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Data science and health economics in precision public health

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Data science and health economics in precision public health

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Table of contents

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Editorial: Data science and health economics in precision public health

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health economics, health data science, decision support systems, precision public health, spatial epidemiology

Editorial on the Research Topic
Data science and health economics in precision public health

Overview of precision public health

Advances in computational and data sciences, such as big data approaches, along with engineering innovations, such as geographic information system (GIS) and artificial intelligence (AI) technologies, have greatly enhanced our capabilities for data management, integration, and visualization (1–3). These scientific developments have prompted demands for more comprehensive and coherent but, most importantly, tailored and targeted strategies to address fundamental issues in public health (4, 5). Combining these novel approaches with more traditional health determinants such as lifestyle, socioeconomic, cultural, and environmental factors has resulted in an exciting new field in the health sciences, Precision Public Health (6).

Theory, methods, and models from AI and data science are already changing the public health landscape in community settings (7) and have already shown promising results in multiple applications in public health, including geocoding health data (8), digital public health (9), predictive modeling and decision support (10), and mobile health (11). Overall, Precision Public Health utilizes tools and methods from the above technologies to extract health and non-health data at different levels of granularity, harmonize and integrate information about populations and communities to tailor cost-effective interventions for specific population groups, improving people's health. The overarching goal of Precision Public Health is to provide the proper intervention to the right population at the right time (12).

Data science in the context of precision public health

Data Science is an interdisciplinary field that is beginning to revolutionize healthcare and public health. This is due to the Digital Revolution that acknowledges the power of digital information and the increasing ability to integrate technologies (13). Novel technological advancements permit the collection and integration of a vast amount of complex and heterogeneous types of data from an increasing array of sources such as genome sequences, social media, satellite remote sensing, earth-observation technologies, electronic health records, Global Positioning System (GPS)-enabled devices, personal sensors, and smartphone application (14). Additionally, there is a considerable decrease in computational costs and abundant storage, processing power, and network connectivity (13). These novel data sources provide the potential to integrate cost-effective and more accurate methods for measuring disease, pathogens, exposomes (the non-genetic exposures experienced over the lifespan), and behaviors that allow better assessment of population health and health determinants (8).

Data Science aims to develop processes and systems to integrate those different data sources, visualize them effectively, and combine advanced analytic methods from several scientific fields such as AI, machine learning, statistics, and high-performance computing to enhance decision-making and develop novel applications in Public Health. In particular, decision-making involves guiding interventions and tailoring public health policies and health promotion programmes, improving early detection of pathogens and infectious disease outbreaks, and enhancing public health surveillance (8). In terms of novel Public Health applications, geospatial applications and predictive modeling techniques identify populations at high risk for a disease, link characteristics of the environment to health changes, explore small area socio-economic inequalities in health, identify and evaluate suspected clusters, and map the risk of diseases.

The development of intelligible, transparent data analytic methods that can be communicated to public health practitioners and easily updated in the face of new data and human judgment will be critical to precision public health (15, 16). Finally, as Mooney and Pejavar stated, the rapid adoption and success of precision public health may depend on how the public health community can embrace a specialized, team science model in training and practice (1).

Health economics in the context of precision public health

The aim of health Economics is to determine and propose the most efficient means a society allocates its resources for healthcare, disease prevention, and health promotion at the population level (17). In an attempt to address these needs, Health Economic Outcomes Research (HEOR) aims to identify alterations and introductions in the health system (both healthcare and public health) which maximize their beneficial impacts on population health with the minimum possible resource utilization, i.e., ideal efficiency and cost-effectiveness (18).

The concept of Precision HEOR has been recently proposed (18) to optimize the efficiency and cost-effectiveness of health services and systems *via* approaches and sciences, such as big data and machine learning, as described in the previous sub-section. This approach is anticipated to lead to optimized and tailored interventions for specific population groups, lowering costs by avoiding wasting resources resulting from suboptimal treatments, inefficient preventive programmes and other prodigal approaches.

In this respect, AI and machine learning are anticipated to utilize real-world health data on whole populations and specific population subgroups, generated by practical data approaches, informing and enabling the device of more cost-effective and targeted public health services and programmes (19, 20). Additionally, such approaches can be utilized for assessing whether specific public health interventions, which overall might be inferior to other alternative interventions, might be beneficial for particular population subgroups (18).

