detected in 126 patients (74.12%), while 44 (25.88%) showed no mutation. Patients who followed the ART recommendations had a significantly higher VL suppression rate (87.72%) than those who did not (70.37%, $p = 0.026$). This association was significant in district hospitals (87.50% *vs.* 60.00%, $p = 0.032$) but not in provincial hospitals (87.93% *vs.* 76.47%, $p = 0.240$). This study highlights the potential clinical benefit of our model in resource-limited situations, particularly where ART management capacity is limited.

***Keywords*:** HIV, drug resistance, virological failure, treatment recommendation, resource-limited situation

Introduction

The global response to HIV has made remarkable progress, with antiretroviral therapy (ART) reaching 29.8 million people by December 2022, up from 7.7 million in 2010. Despite this advancement, HIV drug resistance (DR) has emerged as a significant challenge, with a steadily increasing prevalence that threatens to undermine treatment efficacy and efforts to control the epidemic (*1*). In resource-limited settings, where therapeutic options are constrained, effective strategies for monitoring and managing DR are essential to ensuring the long-term sustainability of available antiretroviral regimens.

Vietnam serves as a particularly illustrative case study of the challenges in managing HIV drug resistance amid a transition in the healthcare system. The country has made significant progress in its HIV response, with a concentrated epidemic primarily affecting key populations. A nationally representative survey conducted in 2023 reported encouraging advancements toward the Joint United Nations Programme on HIV/AIDS (UNAIDS) targets, with 94% of people living with HIV aware of their status, 78% receiving treatment, and 73% of those on treatment achieving viral suppression (*2*). However, this progress is threatened by two concurrent challenges: rising rates of DR and a rapid transition from international donor funding to domestic financing.

HIV drug resistance prevalence in Vietnam has increased from less than 5% to between 5 and 15% over the past decade (*3*). A national survey conducted in 2017-2018 revealed that the prevalence of any pre-treatment HIV drug resistance was 5.8% (95% CI: 3.4–9.5%), with

non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance at 3.4% (*4*). This rising resistance threatens the effectiveness of first-line regimens and underscores the need for robust monitoring systems to guide appropriate treatment decisions.

At the same time, Vietnam is navigating a challenging transition in HIV financing. International funding sources, including the President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund, have historically financed the majority of Vietnam's HIV/AIDS response. However, this support has declined significantly since Vietnam transitioned to lower-middle-income country status (*5,6*). In response, Vietnam has successfully integrated HIV services into its Social Health Insurance (SHI) scheme, with domestic resources funding 53% of the HIV response by 2020 (*6*).

Effective monitoring of HIV drug resistance is essential, but it faces significant barriers in resource-limited settings like Vietnam. Sanger sequencing remains the gold standard for genotyping but is available only at a limited number of reference laboratories, with high capital and operational costs limiting broader implementation (*7*). Most HIV diagnostic facilities in resource-limited settings are centralized, requiring specialized infrastructure and trained personnel, with laboratories often located far from patients' homes. This geographic disconnect can result in delayed testing, lost results, and suboptimal patient management (*8,9*).

The decentralization of HIV care delivery presents both opportunities and challenges. Fewer than 30% of people diagnosed with HIV in resource-limited settings complete the full continuum of care, and globally, fewer than 50% of adults remain in care four years after initiating ART (*7*). Decentralizing HIV treatment and care reduces waiting times, brings services closer to patients' homes, and may improve retention. However, this approach creates a potential disconnect between centralized expertise and decentralized implementation, particularly for complex aspects of care such as interpreting resistance tests and making subsequent treatment decisions.

Growing evidence suggests that HIV resistance testing may be a more effective tool for improving HIV care where treatment options are limited (*10*). However, there is a lack of research on models that effectively bridge the gap between centralized technical expertise and decentralized treatment implementation. This study aimed to examine a pilot model of centralized HIV drug resistance testing paired with decentralized treatment implementation in Vietnam. This approach seeks to leverage specialized expertise in DR interpretation while empowering local healthcare providers to implement appropriate treatment changes.

Patients and Methods

Study design and settings

This observational cohort study was conducted as part of the "Science and Technology Research Partnership for Sustainable Development" (SATREPS) project, a collaboration between the Japanese and Vietnamese governments from October 2019 to September 2023. In this project, 11 healthcare facilities in Vietnam were connected to the HIV Data Network (HDN) system. These facilities included one national hospital (National Hospital for Tropical Diseases, NHTD), seven provincial hospitals (Quang Ninh General Hospital, Hospital 09, Nghe An General Hospital, Dong Da Hospital, Hung Yen Hospital of Tropical Diseases, Hai Duong Hospital of Tropical Diseases, and Center for Disease Control and Prevention (CDC) Ha Tinh), and three district-level healthcare facilities (Nam Tu Liem Clinic, Phu Tho-Thanh Son District Health Center, and Yen Bai-Yen Binh District Health Center). The sites were selected to represent different levels of the healthcare system and serve regions with high HIV prevalence.

Study population and recruitment

In this study, patients' HIV viral loads were assessed every six months over a 48-month period (October 2019 to September 2023). We enrolled 179 HIV-positive patients who met the following inclusion criteria: *i*) confirmed HIV diagnosis, *ii*) receiving care at one at one of the 10 provincial hospitals or district-level healthcare facilities, *iii*) on ART for at least 6 months prior to enrollment, *iv*) plasma viral load > 1,000 copies/ml (regarded as treatment failure) (*11,12*), and *v*) willing to participate and provide written informed consent. No restrictions were placed on ART regimens. Patients were recruited during their routine clinic visits.

Following enrollment, participants underwent HIV viral load testing at six-month intervals. For individuals with a viral load exceeding 1,000 copies/mL - indicative of virologic failure - genotypic resistance testing was initiated. Blood samples were collected at study sites and transported to the NHTD, typically within seven days. Upon receipt, samples were analyzed using the Roche Cobas 6800 system, which is *in vitro* diagnostic (IVD)-certified. Antiretroviral treatment adherence was assessed in accordance with the Ministry of Health's national guidelines, using a combination of patient interviews, medication audits, and other standardized monitoring approaches (*11*).

Treatment monitoring and recommendations

As noted above, patients who enrolled in this study (viral load ≥ 1,000 copies/mL) received DR testing. The DR results were reviewed by doctors at the AIDS Clinical Center (ACC) of the National Center for Global Health and Medicine (NCGM), Japan — now known as the Japan Institute for Health Security (JIHS). Based on these results, treatment recommendations

were sent to local physicians *via* the HDN system. The recommendations were classified into four categories: *i*) Continue current regimen, *ii*) Change regimen, *iii*) Either continue or change recommended, and *iv*) Polymerase Chain Reaction (PCR) failure/invalid data.

Subsequent treatment decisions made by local physicians were classified into four categories: *i*) Changed according to recommendations – the treatment regimen was modified in accordance with the recommendations provided by ACC/NCGM clinicians; *ii*) Changed not according to recommendations – the regimen was modified but not in line with the recommendations; *iii*) Maintained according to recommendations – the regimen was left unchanged, as recommended; and *iv*) Maintained not according to recommendations – the regimen was not changed despite a recommendation to modify it. Treatment decisions were considered in accordance with recommendations if the regimen was either modified according to recommendations *i*) or maintained as recommended *iii*). Conversely, decisions were considered not in accordance with recommendations if the regimen was modified contrary to recommendations *ii*) or remained unchanged despite a recommendation to switch *iv*).

Outcome evaluation

The primary goal was viral suppression (VL < 1,000 copies/mL) assessed at least 90 days after the recommendations. This 90-day period was chosen to ensure sufficient time for any treatment changes to take effect. For each patient, we recorded the ART regimen and viral load at the first follow-up visit and the time interval between the treatment recommendation and that visit. Patients who did not attend their follow-up visits were classified as "waiting" with documented reasons (*e.g.*, loss to follow-up, death, transfer). Treatment changes between Efavirenz (EFV) 600 and EFV 400 were not considered regimen changes. All data were entered into the HDN system with regular quality checks. Patient follow-up was conducted in alignment with their routine care schedule, which occurred every six months over a 48-month period.

Statistical analysis

Patient characteristics were summarized using descriptive statistics. Categorical variables were presented as frequencies and percentages, while continuous variables were reported as means ± standard deviations (SD) or medians with interquartile range (IQR). Comparisons between groups were conducted using the Chi-square or Fisher's exact test for categorical variables, and the Student's *t*-test for continuous variables.

Logistic regression analysis was used to determine factors associated with viral load suppression at least 90 days after the recommendations. The multivariate model included adherence to recommendations, gender, age groups, HIV infection duration, ART duration, and hospital level. Results were presented as odds ratios (OR) with 95% confidence intervals. *P*-values less than 0.05 were considered statistically significant. All analyses were performed using Stata version 22.0.

Ethical considerations

The study was approved by the Human Research Ethics Committee of the National Center for Global Health and Medicine (Reference: NCGM-G-003124-03), the Biomedical Research Ethics Committee of the National Hospital for Tropical Diseases (Reference: 17/HDDD-NDTU) and the Biomedical Research Ethics Committee of the Hanoi Medical University (Reference: 677/GCN-HĐĐĐNCYSH-ĐHYHN). All participants provided written informed consent. Patient data were anonymized for analysis and confidentiality was maintained throughout the study. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Results

Among the 179 enrolled patients, 9 had PCR failures and could not proceed with DR testing. Of the remaining 170 patients with successful PCR, 29 cases were excluded due to a lack of 90-day follow-up (18 were waiting, 6 were lost to follow-up or transferred, and 5 had died). Ultimately, 141 patients were evaluated for treatment outcomes. These evaluable cases were analyzed based on whether they followed the treatment recommendations. Among them, 114 followed the recommendations and 27 did not (Figure 1).