Additionally, stream approaches involving dynamic model data input methods can incorporate health data streams at the population level as it is made available, increasing direct and timely applicability to those with immediate health needs (21).

Finally, improved cost-effectiveness quickly disregards health inequalities (22). The approaches described so far have the potential to address health inequalities simultaneously by improving the efficiency and cost-effectiveness of public health interventions. This "tailoring" of public health interventions and services to population groups in need, including minority and disadvantaged groups, promises to be invaluable for narrowing the socioeconomic gap in health.

RT articles

The ten papers in the current RT (Data Science and Health Economics in Precision Public Health) can be grouped into the following broad and non-exclusive categories: Time series and dynamic models (Sun and Yi; Wei et al.; Zhou et al.), Health Inequalities (Peng and Ren; Xin and Ren; Xu et al.), Internet and Social media for health promotion (Han and Zhao; Tchuenche et al.) and Economic evaluations of health (Feng et al.; Lee et al.).

Conclusion and future steps

Precision Public Health approaches aim to effectively and efficiently implement comprehensive, targeted, and increasingly tailored strategies to address contemporary public health challenges.

Despite the different Public Health fields incorporated in such approaches (e.g., Health Economics and Data Science in this case), there is a relative lack of multidisciplinarity in the design and application of such programmes, as also apparent in the current Research Topic. Incorporation of advances in computational and data sciences (e.g., big data, GIS, AI, and genomics) in more traditional Public Health disciplines (e.g., Health Economics, Health Promotion, Health Protection, Health Inequalities) is anticipated to benefit these disciplines greatly and set the foundations for Public Health practice of the future.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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BRIEF RESEARCH REPORT
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The Influence of the COVID-19 Pandemic on the Imports and Exports in China, Japan, and South Korea

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In this paper, time-series and cross-country data spanning from January 2020 to December 2020 are adopted to empirically investigate the impact of the COVID-19 pandemic on exports and imports in China, Japan, and South Korea. In the models, industrial production, trade openness, government response (including monetary and fiscal intervention), and the pandemic impact of major trade partners are controlled. In addition, the three countries, China, Japan, and South Korea, are also estimated separately in consideration of the cross-country disparity. The results show that domestic epidemics in China, Japan, and South Korea have a non-significant (statistically significant) effect on imports, but are negatively correlated with exports in Japan; epidemics in major trading partners are negatively correlated with imports in Japan and positively correlated with exports in China and South Korea; and government intervention is positively correlated with imports in China and positively correlated with exports in China, Japan, and South Korea.

Keywords: COVID-19, import and export trade, China, Japan and South Korea, government intervention

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INTRODUCTION

The global economy has suffered a severe shock since the outbreak of the COVID-19 pandemic. In April 2020, the World Trade Organization (WTO) predicted that under an optimistic scenario, global trade would shrink by 12.9% in 2020, while a pessimistic scenario predicted 32%. In October 2020, the WTO issued a newly revised forecast in light of the changing situation, projecting that global merchandise trade would fall by 9.2%. This epidemic has a long incubation period, a high transmission rate, and strict control over the gathering and movement of people. Therefore, under the new situation, it is expected that the impact of the epidemic on industry will be greater than that of SARS in 2003, and the impact on the restructuring and layout of domestic economy in China, Japan, and South Korea will be more profound. From the production point of view, the impact of the epidemic on labor-intensive industries such as textiles, garments, construction materials, toys, leather, and furniture manufacturing is greater. These industries are generally characterized by high labor and capital costs. In terms of exports, the epidemic had a greater impact on outward-oriented industries. Yiwen and Xiaomei (1) conducted a quantitative study based on historical data and found that the SARS epidemic significantly inhibited the exports of Chinese enterprises and the impact of the epidemic on exports would not recover in the short term, and there was also a certain negative impact in the long term. According to Zhen and Liwei (2), the current epidemic will have a serious impact on the Chinese manufacturing industry as a whole. China's printing

industry, furniture and other manufacturing industries, textile and leather manufacturing industries, and automobile manufacturing industries have greater trade dependence and are therefore more vulnerable to the global chain of industries brought about by the epidemic. From the consumption point of view, epidemic prevention and control drives the pharmaceutical industry and non-contact industry market surge. Demand for medical protective gear, medical equipment, proprietary Chinese medicines, and anti-viral drugs appeared to increase (3). By April 2020, the epidemic was under control in China, therefore its imports and exports volume had been positive since June, growing 1.9% from a year earlier, which not only made China the only major economy in the world to achieve positive growth in merchandise trade but also pushed its share of global exports, climbing to a record high of 14.2%. As the world's third largest economy, although its import and export trade fell compared to the same period last year, Japan's exports to China grew significantly, increasing by 2.7% for the year. The proportion of Japan's exports to China rose to 22% of its total exports, making China the largest export destination. South Korea's share of total global trade was 3%, reaching an all-time high in 2011, and ranked ninth, the same as the previous year. With the epidemic under better control, China, Japan, and South Korea have become the "growth engines" of the Asian economy and even the world, therefore the value of studying their trades has increased. This research focuses on the following two main areas.

The first is the study of the impact of the COVID-19 pandemic on the trade and economy among China, Japan, and South Korea. Chinese scholars believe that the epidemic has brought new opportunities and challenges for China-Japan-ROK economic and trade cooperation, and many of them are optimistic about the future prospects of China-Japan-ROK cooperation. In an article written by Yongsheng (4), it is argued that as long as the global pandemic is controlled extremely effectively, China-Japan-ROK FTA negotiations are expected to succeed in the near future and the future prospects will be very broad. Yueju (5) not only mentions that the epidemic brought a considerable impact on the economic growth rate and economic and trade relations among China, Japan, and South Korea in the first quarter but also points out that the experience of cooperation against the epidemic, the willingness to recover the economy for China, Japan, and South Korea, and the rapid recovery of the Chinese economy will create more new opportunities for the recovery and development of economic and trade relations among the three countries and their FTA negotiations. Xiao and Yingda (6) summarize post epidemic China-Japan-ROK opportunities as: opportunities for cooperation against the epidemic, the willingness of the three countries to cooperate in economic and trade, the demand for development in high-tech fields, as well as the stability of the situation in northeast Asia. They summarize the challenges affecting the cooperation among the three countries as: racist rhetoric, anti-globalization thinking, unstable bilateral relations, industrial homogenization competition, deteriorating Sino-US relations, and the North/South Korean nuclear issue (6).

Unlike China, scholars in Japan and South Korea are less likely to study the impact of the epidemic on China, Japan, and South Korea as a whole. They focus on the impact of the epidemic on their own countries, on a particular country, or on the world economy as a whole. South Korean domestic scholars are more concerned about the impact of the epidemic on global value chains and their own economies. Dongchul (7), Sungok (8), and Yangmi (9), among others, express concern about damage to global value chains. Hyuntai and Dosook (10) focus their attention on China to propose three aspects of improving Sino-Korean economic relations, including postponing economic restructuring, developing a non-contact economy, and strengthening Sino-Korean economic cooperation, based on the analysis of the impact of the epidemic on the Chinese economy. Economic Laboratory (11) suggests that "reverse globalization and big government" is a global trend after the epidemic which will be a major challenge for the South Korean economy. The trend of de-Sinicization is expected to accelerate after the epidemic. Relative studies by Japanese scholars are few but those that do focus on China, the United States, Russia, North Korea, South Korea, and India. Kazuhiro (12) points out that "the South Korean economy, which has a high degree of external dependence, has suffered a huge blow due to the expansion of the worldwide epidemic infection. In particular, the high dependence on China of the South Korean economy has exposed its vulnerability. The South Korean government has tried to strengthen its economic ties with Association of Southeast Asian Nations (ASEAN) countries and India, but this alone is not enough to mitigate the risk of losing shares in the Chinese market. It is also in the national interest for South Korea to work to improve relations with Japan and to win over the Japanese market." Eri and Kenji (13) argue that the epidemic has impacted the reconstruction of the Global Supply Chain (GSC) and it is important to take appropriate measures to manage global supply chain risk.

The second is specific research on the impact of the COVID-19 pandemic on import and export trade. Domestic Chinese scholars have focused on the impact of the epidemic on domestic import and export trade, and most of the relevant studies have been conducted on data from the early stage of the epidemic. By compiling and analyzing the import and export trade data between China and 249 countries or regions, Xiuyu (14) finds that from January to April 2020 the import and export trade between China and the ASEAN showed an upward trend compared to the same period last year. Some scholars also predict the impact of the epidemic on China's import and export trade based on the impact of major epidemic outbreaks on imports and exports in history. Based on the six public health emergencies of international concern (PHEIC) that WHO has declared since 2005, Qian and Yu (15) predicted that the country's exports would be about 15–20% lower in the first quarter; and about 15% lower in the second quarter. From a full-year perspective, along with the turnaround of the epidemic, exports will rapidly resume growth after the second quarter, and will be about 3–8% lower throughout the year than in 2019. Combining the data related to import and export from January to February after the epidemic, Jingan and Hailong (16), pointed out that despite the global character of the epidemic, it would not have a global impact on China's international economic influence, and the negative impact on China's import and export trade would only be a temporary phase ripple. According to Wonseok (17), the share of exports from Hubei in South Korea's imports from