Patient demographics and group-specific characteristics are presented in Table 1. The mean age was 38.80 years with a predominance of males (64.25%). The mean duration of HIV infection after diagnosis and of antiretroviral (ARV) treatment was 7.42 and 6.88 years, respectively.

Patterns of DR among study participants are shown in Figure 2. Among 170 patients with successful PCR test results, nearly half had dual-class resistance and a quarter had no resistance. These findings revealed that dual-class resistance, particularly Nucleos(t)ide Analogue Reverse Transcriptase Inhibitor (NRTI) and Non-nucleoside Analogue Reverse Transcriptase Inhibitor (NNRTI), was predominant in this patient population, while protease inhibitor (PI) resistance remained relatively uncommon, and no integrase strand transfer inhibitor (INSTI) resistance has been found to date.

ART regimens following the recommendations are listed in Table 2. The recommendations were adopted in 114 cases, while 27 were not. Based on DR results, continuation of the current regimen was advised in 63 cases (44.68%).

As noted in Figure 1, following the recommendations was significantly associated with viral load suppression (followed *vs.* not followed; 87.72% *vs.* 70.37%, p = 0.026). When the outcomes were further analyzed by facility level (Table 3), this association was statistically significant in district hospitals (followed *vs.* not followed; 87.50% *vs.* 60.00%, p = 0.032), but not in provincial hospitals (followed *vs.* not followed; 87.93% *vs.* 76.47%, p = 0.240), despite similar trends. These findings suggest that adherence to centralized DR testing recommendations has a particularly strong impact at the district level, where treatment expertise may be more limited, supporting the value of centralized DR testing with decentralized treatment implementation in resource-limited settings.

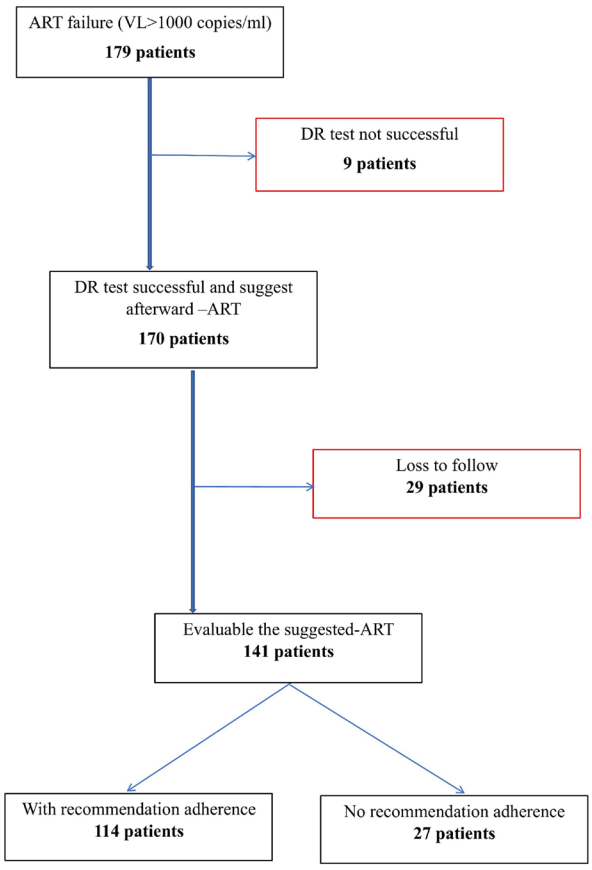

Figure 1. Flow of patients and outcomes.

In both univariate and multivariate analyses, following the recommendations was the only factor significantly associated with viral load suppression (Table 4). Patients who followed the recommendations had approximately three times higher odds of achieving viral suppression in univariate analysis (OR = 3.01, 95% CI: 1.11–8.16, p = 0.031), and this association remained strong after adjusting for other factors (adjusted OR = 3.34, 95% CI: 1.13–9.86, p = 0.029). Other factors showed no significant associations with viral suppression outcomes.

Discussion

This study documented the success of the pilot model combining centralized HIV-1 drug resistance testing with decentralized treatment in Northern Vietnam. The findings support the broader implementation of this model under the national SHI scheme across the country. Patients who followed the recommendations based on DR testing had significantly higher rates of viral suppression. Furthermore, the effectiveness of this

Table 1. Demographics of patients in this study (n = 179)

Demographics	n (%) or mean ± SD			
	Total	Recommendations followed	Recommendations not followed	Loss to follow
Age (years)	38.80 ± 11.99	38.39 ± 11.46	38.14 ± 11.78	40.37 ± 13.75
Age groups				
< 25 years	24 (13.41)	15 (13.16)	5 (18.52)	4 (10.53)
25–34 years	30 (16.76)	19 (16.67)	4 (14.81)	7 (18.42)
35–44 years	77 (43.02)	51 (44.74)	11 (40.74)	15 (39.47)
45–54 years	34 (18.99)	23 (20.18)	5 (18.52)	6 (15.79)
≥ 55 years	14 (7.82)	6 (5.26)	2 (7.41)	6 (15.79)
Gender				
Male	115 (64.25)	78 (68.42)	15 (55.56)	22 (57.89)
Female	64 (35.75)	36 (31.58)	12 (44.44)	16 (42.11)
Duration after HIV diagnosis (years)	7.42 ± 5.00	7.21 ± 4.78	7.19 ± 4.98	8.22 ± 5.72
Duration of ART (years)	6.88 ± 4.71	6.75 ±4.52	6.66 ± 4.66	7.41 ± 5.33
Route of transmission				
Sexual transmission	81 (45.25)	44 (38.60)	15 (55.56)	22 (57.89)
Injection drug use	54 (30.17)	38 (33.33)	7 (25.93)	9 (23.68)
Mother-to-child	12 (6.70)	8 (7.02)	2 (7.41)	2 (5.26)
Blood transfusion	1 (0.56)	0	0	1 (2.63)
Others/Unknown	31 (17.32)	24 (21.05)	3 (11.11)	4 (10.53)
Healthcare facilities				
7 provincial level hospitals	94 (52.51)	58 (50.88)	17 (62.96)	19 (50.0)
3 district level hospitals	85 (47.49)	56 (49.12)	10 (37.04)	19 (50.0)

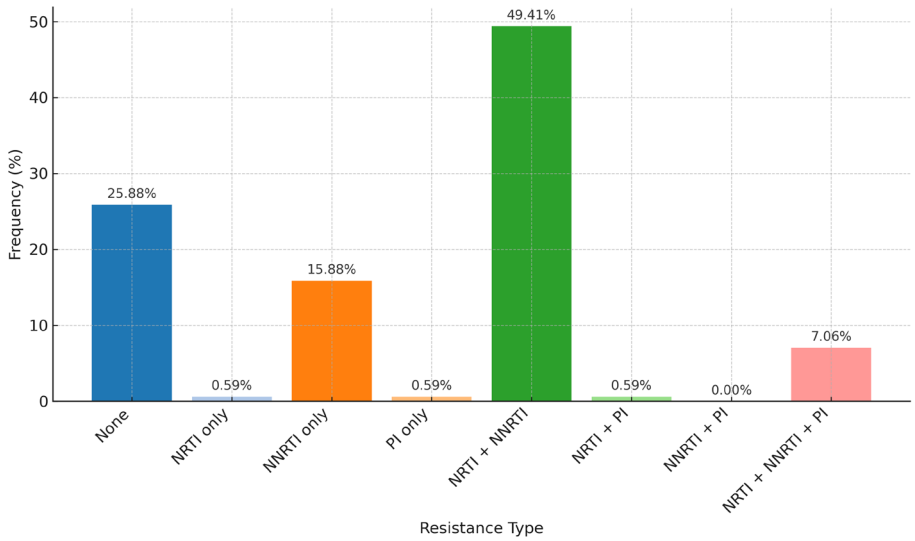

Figure 2. HIV drug resistance patterns.

Table 2. ART regimen following recommendations based on DR test results (*n* = 141)

ART after recommendations	*n*	%
Recommendations followed	114	80.85
Continued the same regimen	63	44.68
Changed key drug	51	36.17
EFV → LPV/r	28	19.86
TDF/3TC/EFV→TDF/3TC/LPV/r	12	8.51
TDF/3TC/EFV→AZT/3TC/LPV/r	14	9.93
AZT/3TC/EFV→TDF/3TC/LPV/r	2	1.42
NVP→ LPV/r	2	1.42
AZT/3TC/NVP→AZT/3TC/LPV/r	1	0.71
AZT/3TC/NVP→TDF/3TC/LPV/r	1	0.71
EFV → DTG	10	7.09
TDF/3TC/EFV→TDF/3TC/DTG	9	6.38
AZT/3TC/EFV→TDF/3TC/DTG	1	0.71
NVP → DTG	3	2.13
AZT/3TC/NVP→TDF/3TC/DTG	3	2.13
LPV/r → DTG	8	5.67
TDF/3TC/LPV/r→TDF/3TC/DTG	7	4.96
AZT/3TC/LPV/r→ TDF/3TC/DTG	1	0.71
Recommendations not followed	27	19.15
Changed to different regimen from recommendations	15	10.64
Continued the same regimen without following recommendations	12	8.51

ART, antiretroviral therapy; DR, drug resistance; EFV, Efavirenz; NVP, Nevirapine; LPV/r, Lopinavir/ritonavir; DTG, Dolutegravir; TDF, Tenofovir disoproxil fumarate; 3TC, Lamivudine; AZT, Zidovudine.