China is negligible (1.0% in 2018), and the impact on South Korean exports is expected to be small. However, compared to the SARS period (2003), South Korea's value chain to China has further deepened, and the negative impact on the South Korean economy will increase if the blunting of China's exports and consumption is prolonged. Fernando and Ana Maria (18) found that the impact of international trade of essential goods during the epidemic depends crucially on the countries' trade imbalances in essential goods. For example, net importers of these goods are relatively worse off during a pandemic than net exporters. The welfare losses of net importers are lower in a world with high trade barriers, while the reverse is the case for net exporters. Yet, once a pandemic arrives, net exporters of essential goods benefit from an increase in trade barriers, while net importers benefit from a decrease in them.

From the above studies, it can be seen that, compared with Chinese scholars, scholars from Japan and South Korea seldom study China, Japan, and South Korea as a whole, and there are even some de-Sinicization propositions and views in the Japanese and South Korean studies. In terms of research content, there are not many studies involving the impact of import and export trade, and most of them are about the impact on China's import and export trade, with no studies involving China, Japan, and South Korea yet. In terms of research time, most of the relevant studies appear in the time of the epidemic. In terms of research methodology, most of the studies on the impact of the epidemic are based on the historical situation of the epidemic or the data of the early stage of the epidemic, while impact factors outside the epidemic are not taken into consideration, which makes it difficult to accurately grasp the real situation of the impact of the epidemic. In order to overcome the shortcomings mentioned above, this thesis investigates the impact of the COVID-19 pandemic on China-Japan-South Korea economies and trade through the empirical analysis method based on the monthly changes of the pandemic in 2020, aiming to reveal the relationship between the COVID-19 pandemic and China-Japan-South Korea economies and trade. Then, this thesis outlines the change of import and export trade under the influence of the epidemic, and explores the regional economic and trade cooperation under the continuous downturn of the external market.

DATA AND METHODOLOGY

This paper intends to study the impact of COVID-19 on China, Japan, and South Korea's international trade since its outbreak, covering the period from January 2020 to December 2020, largely dictated by the availability of the data on time span. Each country's import (henceforth IMPT) and export (henceforth EXPT) are measured by the growth rates compared to the same months of the previous year, which are drawn from the website of related government departments (detailed sources are shown in **Table A1** in Appendix). Import and export are separately investigated to account for the differences in the impacts of COVID-19. The original data used to calculate the COVID-19 outbreak degree of the three countries (henceforth NIF), which is new infections per 10,000 people, sourced from WHO.

$$NIF = \textit{New infections per month} \times 10,000 \,/\, \textit{Total population}$$

The higher the NIF value is, the more serious the epidemic is in the corresponding country. In the estimation, to consider the possible impact of the country's main trade partners' epidemic outbreak, a variable of the epidemic outbreak degree of main trade partners (henceforth PNIF) are introduced with the same calculation method of NIF, the data of which are also sourced from WHO. Specifically, China, Japan, and South Korea's top 20 trade partners consist of their most international trade, with 64.8, 82.4, and 81% in import, and 66.7, 76.7, and 78.9% in export, respectively. Hence we mainly consider the epidemic situation of their top 20 trade partners in measuring PNIF, while these three country's main trade partners are also highly overlapped (countries are shown in **Table A2** in Appendix).

Moreover, a country's government power, or government intervention (henceforth GovI) is measured by the ratio of government expenditure to the nation's economic size, following Nurudeen and Usman (19), as

$$GovI_{it} = \frac{\sum_{j=1}^{t} GEX_{ij}}{GDP_i}$$

Here, GEX_{ij} represents the government expenditure coping with the impact of the epidemic in country i and month j. The special government bond and special public expenditure confronting the epidemic are used to approximately measure government intervention (GEX). These data are drawn from the Ministry of Finance (China, Japan) and the Ministry of Economy & Finance (South Korea). As the effect of government fiscal expenditure is consistent and accumulative, we use the cumulant from month 1 to t to measure government intervention in month t. GDP_i is the whole year's (2020) gross domestic product in country I, used as a proxy of a country's size of economy.