Table 3. Outcomes in different levels of hospitals by following recommendations (*n* = 141)

Level of hospital	Did not follow recommendations	Followed recommendations	Total	*p* value
Provincial hospitals				0.240
Not suppressed	4 (23.53)	7 (12.07)	11 (14.7)	
Suppressed	13 (76.47)	51 (87.93)	64 (85.3)	
District hospitals				0.032
Not suppressed	4 (40.00)	7 (12.50)	11 (16.7)	
Suppresse	6 (60.00)	49 (87.50)	55 (83.3)	

Not suppressed: VL ≥ 1,000 copies/mL; Suppressed: VL < 1,000 copies/mL. Data presented as *n* (%). *P* values from Pearson chi-square test.

Table 4. Univariate and multivariate logistic regression analyses of factors associated with viral load suppression (*n* = 141)

Characteristics	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Following the recommendation				
No	1.0 (Reference)	-	1.0 (Reference)	-
Yes	3.01 (1.11– 8.16)	0.031	3.34 (1.13– 9.86)	0.029
Gender				
Male	1.0 (Reference)	-	1.0 (Reference)	-
Female	1.13 (0.43–2.98)	0.811	1.66 (0.56–4.93)	0.359
Age group				
< 25 years	1.0 (Reference)	-	1.0 (Reference)	-
25–34 years	0.94 (0.24–3.74)	0.935	0.70 (0.14–3.52)	0.667
35–44 years	2.62 (0.73–9.44)	0.141	2.22 (0.57–8.70)	0.253
45–54 years	2.78 (0.58–13.32)	0.202	2.57 (0.48–13.83)	0.272
≥ 55 years	0.94 (0.24–3.74)	0.935	0.70 (0.14–3.52)	0.667
Duration of HIV infection				
< 5 years	1.0 (Reference)	-	1.0 (Reference)	-
5–9 years	1.19 (0.37–3.84)	0.769	0.49 (0.04–6.51)	0.586
≥ 10 years	1.34 (0.47–3.82)	0.587	NA	0.994
Duration of ART				
< 1 year	1.0 (Reference)	-	1.0 (Reference)	-
1–4 years	1.06 (0.20–5.77)	0.945	1.00 (0.16–6.22)	0.999
5–9 years	1.50 (0.23–9.61)	0.669	1.92 (0.08–47.61)	0.689
≥ 10 years	1.27 (0.23–7.16)	0.787	NA	0.994
Hospital level				
District	1.0 (Reference)	-	1.0 (Reference)	-
Provincial	1.16 (0.47–2.89)	0.744	1.33 (0.46–3.87)	0.595

OR, odds ratio; CI, confidence interval; NA, not available due to perfect prediction. Model fit: Pearson χ^2 (59) = 49.91, p = 0.7944.

model was prominent in district-level healthcare facilities where HIV treatment experience, especially experience in managing ART failure, is still limited. Multivariate analysis confirmed that following the recommendations was the only significant factor associated with viral suppression (adjusted OR = 3.34). This supports existing evidence that affordable monitoring technologies are essential for ensuring the effectiveness of limited antiretroviral regimens in resource-limited settings (*5*).

Our study showed a viral suppression rate of 87.72% among patients following centralized DR testing recommendations, compared to 70.37% among those who did not. These results, achieved with a limited budget, are comparable to the following Vietnamese studies. A cross-sectional survey across four provinces found 93% viral suppression among patients on ART for at least one year (*13*). A Hanoi study showed suppression rates above 90% until 42 months on first-line ART (*14*), and research among drug users reported rates as low as 73% (*15*). Earlier evaluations in Ho Chi Minh City found 70% suppression, with viremia associated with prior ART exposure and immunologic failure (*16*). International research suggested that adherence support and prompt action on viral rebound might be more critical than resistance testing in some contexts (*17,18*). However, studies in resource-limited settings indicated that resistance testing improved care outcomes where treatment options were limited (*10*).

The results of our model demonstrated that centralized expertise guiding local treatment decisions significantly improved outcomes even with limited resources and treatment options. Therefore, our model offers a promising approach in Vietnam's evolving healthcare landscape to maximize effectiveness on a minimal budget. In traditional settings, most HIV diagnostic facilities have historically been centralized, requiring specialized infrastructure and trained staff, with laboratories often located far from patients' homes, resulting in high rates of loss to initiation and poor retention in care. This has prompted the need to find alternatives to traditional centralized laboratories, which paradoxically add more cost (*19*).

Our study is particularly timely as Vietnam navigates the challenging transition from international donor funding to domestic financing through SHI. International funding for HIV treatment and prevention has dramatically declined since Vietnam transitioned from a low-income to a lower-middle-income country in 2010, with estimates suggesting that available resources could fall from US$113 million in 2012 to just US$53 million by 2020 (*3,20,21*). This funding gap coincides with increased treatment needs. Mathematical models have projected that the number of people on ART in Vietnam will increase from approximately 98,000 in 2015 to 189,000 by 2030 (*3*). Our centralized-decentralized model offers a potential approach to maximize treatment effectiveness within these resource constraints.

Our findings have several important implications for HIV policy and practice in Vietnam and similar resource-limited settings. First, investment in centralized resistance testing infrastructure, paired with knowledge transfer to decentralized treatment sites, should be encouraged.

Second, the particular value of expert guidance for healthcare facilities with limited HIV treatment experience suggests that implementation should be prioritized for district-level hospitals. Third, meaningful improvements in treatment outcomes are achievable even within the constraints of Vietnam's transitioning financing landscape. These findings highlight the value of targeted interventions to reduce HIV drug resistance, when Vietnam scales up viral load testing and moves toward domestic financing of HIV services (*3,22*).

The study has several limitations. First, as a small pilot in selected healthcare facilities, our findings may not be fully generalizable across all settings in Vietnam. Second, the follow-up period was relatively short, and longer-term outcomes have yet to be evaluated. Third, we did not conduct a comprehensive economic analysis, which would be valuable for policy decisions regarding the nationwide implementation. Fourth, the study did not comprehensively analyze differences in adherence support strategies across study sites, nor did it assess patients' actual treatment adherence — both of which could have influenced treatment outcomes. Nevertheless, as all study sites were part of the public healthcare system, the potential for adherence-related bias may have been partially mitigated through the implementation of a standardized protocol issued by the Vietnam Ministry of Health (*11*). However, future studies should examine adherence-related factors more thoroughly to gain a deeper understanding of their impact on treatment effectiveness.

Future research should examine the cost-effectiveness of this approach within the SHI financing framework and explore adaptations to reach key populations who may face barriers to accessing facility-based care. The integration of point-of-care testing with centralized resistance monitoring could address the "total coverage model", which ensures access for the entire national population.

Conclusion

Our model in Northern Vietnam demonstrated significant clinical benefit with substantially higher viral suppression rates among patients who followed the recommendations. This effect was particularly pronounced in non-specialized HIV treatment centers. These findings support the expansion of our model to strengthen HIV treatment capacity across the whole country.

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Assessing the sufficiency of patient information transfer from hospitals to psychiatric home-visit nurses: A nationwide cross-sectional survey

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Abstract: Effective information transfer from hospitals to psychiatric home-visit nurses is essential for ensuring continuity of care. However, previous studies have suggested that discharge information is often inadequate, particularly regarding the psychosocial aspects of patient care. This study assessed home-visit nurses' subjective evaluations of the adequacy of patient information provided by hospitals in psychiatric home-visit nursing. A nationwide cross-sectional survey was distributed to 2,000 home-visit nursing agencies across Japan, yielding 482 responses. After excluding one invalid response, 481 responses were analyzed (response rate: 8.0%). The sufficiency of patient information was calculated as the logarithm of the ratio between the information received and the information requested by nurses. Wilcoxon signed-rank tests confirmed that all gaps between the information received and requested were significant ($p < 0.001$). The information that was least adequately provided included "psychological test results" (mean adequacy score = −0.23, SD = 0.28), "signs of worsening psychiatric symptoms" (mean adequacy score = −0.21, SD = 0.23), and "coping strategies for psychiatric symptoms" (mean adequacy score = −0.21, SD = 0.23). The information that was most adequately provided was "prescription details" (mean adequacy score = −0.07, SD = 0.16) and "diagnosis" (mean adequacy score = −0.09, SD = 0.18). To enhance information transfer, hospitals should review and revise discharge summaries to ensure the inclusion of critical items with low adequacy scores.