In addition, as GDP at the month level lack data in these three countries and approximately 70% of their international trade in goods are industry products, therefore, we use the SP to represent the value of industrial production, and then the growth rate of industrial production (hereafter InP) is used as a proxy for economic output growth. Also, using

$$TRO_{it} = \frac{IMPT_{it}+EXPT_{it}}{SP_{it}}$$

to measure trade openness.

The data are obtained from China's National Bureau of Statistics and Organization for Economic Co-operation and Development (OECD) data. In the estimation, we consider four samples, which are China, Japan, South Korea, and these three northeast countries as a whole. **Table 1** contains statistics summarized from the above major variables.

TABLE 1 | Summary statistics of selected variables from January 2020 to December 2020.

	Mean	Median	Maximum	Minimum	Std. dev.	Observations
IMPT	−6.55	−5.5	12.70	−26.1	9.13	48
EXPT	−3.83	−3.00	20.60	−40.6	13.17	48
InP	−2.12	−0.54	7.30	−32.73	8.83	48
NIF	0.57	0.14	3.67	0.00	0.91	48
GovI	0.03	0.02	0.07	0.00	0.02	48
TRO	36.92	30.91	65.35	24.12	13.94	48
PNIF	11.38	8.35	40.17	0.00	10.79	48

IMPT, EXPT, INP, NIF, TRO, PNIF, and GovI denote import, export, industry product, new infections, trade openness, main trade partners' new infections, and government intervention, respectively.

TABLE 2 | Correlation analysis.

	IMPT	EXPT	InP	INF	GovI	TRO	PNI
IMPT	1.00						
EXPT	0.49	1.00					
InP	0.36	0.86	1.00				
NIF	−0.18	−0.01	−0.16	1.00			
GovI	0.56	0.71	0.57	−0.12	1.00		
TRO	0.12	0.06	0.29	0.05	0.04	1.00	
PNI	0.34	0.67	0.40	0.29	0.81	−0.13	1.00

IMPT, EXPT, INP, NIF, TRO, PNIF, and GovI denote import, export, industry product, new infections, trade openness, main trade partners' new infections, and government intervention, respectively.

Correlation Analysis

Table 2 provides the bivariate association between variables.

Based on the above theoretical background and data, the first time-series empirical regression takes the following linear form:

$$\ln(X)_i = c + \alpha_1 \ln(InP)_i + \alpha_2 \ln(InNIF)_i + \sum_{j=3}^{4} \partial_j \ln(InZ)_i + \varepsilon_i$$

Here, the subscripts i denotes countries; c is constant; α_j (j = 1,...,4) are the estimated coefficients of corresponding independent variables; X is import (IMPT) or export (EXPT); Z is also a set of explanatory variables including NIF and TRO; and ε is the error term. In the estimation, we add 45 to each number of IMPT & EXPT and add 35 to each number of Inp before the logarithm of them.

Then we consider the possible impact of the visible hand—government intervention (GovI), the empirical form is as follows:

$$\ln(X)_i = c + \alpha_1 \ln(InP)_i + \alpha_2 \ln(InNIF)_i + \alpha_3 \ln(InGovI)_i + \sum_{j=4}^{5} \partial_j \ln(InZ)_i + \varepsilon_i$$

We also use panel data for empirical estimation as an overall analysis both in import (IMPT) and export (EXPT), compared to the previous time series estimation. Two typical models are used in the estimation, the fixed effect (FE) model and the random effect (RE) model, which use a fixed average value, an error term of time-series, and cross-section characteristics, respectively. The estimating equation is as follows:

$$\ln(X)_{it} = c + \alpha_1 \ln(InP)_{it} + \alpha_2 \ln(InNIF)_{it} + \alpha_3 \ln(InGovI)_{it} + \sum_{j=4}^{5} \partial_j \ln(InZ)_{it} + \varepsilon_{it} + \mu_{it}$$

Here, the subscripts i and t also represent countries and months; except for the error term of ε, μ denotes the random unobservable country effects. The selection of an FE or RE model is determined by the Hausman test.

Hausman test.

H0: ε_I is not correlated with LnP, LnNIF, LnGovI, and InZ.
H1: ε_I is correlated with LnP, LnNIF, LnGovI, and InZ.