Keywords: psychiatric home-visit nursing, community care, psychiatric nursing, patient information, discharge planning

Introduction

In Japan's mental health and welfare system, a reform vision titled "From Hospital-Based Care to Community-Based Living" was introduced in 2004 (*1*). Since the 2017 discussion on the "Future Directions for Mental Health and Welfare", efforts to build a "Comprehensive Community Care System Including Support for Mental Disorders" have been actively promoted (*2*). One of the key community support services for individuals with mental illnesses — psychiatric home-visit nursing — has been shown to prevent re-hospitalization (*3,4*), shorten hospital stays (*5,6*), and improve daily functioning (*7*). From 2011 to 2021, the number of patients receiving psychiatric home-visit nursing services increased from 7,651 to 51,420 (*8*). Among these patients, the majority had a history of multiple hospitalizations, with many having been admitted three to ten times (*9*). This suggests that psychiatric home-visit nursing is primarily introduced for patients who experience repeated hospital admissions and discharges, underscoring its critical role in supporting community-based care and preventing re-hospitalization. The proportion of home-visit nursing agencies providing psychiatric home-visit services also steadily increased, from 35.5% in 2006 to 58.3% in 2016 (*10*). According to Setoya *et al*., home-visit nursing agencies providing psychiatric home-visit nursing vary in their affiliation and structure. In home-visit nursing agencies, where more than 80% of patients have mental disorders, there is a particularly strong need for a well-structured regional collaboration system and the development of a strong networking foundation (*11*).

Psychiatric home-visit nurses primarily receive patient information through discharge summaries and discharge conferences with hospital staff; however, approximately 50% of them reported that the quality of hospital information received was insufficient (*12*). Therefore, this study aimed to clarify the subjective evaluations of home-visit nurses regarding the adequacy of patient information provided by hospitals in

psychiatric home-visit nursing. This study also sought to improve the quality of information transmission from hospitals to home-visit nurses.

Methods

Study design

A cross-sectional questionnaire survey was conducted between January 11 and 31, 2023.

Participants

The study targeted nurses and assistant nurses engaged in psychiatric home-visit nursing.

Participant selection method

Home-visit nursing agencies were selected from designated psychiatric outpatient care agencies providing independent support for medical care in the most populous city of each of Japan's 47 prefectures. The population ratios of these 47 cities were calculated, and 2,000 agencies were randomly selected in proportion to the population of each city using a random number generator. From each selected agency, three psychiatric home-visit nurses were invited to participate, with selections based on the alphabetical order of their surnames.

Data collection method

A written request for research cooperation was sent to the administrators of the home-visit nursing agencies. The administrators were asked to distribute cooperative request documents to eligible psychiatric home-visit nurses in their agencies. Participants who agreed to participate accessed the questionnaire *via* the QR code provided in the document (Google Forms). All responses were mandatory in order to prevent missing data.

Survey items

The survey items comprised basic attributes and questions regarding patient information transmission between psychiatric hospitals and home-visit nurses.

Basic attributes

Participants were asked to provide information on the following: age, gender, years of experience as a nurse, experience working in a psychiatric hospital, years of psychiatric nursing experience, years of home-visit nursing experience, years of psychiatric home-visit nursing experience, proportion of psychiatric home-visit nursing in overall work (0%–25%, 25%–50%, 50%–75%, 75%–100%), highest level of nursing education (high school nursing program, vocational school, university, graduate school), and nursing qualifications (registered nurse, licensed practical nurse, certified nurse specialist, certified nurse).

Information transmission from hospitals

A questionnaire was developed based on an interview survey conducted by Takashima *et al*. with psychiatric home-visit nurses with over five years of experience regarding the information they require from psychiatric hospital nurses (*13*). A pre-test was conducted with 20 psychiatric home-visit nurses to assess the clarity of the questions and ceiling/floor effects, resulting in the finalization of 32 questions.

Participants were asked two key questions for each item using a 7-point Likert scale (1 = strongly disagree to 7 = strongly agree) on Google Forms: *i*) "Do you need this information from hospitals?" and *ii*) "Do you receive sufficient information from hospitals?"

"Patient Information Required by Psychiatric Home-Visit Nurses from Hospitals" was defined as the information psychiatric home-visit nurses need from hospitals, while "Patient Information Received by Psychiatric Home-Visit Nurses from Hospitals" was defined as the information actually provided by hospitals to psychiatric home-visit nurses.

Data analysis method

Analysis of basic attributes

Descriptive statistics were used to confirm the response status of participants' basic attributes. Mean values were presented along with standard deviations (± SD).

Comparison of "Patient Information Required by Psychiatric Home-Visit Nurses from Hospitals" and "Patient Information Received by Psychiatric Home-Visit Nurses from Hospitals"

A simple tabulation was conducted to compare the information needs and supply. Means, standard deviations, medians, and interquartile ranges were calculated. The Kolmogorov-Smirnov test was used to assess normality. The Wilcoxon signed-rank test was used to compare "Patient Information Required by Psychiatric Home-Visit Nurses from Hospitals" and "Patient Information Received by Psychiatric Home-Visit Nurses from Hospitals", and the effect size (r) was calculated. Effect sizes were interpreted using Cohen's criteria: $r = 0.10$ for small, $r = 0.30$ for medium, and $r = 0.50$ for large effects (*14*). The significance level was set at 0.05, and the Bonferroni correction was applied ($\alpha = 0.05/32 = 0.00156$) to account for multiple comparisons. All statistical analyses were performed using SPSS version 29.0.

Adequacy of patient information

The adequacy of patient information was calculated as the logarithm of the ratio of the "Patient Information Received by Psychiatric Home-Visit Nurses from Hospitals" to the "Patient Information Required by Psychiatric Home-Visit Nurses from Hospitals" using the following formula:

Adequacy of Patient Information =

$$\log_{10} \frac{\text{Patient Information Received by Psychiatric Home–Visit Nurses from Hospitals}}{\text{Patient Information Required by Psychiatric Home–Visit Nurses from Hospitals}}$$

When the required and received information were balanced, the adequacy value was 0. The values ranged from a minimum of -0.85 to a maximum of 0.85. A simple tabulation was conducted to analyze the adequacy of the patient information.

Ethical considerations

This study was approved by the Research Ethics Committee of BAIKA Women's University (Approval Number: 2022-0226), the first author's previous affiliation. The study was designed and initiated while the first author was affiliated with BAIKA Women's University. Participation was voluntary and the protection of private information and strict data handling were guaranteed. The participants provided consent by checking the research consent box in the questionnaire. To protect participants' privacy, the survey was designed to avoid the collection of personally identifiable information (*e.g.*, email and IP addresses).

Results and Discussion

Analysis of basic attributes

The questionnaire was distributed to 2,000 home-visit nursing agencies. From each selected agency, three psychiatric home-visit nurses were invited to participate in the survey, resulting in responses from 482 participants. After excluding one response due to abnormal attribute data, 481 responses were included in the analysis (response rate, 8.0%). The mean (± SD) years of nursing experience, psychiatric hospital experience, and home-visit nursing experience were 20.4 ± 9.6, 3.2 ± 6.4, and 6.9 ± 6.1 years, respectively. The mean (± SD) age of participants was 45.1 ± 15.5 years, which was 3.8 years higher than the national average age of nursing staff in Japan (41.3 years). Similarly, the average years of nursing experience among the participants exceeded the national average of 17.8 years by 2.6 years (*15*).

The distribution of participants by gender was as follows: 424 (88.2%) women, 55 (11.4%) men, and one (0.2%) each identifying as "other" or preferring not to answer. The proportion of psychiatric home-visit nursing services varied among the participants: 298 (62.0%) engaged in psychiatric home-visit nursing less than 25% of the time, 37 (7.7%) between 25% and 50%, 25 (5.2%) between 50% and 75%, and 121 (25.1%) more than 75% (Table 1).

Given the standard deviations observed in this study, these differences were not considered significant enough to undermine the representativeness of the study sample. Regarding gender distribution, 11.4% of the participants were men, compared to 9.1% of men nurses in Japanese home-visit nursing agencies (*16*), reflecting a difference of 2.3%. Among the 482 participants in this study, this difference corresponded to approximately 11.2 individuals, which was unlikely to substantially impact the overall analysis. Therefore, the sample characteristics in this study can be considered reasonably representative of the broader population of psychiatric home-visit nurses.

Comparison of "Patient Information Required by Psychiatric Home-Visit Nurses from Hospitals" and "Patient Information Received by Psychiatric Home-Visit Nurses from Hospitals"

The Kolmogorov-Smirnov test indicated significant differences for all items. In all areas, patient information needed from hospitals received significantly stronger agreement than information actually received from hospitals ($p < 0.001$). After applying the Bonferroni correction for multiple comparisons (adjusted significance level: $p < 0.00156$), all results remained statistically significant. Effect sizes (r) ranged from 0.46 to 0.73. Twenty-nine of the 30 items showed effect sizes greater than 0.5, indicating large effects. Only

Table 1. Participants' demographic characteristics (n = 481)

Characteristic	Mean	SD
Age	45.1	15.5
Years of nursing experience	20.4	9.6
Years of psychiatric hospital experience	3.2	6.4
Years of psychiatric nursing experience	6.5	7.1
Years of home-visit nursing experience	6.9	6.1
	n	%
Gender		
Women	424	88.2
Men	55	11.4
Preferring not to answer	1	0.2
Other	1	0.2
Nursing qualifications		
Registered Nurse	461	95.8
Licensed Practical Nurse	14	2.9
Certified Nurse Specialist	1	0.3
Certified Nurse	5	1.0
Education level		
Vocational school	360	74.8
University	87	18.0
High school (nursing program)	26	5.4
Graduate school	8	1.6
Proportion of psychiatric home-visit nursing among all home-visit nursing services		
0–25	298	62.0
25–50	37	7.7
50–75	25	5.2
75–100	121	25.1

"prescription details" had an effect size below 0.5 (r = 0.46), suggesting a medium effect. The six items with the largest effect sizes were: "Signs of worsening psychiatric symptoms" (r = 0.73), "Family relationships and support system" (r = 0.73), "Coping strategies for psychiatric symptoms" (r = 0.72), "Life skills and strengths" (r = 0.72), "Interpersonal relationships" (r = 0.71), and "Hopes for life after discharge" (r = 0.70) (Table 2).

A significant difference was observed between hospitals' information needs and the information actually received across all items. Similarly, Kato's (*17*) study on discrepancies in information transmission between hospitals and home-visit nurses reported that home-visit nurses perceived a lack of information on all surveyed items. This finding aligns with that of the present study, indicating that insufficient information transmission is prevalent among psychiatric home-visit nurses.

Adequacy of patient information

The adequacy of patient information and the difference between the patient information needed from hospitals and what was actually received is shown in Table 2. The items with the lowest adequacy scores included "psychological test results" (mean adequacy score = −0.23, SD = 0.28), "signs of worsening psychiatric symptoms" (mean adequacy score = −0.21, SD = 0.23), "coping strategies for psychiatric symptoms" (mean adequacy score = −0.21, SD = 0.23), "life skills and strengths" (mean adequacy score = −0.21, SD = 0.23), "hopes for life after discharge" (mean adequacy score = −0.20, SD = 0.24), "prediction of life after discharge" (mean adequacy score = −0.20, SD = 0.24), "family relationships and support system" (mean adequacy score = −0.19, SD = 0.22), "interpersonal relationships" (mean adequacy score = −0.19, SD = 0.22), "primary physician's assessment and future predictions" (mean adequacy score = −0.19, SD = 0.23) and "characteristics of thoughts and behaviors" (mean adequacy score = −0.19, SD = 0.23). The item with the most balanced adequacy score, closest to zero, was "prescription details" (mean adequacy score = −0.07, SD = 0.16) followed by "diagnosis" (mean adequacy score = −0.07, SD = 0.16). These findings suggest that hospital discharge summaries frequently omit psychosocial details critical to continuity of care in psychiatric home-visit nursing.

Psychiatric home-visit nurses often face difficulties in assessing the daily lives of patients outside their visits (*18*). Therefore, they sought information from hospitals regarding "life skills and strengths", "signs of worsening psychiatric symptoms", "coping strategies for psychiatric symptoms", "prediction of life after discharge", "hopes for life after discharge", and "interpersonal relationships". Receiving such information enables nurses to assess psychiatric symptoms based on the patient's lifestyle during the initial stages of home-visit nursing.

A study by Setoya *et al.* identified the most common challenges in psychiatric home-visit nursing as "refusal of care by patients or families" (56.3%), "management of psychiatric symptoms" (54.0%), and "assessment of psychiatric symptoms" (49.1%) (*11*). Receiving information on "patients' perceptions of home-visit nursing" and "family relationships and support systems" may assist in assessing the risk of care refusal and aid in decision-making for home-visit nursing interventions. Additionally, providing psychiatric home-visit nurses with information on "signs of worsening psychiatric symptoms" and "coping strategies for psychiatric symptoms" from hospitals may alleviate the challenges in psychiatric home-visit nursing and improve the quality of psychiatric symptom management. Meanwhile, "prescription details" and "diagnosis" were among the most balanced items in terms of information adequacy.

Enhancing collaboration between hospitals and psychiatric home-visit nursing services

When transmitting patient information from hospitals to psychiatric home-visit nurses, it is essential to actively provide information in areas with low adequacy scores. The satisfaction of psychiatric home-visit nurses with information provision was significantly influenced by the quality of the information they receive (*12*). To improve the quality of information transmission, hospitals should review and revise their discharge summaries to ensure that items with low adequacy are included. Schwarz *et al.* highlighted the benefits of tailored discharge summaries in improving patient safety and health literacy (*19*). These findings support the conclusions of the present study.

Implications and future research

This study underscores the need to improve the quality and quantity of patient information transferred from hospitals to psychiatric home-visit nurses, particularly regarding psychosocial care aspects. The findings can inform the development of standardized discharge summary formats or checklists to ensure the inclusion of information essential to community-based psychiatric nurses. Such tools could strengthen collaboration between hospital and community settings, thereby enhancing the continuity and quality of mental health care.

Research limitations

This study was limited to the most populous cities in the 47 prefectures of Japan. In less populated areas, the number of home-visit nursing agencies and hospitals is limited, which may restrict information exchanges between them.

Conclusion

A survey on information provision between hospitals

Table 2. Adequacy of patient information and comparison of information required by psychiatric home-visit nurses and information actually received from hospitals

Items	Patient Information Required by Psychiatric Home-Visit Nurses from Hospitals			Patient Information Received by Psychiatric Home-Visit Nurses from Hospitals				Effect size (*r*)	Adequacy of Patient Information	
	Mean	SD	Median (IQR)	Mean	SD	Median (IQR)	*p*		Mean	SD
Psychological test results	4.7	1.7	4 (4−6)	3.0	1.6	3 (1−4)	***	0.65	−0.23	0.28
Signs of worsening psychiatric symptoms	6.0	1.5	7 (5−7)	3.9	1.5	4 (3−5)	***	0.73	−0.21	0.23
Coping strategies for psychiatric symptoms	5.9	1.5	7 (5−7)	3.9	1.6	4 (3−5)	***	0.72	−0.21	0.23
Life skills and strengths	5.6	1.6	6 (4−7)	3.6	1.6	4 (2−5)	**	0.72	−0.21	0.23
Hopes for life after discharge	5.7	1.6	6 (5−7)	3.8	1.5	4 (3−5)	***	0.70	−0.20	0.24
Prediction of life after discharge	5.4	1.7	6 (4−7)	3.6	1.5	4 (2−5)	***	0.69	−0.20	0.24
Family relationships and support systems	5.9	1.5	7 (5−7)	4.0	1.5	4 (3−5)	***	0.73	−0.19	0.21
Interpersonal relationships	5.6	1.6	6 (5−7)	3.8	1.5	4 (3−5)	***	0.71	−0.19	0.22
Primary physician's assessment and future predictions	5.7	1.5	6 (5−7)	3.9	1.5	4 (3−5)	***	0.69	−0.19	0.23
Characteristics of thoughts and behaviors	5.6	1.6	6 (5−7)	3.8	1.5	4 (3−5)	***	0.69	−0.19	0.24
Troubles with previous home-visit nursing agencies	5.7	1.6	6 (5−7)	3.9	1.6	4 (3−5)	***	0.69	−0.19	0.23
Personalities, interests, and concerns	5.5	1.7	6 (4−7)	3.7	1.5	4 (3−5)	***	0.69	−0.19	0.24
Nursing care that hospital nurses want to be continued in home-visit nursing	5.6	1.6	6 (4−-7)	3.9	1.6	4 (3−5)	***	0.69	−0.19	0.24
History of upbringing related to the disease	5.6	1.6	6 (5−7)	3.8	1.5	4 (3−5)	**	0.68	−0.19	0.24
History of discontinuing home-visit nursing	5.5	1.7	6 (4−7)	3.8	1.6	4 (3−5)	***	0.67	−0.19	0.24
Awareness of the disease	5.7	1.6	6 (5−7)	3.9	1.6	4 (3−5)	***	0.69	−0.18	0.23
Awareness of medication treatment	5.8	1.6	6 (5−7)	4.0	1.6	4 (3−5)	***	0.69	−0.18	0.22
Nursing care for physical comorbidities	5.7	1.5	6 (5−7)	4.0	1.5	4 (3−5)	***	0.68	−0.18	0.22
Clinical test data	5.4	1.7	6 (4−7)	3.7	1.7	4 (3−5)	***	0.66	−0.18	0.25
Patients' perceptions of home-visit nursing	5.4	1.6	6 (4−7)	3.7	1.6	4 (3−5)	***	0.65	−0.18	0.24
Use of social resources	5.6	1.6	6 (4−7)	4.0	1.7	4 (3−5)	***	0.69	−0.17	0.21
Awareness of inpatient treatment	5.6	1.6	6 (5−7)	3.9	1.6	4 (3−5)	***	0.66	−0.17	0.23
Progress since the onset of the disease	5.7	1.5	6 (5−7)	4.1	1.6	4 (3−5)	***	0.67	−0.16	0.21
Self-care	5.6	1.6	6 (4−7)	4.0	1.5	4 (3−5)	***	0.67	−0.16	0.20
Time of onset and episodes at onset	5.6	1.6	6 (4−7)	4.0	1.5	4 (3−5)	***	0.67	−0.16	0.22
Life in the hospital ward	5.5	1.6	6 (4−7)	4.0	1.6	4 (3−5)	***	0.65	−0.16	0.21
Reasons and circumstances leading to hospitalization	5.9	1.4	7 (5−7)	4.4	1.7	4 (3-6)	***	0.67	−0.15	0.20
Episodes of harm to others	6.0	1.5	7 (5−7)	4.4	1.6	4 (3-6)	***	0.66	−0.15	0.21
Physical comorbidities	5.7	1.5	6 (5−7)	4.3	1.5	4 (3-5)	***	0.66	−0.14	0.19
Treatment details during hospitalization	5.7	1.5	6 (5−7)	4.4	1.6	4 (3-6)	***	0.63	−0.13	0.19
Diagnosis	5.8	1.5	7 (5−7)	4.8	1.6	5 (4-6)	***	0.53	−0.09	0.18
Prescription details	5.7	1.5	6 (5−7)	5.0	1.5	5 (4-6)	***	0.46	−0.07	0.16

The Wilcoxon signed-rank test was employed to compare the ratings of information needed from hospitals versus information received. The effect size (*r*) was calculated for each item. The standard significance level was set at 0.05 (***$p < 0.001$), and the Bonferroni-corrected significance threshold was $p < 0.00156$. Participants rated two items per question using a 7-point Likert scale (1 = strongly disagree to 7 = strongly agree): *i*) "Do you need this information from hospitals?" and *ii*) "Do you receive sufficient information from hospitals?". The adequacy of patient information was calculated as: Adequacy of Patient Information = $\log_{10}$ (Patient Information Received by Psychiatric Home-Visit Nurses from hospitals/ Patient Information Required by Psychiatric Home-Visit Nurses from Hospitals). A value of 0 indicates balance between required and received information. Values ranged from -0.85 to 0.85, and simple tabulation was used to analyze the distribution of information adequacy.

and psychiatric home-visit nurses revealed significant discrepancies between the information needed by home-visit nurses and the information actually received across all assessed categories. In particular, there was a notable lack of information regarding "psychological test results", "signs of worsening psychiatric symptoms", "coping strategies for psychiatric symptoms", "life skills and strengths", and "hopes for life after discharge". These findings highlight the need to improve the provision of this specific type of information to enhance the quality of psychiatric home-visit nursing services and ensure better continuity of care.