EMPIRICAL RESULTS

Import

The estimated results of the import based on the time-series data are summarized in **Table 3**. Except for the sample of China, Japan, and South Korea, "The three" takes these three northeast countries as a whole. The difference between models (A) and (B), models (C) and (D), models (E) and (F), and models (G) and (H) is the inclusion of GovI as an explanatory variable.

The estimated coefficient of InP in models (A), (B), (C), and (D) are positive and statistically significant at a 5–10% significance level. It implies that a higher level of industry output growth tends to increase the growth rate of import in Japan and South Korea. This is probably due to the fact that an expansion in production leads to an increase in consumption capacity of goods abroad, as well as demand of the intermediate or raw materials for further production. However, the NIF coefficients and PNIF coefficients [except model (C)] are all statistically insignificant at the conventional significance level without model specifications. A plausible explanatory is that the time span covers just 12 months, limited by the fact that the outbreak of the epidemic began around January 2020. The negative impact of PNIF shown in model (C) is significant at the 10% significance level, albeit with a very tiny coefficient (0.00 after rounding). It means that the seriousness of the epidemic situation may slightly decrease Japan's import. As Japan is a highly industrialized open economy occupying the high end of the international value chain, the deterioration of its main partners' epidemic situation may affect its import through two ways: One is that it may directly decrease these countries' intermediate products' productivity which is needed for further production. The other can be that it decreases these countries' demand of Japan's goods which are produced from raw materials or intermediate products imported abroad.

Particularly, the GovI coefficient in model (B) is positively associated with IMPT and statistically significant at the conventional significance level, whereas they are statistically insignificant in model (D) and (H). It suggests that China's

TABLE 3 | Estimated results on import.

	China		Japan		South Korea		The Three	
	Model (A)	**Model (B)**	**Model (C)**	**Model (D)**	**Model (E)**	**Model (F)**	**Model (G)**	**Model (H)**
C	0.72 (6.75)	3.80 (5.96)	12.56* (5.52)	12.15** (5.04)	−3.96 (4.78)	2.10 (5.41)	6.02 (7.62)	7.74 (7.91)
InP	−0.07 (0.12)	−0.09 (0.11)	0.48* (0.23)	0.59** (0.23)	1.49** (0.57)	1.51** (0.51)	−0.01 (0.23)	−0.05 (0.23)
NIF	0.08 (0.09)	0.07 (0.07)	−0.03 (0.10)	−0.02 (0.09)	0.02 (0.04)	0.04 (0.03)	0.11 (0.06)	0.07 (0.07)
TRO	1.04* (1.94)	0.48* (1.68)	−3.10 (1.55)	−3.47 (1.42)	0.55 (1.40)	−0.40 (1.39)	−0.61 (2.24)	−0.88 (2.28)
PNIF	0.05 (0.03)	−0.02 (0.04)	−0.00* (0.08)	0.06 (0.08)	0.01 (0.04)	−0.20 (0.13)	0.01 (0.02)	−0.02 (0.04)
GovI		0.32* (0.17)		−0.26 (0.16)		0.50 (0.31)		0.19 (0.20)
R^2	0.44	0.65	0.67	0.76	0.83	0.88		0.45
Observations	12	12	12	12	12	12	12	12

IMPT, EXPT, InP, NIF, TRO, PNIF, and GovI denote import, export, industry product, new infections, trade openness, main trade partners' new infections, and government intervention, respectively.

Standard errors are in parentheses.

(**), and (*): significant at 5, and 10% level, respectively. C, constant term; R^2, reliability squaring.

TABLE 4 | Estimated results on export.