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Factors related to feelings toward nursing practices for foreign pregnant and postpartum residents among midwives and nurses at perinatal medical centers in Osaka, Japan: A questionnaire survey

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Abstract: The number of foreign residents in Japan continues to increase, and many are of reproductive age. Foreign residents report many difficulties when receiving nursing care. Midwives and nurses also experience negative feelings about nursing care for foreigners. This study clarified the factors related to feelings toward nursing practices for foreign pregnant and postpartum residents among midwives and nurses at perinatal medical centers in Osaka, Japan. A web-based survey was conducted from 1 October to 31 December 2023. A research request form was distributed to 309 midwives and nurses working at nine perinatal medical centers in Osaka. Data for 82 participants were analyzed (response rate: 26.5%). The mean age was 35.7 ± 10.6 years; 76 participants (92.7%) were midwives. Logistic regression analysis was conducted to examine associations between several factors and the proportion of participants scoring above the median on each feeling. Participants with poor English-language skills reported significantly more frustration (multivariable-adjusted odds ratios [ORs] and 95% confidence intervals [CIs] for above-median scoring: 3.16 [1.03–9.66]). Participants who had not attended workshops on nursing care for foreign residents experienced more difficulty (OR: 4.60; 95% CI: 1.32–16.01), helplessness (OR: 4.39; 95% CI: 1.28–15.04), and uncertainty (OR: 5.29; 95% CI: 1.52–18.43). To reduce feelings of difficulty and increase positivity in providing nursing care to foreign residents with different languages, cultures, and customs, it is important to improve cross-cultural competency. Education programs, especially web-based interventions and individualized education programs that include workshops on cross-cultural competence, could be effective.

***Keywords*:** Immigrants, non-Japanese residents, emotions, midwifery, healthcare worker

Introduction

The number of foreign residents in Japan continues to increase. As of June 2024, there were approximately 3.58 million foreign residents in Japan, a 5.2% increase over the previous year and a record high (*1,2*). Approximately 85% of Asian foreign residents are from China, Vietnam, Korea, or the Philippines, in that order; many are in their 20s and 30s and are thus of reproductive age (*2*). Osaka Prefecture has the third highest number of foreign residents in Japan (*1*), so many foreign pregnant and postpartum women visit the obstetric outpatient departments at medical centers in Osaka.

Previous studies (*3-5*) have reported on various difficulties experienced by foreigners when receiving healthcare in other countries, including language barriers and cultural differences. Language barriers negatively affect patient outcomes, and linguistic assistance is essential for adequate healthcare provision (*4*). The increased susceptibility of migrant women to poor perinatal outcomes is associated with socioeconomic instability, limited healthcare access, and cultural and linguistic barriers (*5,6*). Hospitals and healthcare professionals can be rather reluctant to accept foreign patients because of difficulties providing translation services and culturally diverse care, lack of sufficient staff owing to increasing numbers of Japanese patients, and other reasons (*7*). Previous studies have found that the two main areas of difficulty for nurses providing care to immigrants are communication and cultural differences (*8-10*). There is also evidence that cultural differences are a major obstacle in the delivery of nursing services (*11*). Additionally, a previous study suggested that cultural differences and language barriers are factors that affect work experience (*10*). Effective communication between patients and healthcare

professionals is essential for the provision of safe, high-quality care (*8*); however, many immigrants from Asian countries experience communication challenges because they do not have native language skills in either Japanese or English.

In a previous study, we found that midwives experienced negative feelings such as frustration and helplessness when trying to convey their meaning, and difficulties making themselves understood, when explaining concepts and providing health guidance to foreign mothers at a perinatal medical center in Japan (*12*).

Although there are clearly challenges for both patients and healthcare providers in the provision of nursing care for foreign patients, there have been no studies focusing on the feelings of midwives and nurses when providing nursing care to foreign patients. Therefore, the purpose of this study was to identify factors related to feelings toward nursing practices for foreign pregnant and postpartum residents among midwives and nurses at perinatal medical centers in Osaka, Japan.

Materials and Methods

Study participants and procedure

This web-based questionnaire survey was conducted from 1 October to 31 December 2023. The questionnaire was originally developed by our research team from several references (*9,10,12-15*). Target participants were all midwives and nurses working in obstetric wards at 23 perinatal medical centers in Osaka, Japan. A research request form was distributed to 309 midwives and nurses working at nine perinatal medical centers in Osaka where research was permitted. In total, 93 (30.1%) midwives and nurses agreed to participate in the survey. After excluding 9 participants with missing data, a total of 82 (26.5%) midwives and nurses were included in the analysis.

Feelings toward nursing practices for foreign pregnant and postpartum residents among midwives and nurses: Outcomes

Feelings toward nursing practice for foreign pregnant and postpartum residents among midwives and nurses were assessed using the following five items: feelings of frustration at not being able to convey their meaning (frustration), a sense of difficulty in making themselves understood (difficulty), feelings of helplessness when trying to communicate explanations (helplessness), feelings of uncertainty about whether they are being understood (uncertainty), and feelings of satisfaction in providing nursing care to foreigners (satisfaction). Responses were on a visual analog scale.

Exposure factors and potential confounding factors

The following demographic information was obtained using a web-based, self-administered questionnaire: age, midwifery and nursing work experience (cumulative), type of certification (midwife or nurse), educational background (graduate school, university, junior college, or vocational school), number of experienced nurses to foreign patients (cumulative), self-reported English-language level (able to use medical terms, able to hold daily conversations, able to communicate using gestures and simple words, unable to communicate in English at all), foreign language learning experience (presence or absence), global nursing study experience as a student (presence or absence), and participation in workshops on nursing care for foreign residents as a midwife or a nurse (presence or absence).

Statistical analysis

Descriptive statistics were calculated for all data collected. The normality of continuous data was confirmed using the Shapiro–Wilk test, and these data were presented as mean (standard deviation), or median (interquartile range; IQR). Continuous data were classified into two groups according to the median because of the non-normal distribution. The visual analog scale scores for feelings were also non-normally distributed; therefore, the median was calculated and analyzed separately for two groups: those scoring above and those scoring below the median. Differences in demographic characteristics and feelings toward nursing practice for foreign pregnant and postpartum residents were analyzed using the chi-squared test and shown as percentages. Logistic regression models were used to estimate the multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of each factor (response variable: 1 = the feelings score is above the median, 0 = the feelings score is below the median). Work experience (> 9.5 years or ≤ 9.5 years), number of experienced nurses to foreign patients (≥ 31 or ≤ 30), English level (very good/good/average or poor), and participation in workshops on nursing care for foreign residents (presence or absence) were included in the model. All data were analyzed using SPSS statistical software version 27 for Windows (IBM SPSS Japan, Tokyo, Japan). All reported *p*-values were two-tailed, and values < 0.05 were considered statistically significant.

Ethical considerations

The study protocol was prepared in accordance with the Declaration of Helsinki and was approved by the Institutional Review Boards of Osaka Metropolitan University (date of approval: 27 September 2023; approval no. 2023-38). Informed consent was obtained from all participants whose data were included in the study.

Results and Discussion

Participant characteristics and feelings toward nursing practice for foreign pregnant and postpartum residents

A total of 82 midwives and nurses completed the survey (response rate: 26.5%). Descriptive data for the demographic characteristics of participants in this study are shown in Table 1. The mean age was 35.7 ± 10.6 years, the median (IQR) years of midwifery and nursing experience was 9.50 (4.00–20.25) years. Most participants were midwives (92.7%); four had attended graduate school (4.9%) and 37 (45.1%) had attended university. More than half of participants (56.1%) had experience in providing nursing care to foreign pregnant and postpartum residents aged under 30 years. A total of 37 participants (45.1%) had foreign language learning experience and 62 (75.6%) self-reported very good, good, or average English-language skills. Only 24 participants (29.3%) had had global nursing study experience as a student, and 19 (23.2%) had participated in workshops on nursing care for foreign residents.

Table 2 shows the scores for feelings toward nursing practice for foreign pregnant and postpartum residents among midwives and nurses. The highest score (median [IQR]) was for frustration (87.00 [77.00–97.25]). The next highest scores were for difficulty (80.00 [71.75–95.25]), helplessness (79.00 [60.00–88.50]), and uncertainty (68.50 [52.00–85.25]). The lowest score was for satisfaction (52.00 [39.00–70.25]).

Previous studies (*3-12*) have shown that the main challenges experienced by medical professionals in providing nursing care to foreign residents are differences in language and cultural values. Of these, language is reportedly the greatest challenge for nurses who provide medical care to foreign patients (*13*). Most of our participants could communicate in English using gestures and simple words. However, almost all the foreign residents in Japan are from Asia and are not native speakers of either Japanese or English (*2,14,15*). Therefore, communicating in a language in which both parties are not native speakers can lead to difficulty and anxiety. Of participants' reported feelings, the highest scores were for frustration. The field of obstetrics is unique in that care for deliveries must be provided 24 hours a day, 365 days a year. Additionally, in many deliveries, the health and mortality risk of mothers and children are directly related. Although it is desirable to have interpreters available 24 hours a day in obstetrics departments, where emergencies often occur and medical explanations are required, many facilities (even perinatal medical centers) do not have them (*14*). Even though many foreign residents from Asia are not native English speakers, healthcare personnel in Japan often use simple English words when communicating with them. Although it is difficult for midwives and nurses to develop high proficiency in another language, it is likely that learning English vocabulary commonly used in daily nursing would help to reduce frustration and improve communication even with patients who are not native English speakers.

Table 1. Demographic characteristics among midwives and nurses (*n* = 82)

Characteristics	Mean ± SD M (IQR)
Age, years	35.7 ± 10.6 33.00 (26.00–45.25)[a]
Work experience, years (cumulative)	12.39 ± 9.64 9.50 (4.00–20.25)[a]
	***n* (%)**
Type of certification, %	
Midwife	76 (92.7)[b]
Nurse	6 (7.3)
Educational background, %	
Graduate school	4 (4.9)
University	37 (45.1)
Junior college	6 (7.3)
Vocational school	35 (42.7)
Number of foreign patients (cumulative)	
1–10	17 (20.7)
11–30	29 (35.4)
31–50	21 (25.6)
51–100	7 (8.5)
> 100	8 (9.8)
Self-reported English-language level, %	
Able to use medical terms: very good	1 (1.2)
Daily conversation is possible: good	2 (2.4)
Able to use gestures and simple words: average	59 (72.0)
Unable to communicate in English at all: poor	20 (24.4)
Foreign language learning experience: presence, %	37 (45.1)
Global nursing study experience as a student: presence, %	24 (29.3)
Participation in workshops on foreign patient nursing as a midwife or nurse: presence, %	19 (23.2)

SD: standard deviation; M: median; IQR: interquartile range. [a]The Shapiro–Wilk test was used to confirm the normality of continuous data, which are presented as median (interquartile range). [b]Dichotomous and categorical data are presented as number (percentage).

Table 2. Feelings toward nursing practice for foreign pregnant and postpartum residents among midwives and nurses (*n* = 82)

Feelings[a]	M (IQR)[b]
Frustration	87.00 (77.00–97.25)
Difficulty	80.00 (71.75–95.25)
Helplessness	79.00 (60.00–88.50)
Uncertainty	68.50 (52.00–85.25)
Satisfaction	52.00 (39.00–70.25)[c]

M: median; IQR: interquartile range. [a]The scores on feelings toward nursing practice for foreign pregnant and postpartum residents were evaluated using a visual analog scale (range: 0–100). [b]The Shapiro–Wilk test was used to confirm the normality of continuous data, which are presented as median (IQR). [c]Normal distribution.

Factors related to feelings toward nursing practice for foreign pregnant and postpartum residents among midwives and nurses

Table 3 shows the differences in demographic characteristics and feelings toward nursing practice for foreign pregnant and postpartum residents among midwives and nurses, along with the multivariable-adjusted ORs and 95% CIs for each factor (response variable: 1 = feelings score above the median, 0 = feelings score below the median). The table shows the associations between several factors and the proportion of participants scoring above the median for each assessed feeling.

Participants with poor English-language skills experienced significantly higher frustration ($p = 0.029$). Having experience of nursing more than 31 foreign patients and lack of participation in workshops on nursing care for foreign residents were significantly associated with greater difficulty ($p = 0.048$, $p = 0.025$, respectively). Lack of participation in workshops on nursing care for foreign residents was significantly associated with greater helplessness ($p = 0.008$) and uncertainty ($p = 0.004$). Finally, participants with less than 9.5 years of midwifery and nursing experience and those who had experience learning a foreign language experienced significantly greater satisfaction ($p = 0.015$, $p = 0.016$, respectively).

After adjustment for work experience (> 9.5 years or ≤ 9.5 years), number of foreign patients nursed (≥ 31 or ≤ 30), English-language level (very good/good/average or poor), and participation in workshops on nursing care for foreign residents (presence or absence), the multivariable-adjusted ORs and 95% CIs for scoring above the median on frustration were 3.16 (1.03–9.66) for participants with poor English-language level (*vs.* very good/good/average). The multivariable-adjusted ORs and 95% CIs for scoring above the median on difficulty were 0.30 (0.11–0.83) for participants with ≤ 30 years of experience nursing foreign patients (*vs.* ≥ 31) and 4.60 (1.32–16.01) for those who had not attended workshops on nursing care for foreign residents (*vs.* presence). The multivariable-adjusted ORs and 95% CIs for scoring above the median on helplessness were 4.39 (1.28–15.04) for participants who had not attended workshops on nursing care for foreign residents (*vs.* presence), and the multivariable-adjusted ORs and 95% CIs for scoring above the median on uncertainty were 5.29 (1.52–18.43) for those who had not attended workshops on nursing care for foreign residents (*vs.* presence). Finally, the multivariable-adjusted ORs and 95% CIs for scoring above the median on satisfaction were 3.17 (1.25–8.04) for participants with ≤ 9.5 years of nursing experience (*vs.* > 9.5).

A previous review study identified a communication barrier between patients and healthcare workers who demonstrate low cultural competency (*10*). A key way of reducing the sense of difficulty and increasing positive feelings in practicing nursing care for foreign pregnant women and postpartum mothers with different languages, cultures, and customs is to improve cross-cultural competency. Such competency is generally defined as "the ability to work and communicate effectively and appropriately with people from culturally different backgrounds" (*16*). The development of cross-cultural competency in healthcare professionals is a useful strategy for reducing cultural disparities in healthcare. Conceptualizations of cultural competence refer to the attitudes, knowledge, and skills of professionals when working with culturally diverse populations (*17*). Cross-cultural competence is also considered essential in understanding the client's cultural context and delivering effective and culturally responsive services to diverse clients (*18*). A previous study suggested that cross-cultural competency is associated with experiences of travel abroad, foreign language skills, and training in intercultural care, and that learning about cross-cultural care is necessary to improve the cross-cultural competency of healthcare professionals (*19*). Thus, learning opportunities to improve foreign language proficiency and cross-cultural competence are important for midwives and nurses.

In our previous study (*14*), the respondents wanted more learning opportunities in foreign nursing to improve their nursing practice with foreign pregnant women and postpartum mothers; such opportunities are effective in improving cross-cultural competence. It is possible that greater cross-cultural competence and confidence in nursing foreign patients would increase the positive experiences of nurses and midwives. In one previous study of nurses in Japan, only 16% of participants reported having training in cross-cultural nursing, and there was no significant difference between age groups in the data (*19*). In the present study, less than 30% of midwives and nurses had participated in workshops on nursing care for foreign residents. This figure is notably different from data from previous studies in Europe, which reported that most participants had been trained in cross-cultural care (*17,20*). A previous study suggested that some nurses are interested in intercultural care but lack the opportunity to receive training to improve their cross-cultural nursing skills (*19*). Many training programs for midwives and nurses are organized within the hospital, and training protocols are established according to the level and years of experience of midwives and nurses. However, in Japan, such programs contain little content related to nursing foreign patients or improving cross-cultural competence. The present findings that midwives and nurses who had attended workshops on nursing care for foreign residents had experienced less difficulty, helplessness, and uncertainty indicate the need to implement training for all midwives and nurses nursing foreign patients to reduce negative feelings.

Table 3. Logistic regression analysis of factors related to feelings toward nursing practice for foreign pregnant and postpartum residents among midwives and nurses (*n* = 82)

Factors	Comparison[a]	Proportion scoring > median on frustration, % (case/n)[b]	Logistic regression ORs (95% CIs) for frustration scores > median
Age, years	> 33.00	44.7 (17/38)	
	≤ 33.00	52.3 (23/44)	
		p = 0.496	
Work experience, years	> 9.5	46.3 (19/41)	1.0
	≤ 9.5	51.2 (21/41)	1.41 (0.55–3.57)
		p = 0.659	*p* = 0.474
Number of foreign patients	≥ 31	50.0 (18/36)	1.0
	≤ 30	47.8 (22/46)	0.82 (0.32–2.11)
		p = 0.845	*p* = 0.683
Educational background	Graduate school, university, Junior college, vocational school	43.9 (18/41) 53.7 (22/41)	
		p = 0.377	
Foreign language learning experience	Presence	40.5 (15/37)	
	Absence	55.5 (25/45)	
		p = 0.176	
English-language level	Very good/good/average	41.9 (26/62)	1.0
	Poor	70.0 (14/20)	3.16 (1.03–9.66)
		p = 0.029	*p* = 0.043
Participation in workshops on nursing foreign patients	Presence	31.6 (6/19)	1.0
	Absence	54.0 (34/63)	2.40 (0.78–7.44)
		p = 0.087	*p* = 0.129
Factors	**Comparison**	**Proportion scoring > median on difficulty, % (case/n)**	**Logistic regression ORs (95% CIs) for difficulty scores > median**
Age, years	> 33.00	52.6 (20/38)	
	≤ 33.00	40.9 (18/44)	
		p = 0.812	
Work experience, years	> 9.5	48.8 (20/41)	1.0
	≤ 9.5	48.8 (20/41)	1.28 (0.49–3.36)
		p = 1.000	*p* = 0.617
Number of foreign patients	≥ 31	61.1 (22/36)	1.0
	≤ 30	39.1 (18/46)	0.30 (0.11–0.83)
		p = 0.048	*p* = 0.020
Educational background	Graduate school, university Junior college, vocational school	53.7 (22/41) 48.8 (20/41)	
		p = 0.659	
Foreign language learning experience	Presence	40.5 (15/37)	
	Absence	55.6 (25/45)	
		p = 0.176	
English-language level	Very good/good/average	43.5 (27/62)	1.0
	Poor	65.0 (13/20)	2.16 (0.70–6.64)
		p = 0.095	*p* = 0.181
Participation in workshops on nursing foreign patients	Presence	26.3 (5/19)	1.0
	Absence	55.6 (35/63)	4.60 (1.32–16.01)
		p = 0.025	*p* = 0.016

ORs: odds ratios; CIs: confidence intervals. [a]Differences in demographic characteristics and feelings toward nursing practice for foreign pregnant and postpartum residents were determined using chi-squared tests. [b]Response variable: 1 = The feelings score is above the median and 0 = The feelings score is below the median. Adjusted for years of nursing experience (> 9.5 years or ≤ 9.5 years), Number of foreign patients (≥ 31 people or ≤ 30 people), English-language level (very good/good/average or poor), participation in workshops on foreign nursing (presence or absence).

Table 3. Logistic regression analysis of factors related to feelings toward nursing practice for foreign pregnant and postpartum residents among midwives and nurses (*n* = 82) (continued)

Factors	Comparison[a]	Proportion scoring > median on frustration, % (case/n)[b]	Logistic regression ORs (95% CIs) for frustration scores > median
Age, years	> 33.00	42.1 (16/38)	
	≤ 33.00	52.3 (23/44)	
		p = 0.358	
Work experience, years	> 9.5	43.9 (18/41)	1.0
	≤ 9.5	51.2 (21/41)	1.40 (0.55–3.58)
		p = 0.507	*p* = 0.479
Number of foreign patients	≥ 31	44.4 (16/36)	1.0
	≤ 30	50.0 (23/46)	1.04 (0.40–2.68)
		p = 0.617	*p* = 0.944
Educational background	Graduate school,university	48.8 (20/41)	
	Junior college,vocational school	46.3 (19/41)	
		p = 0.825	
Foreign language learning experience	Presence	43.2 (16/37)	
	Absence	51.1 (23/45)	
		p = 0.478	
English-language level	Very good/good/average	43.5 (27/62)	1.0
	Poor	60.0 (12/20)	1.84 (0.62–5.44)
		p = 0.200	*p* = 0.272
Participation in workshops on nursing foreign patients	Presence	21.1 (4/19)	1.0
	Absence	76.1 (35/46)	4.39 (1.28–15.04)
		p = 0.008	*p* = 0.019
Factors	**Comparison**	**Proportion scoring > median on uncertainty, % (case/n)**	**Logistic regression ORs (95% CIs) for uncertainty scores > median**
Age, years	> 33.00	44.7 (17/38)	
	≤ 33.00	54.5 (24/44)	
		p = 0.376	
Work experience, years	> 9.5	46.3 (19/41)	1.0
	≤ 9.5	53.7 (22/41)	1.50 (0.58–3.89)
		p = 0.508	*p* = 0.405
Number of foreign patients	≥ 31	50.0 (18/36)	1.0
	≤ 30	50.0 (23/46)	0.78 (0.30–2.06)
		p = 1.000	*p* = 0.616
Educational background	Graduate school, university	46.3 (19/41)	
	Junior college, vocational school	53.7 (22/41)	
		p = 0.508	
Foreign language learning experience	Presence	45.9 (17/37)	
	Absence	53.3 (24/45)	
		p = 0.506	
English-language level	Very good/good/average	45.2 (28/62)	1.0
	Poor	65.0 (13/20)	2.12 (0.69–6.49)
		p = 0.123	*p* = 0.189
Participation in workshops on nursing foreign patients	Presence	21.1 (4/19)	1.0
	Absence	58.7 (37/63)	5.29 (1.52–18.43)
		p = 0.004	*p* = 0.009

ORs: odds ratios; CIs: confidence intervals. [a]Differences in demographic characteristics and feelings toward nursing practice for foreign pregnant and postpartum residents were determined using chi-squared tests. [b]Response variable: 1 = The feelings score is above the median and 0 = The feelings score is below the median. Adjusted for years of nursing experience (> 9.5 years or ≤ 9.5 years), Number of foreign patients (≥ 31 people or ≤ 30 people), English-language level (very good/good/average or poor), participation in workshops on foreign nursing (presence or absence).

Table 3. Logistic regression analysis of factors related to feelings toward nursing practice for foreign pregnant and postpartum residents among midwives and nurses (*n* = 82) (continued)

Factors	Comparison[a]	Proportion scoring > median on frustration, % (case/n)[b]	Logistic regression ORs (95% CIs) for frustration scores > median
Age, years	> 33.00	39.5 (15/38)	
	≤ 33.00	54.5 (24/44)	
		p = 0.173	
Work experience, years	> 9.5	34.1 (14/41)	1.0
	≤ 9.5	61.0 (25/41)	3.17 (1.25–8.04)
		p = 0.015	*p* = 0.015
Number of foreign patients	≥ 31	47.2 (17/36)	1.0
	≤ 30	47.8 (22/46)	1.07 (0.42–2.74)
		p = 0.957	*p* = 0.887
Educational background	Graduate school, university	51.2 (21/41)	
	Junior college, vocational school	43.9 (18/41)	
		p = 0.507	
Foreign language learning experience	Presence	62.2 (23/37)	
	Absence	35.6 (16/45)	
		p = 0.016	
English-language level	Very good/good/average	48.4 (30/62)	1.0
	Poor	45.0 (9/20)	0.93 (0.32–2.71)
		p = 0.792	*p* = 0.896
Participation in workshops on nursing foreign patients	Presence	57.9 (11/19)	1.0
	Absence	44.4 (28/63)	0.54 (0.18–1.61)
		p = 0.303	*p* = 0.267

ORs: odds ratios; CIs: confidence intervals. [a]Differences in demographic characteristics and feelings toward nursing practice for foreign pregnant and postpartum residents were determined using chi-squared tests. [b]Response variable: 1 = The feelings score is above the median and 0 = The feelings score is below the median. Adjusted for years of nursing experience (> 9.5 years or ≤ 9.5 years), Number of foreign patients (≥ 31 people or ≤ 30 people), English-language level (very good/good/average or poor), participation in workshops on foreign nursing (presence or absence).

Midwives and nurses require ongoing professional development to help foreign patients address their multifaceted needs. However, it is often difficult for nursing professionals to attend workshops, seminars, and training during their busy daily work schedules. Web-based education models and organizational support can provide educational opportunities to midwives and nurses with limited time and opportunity to improve their competency. Previous intervention studies (*21-24*) have found that web-based individual education programs are effective in improving competency, knowledge, skills, and resilience in nurses and health professionals. There are no studies on the effects of web-based cross-cultural seminars or education for clinical midwives and nurses. However, cross-cultural competency is associated with relevant training *(20,25*), and the development of web-based programs that are free and demand minimal time may be effective.

The midwives and nurses in this study experienced not only negative feelings such as frustration and difficulty, but also positive feelings such as satisfaction. Previous research shows that midwives and nurses caring for foreign patients have positive experiences of joy and satisfaction from being understood, relied upon, and appreciated (*12,14*). The successful experience of building relationships and feeling rewarded and happy while transcending language barriers can improve midwifery and nursing practice skills. Nurses who attend training on nursing care for foreign patients to improve their cross-cultural competency would likely find it more rewarding to care for foreign patients. Such positive experiences would lead to better midwifery and nursing care, thus improving the quality of midwifery and nursing care for foreign patients.

This study had several study limitations. First, the cross-sectional design precludes any conclusions about the causal nature of the observed associations. Therefore, a prospective study is needed to confirm our findings. Second, data were obtained only from midwives and nurses who agreed with the study aims and fully completed the questionnaire. As such, there is a possibility of selection bias because of the low response rate (26.5%); additionally, the sample was small and drawn from only one prefecture in Japan. Third, other potential confounding factors that were not considered in this study include living environment and personality differences. Despite these potential limitations, these findings are important as they clarify the current state

of nursing care for foreign pregnant and postpartum residents in perinatal medical centers in Japan, which provide care for many foreign patients.

In conclusion, this study findings showed that participants who had fewer English-language skills experienced greater frustration nursing foreign patients. We also found that the experience of participating in workshops on support for foreign patients was effective in eliminating negative feelings such as difficulty, helplessness, and uncertainty. Therefore, to reduce negative feelings toward nursing foreign patients, participation in educational programs — especially web-based interventions and individualized education programs on nursing care for foreign residents — and daily simple English-language education could be effective in improving nurses' cross-cultural competency and English-language skills.

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