	China		Japan		South Korea		The Three	
	Model (A)	**Model (B)**	**Model (C)**	**Model (D)**	**Model (E)**	**Model (F)**	**Model (G)**	Model (H)
C	3.10 (2.85)	4.87** (1.76)	−0.89 (3.94)	−0.51 (3.13)	−14.6 (8.21)	2.55 (6.69)	−1.09 (2.02)	−0.03 (1.27)
InP	0.90*** (0.05)	0.90*** (0.03)	1.08*** (0.17)	0.98*** (0.14)	1.08 (1.07)	1.13 (0.63)	0.96*** (0.06)	0.94*** (0.04)
NIF	0.10 (0.04)	0.09 (0.02)	−0.02* (0.07)	−0.03* (0.06)	0.00 (0.06)	0.05 (0.04)	0.11 (0.02)	0.08 (0.01)
TRO	−0.61 (0.82)	−0.93 (0.50)	0.25* (1.10)	0.58* (0.89)	3.50* (2.62)	0.78 (1.71)	0.49 (0.59)	0.33 (0.36)
PNIF	0.04*** (0.01)	0.00 (0.01)	0.02 (0.05)	0.03 (0.05)	0.09 (0.07)	0.50** (0.16)	0.01 (0.01)	0.01* (0.01)
GovI		0.19*** (0.05)		0.23* (0.10)		1.42*** (0.38)		0.12** (0.03)
R^2	0.67	0.99	0.92	0.96	0.73	0.92	0.98	0.99
Observations	12	12	12	12	12	12	12	12

IMPT, EXPT, InP, NIF, TRO, PNIF, and GovI denote import, export, industry product, new infections, trade openness, main trade partners' new infections, and government intervention, respectively.

Standard errors are in parentheses.

(***), (**), and (*): significant at 1, 5, and 10% level, respectively. C, constant term; R^2, reliability squaring.

government intervention against the impact of COVID-19 has a positive effect on its import. A plausible expansion is that it stimulates China's investment and consumption which demand raw and processed materials and goods from abroad. The impact of TRO is positive in the sample of China (models A and B) and statistically significant, which is consistent with the existing literature as (20).

Export

The estimated results of the export are summarized in **Table 4**, following the same approach as the previous results in import. It is found that a negative association exists between NIF and EXPT with the coefficients statistically significant in models (C) and (D), but they are statistically insignificant in the remaining models. It suggests that the control of the epidemic contributed to Japan's export. On the other hand, the coefficients of PNIF are positive and statistically significant in models (A) and (F), implying that China and South Korea's export growth rate is not only related to their own epidemic situation, but also their main trade partners'. That is, the more serious their partners' epidemic situation is, the higher export growth rate they have.

The coefficients of government intervention (GovI) on export growth rate (IMPT) are positive and statistically significant in all models. The results show that China, Japan, and South Korea governments' intervention against the epidemic contribute significantly to the recovery and re-booming of their export. InP and TRO show similar correlations with previous estimations in import.

In addition to the time-series estimation on the impact in each country, panel data consisting of these three countries are simultaneously analyzed to investigate the overall impact on the northeast countries as a whole, which to a certain extent can be used as a robust check. The estimation results are demonstrated in **Table 5**. It shows that the epidemic outbreak had a negative impact on the export of these northeast countries, whereas the estimated coefficients are statistically insignificant on the import. The results in model (A) and model (D) also show that the deterioration of the epidemic in their main trade partner has a negative association with the northeast countries' import and a positive association with their export, both of the coefficients are statistically significant at the conventional significance level. Moreover, in models (B) and (C), it also

TABLE 5 | Estimated results of the north-east countries.

	Import		Export	
	Model (A)	**Model (B)**	**Model (C)**	**Model (D)**
C	2.84*** (0.32)	4.45*** (0.79)	1.29*** (0.26)	2.00*** (0.69)
InP	−0.12 (0.09)	−0.13 (0.08)	0.87*** (0.07)	0.86*** (0.07)
NIF	−0.08 (0.02)	−0.03 (0.03)	−0.01* (0.01)	−0.01* (0.03)
TRO	0.29*** (0.09)	0.08 (0.13)	−0.18 (0.07)	−0.28 (0.11)
PNIF	−0.04* (0.05)	0.10 (0.08)	0.01 (0.04)	0.07* (0.07)
GovI		0.21** (0.10)		0.09* (0.08)
X2 [*p*-value]	15.93 [0.00]	5 [0.01]	5 [0.03]	28.35 [0.00]
Estimation method	Fixed effect	Fixed effect	Fixed effect	Fixed effect
R^2	76	0.81	0.95	0.96
Observations	36	36	36	36

IMPT, EXPT, InP, NIF, TRO, PNIF, and GovI denote import, export, industry product, new infections, trade openness, main trade partners' new infections, and government intervention, respectively.

Standard errors are in parentheses.

(***), (**), and (*): significant at 1, 5, and 10% level, respectively. C, constant term; R^2, reliability squaring.

suggests that the impact of government intervention (GovI) is positive both on import and export. The very similar results from the panel data estimation reconfirm the previous investigation in **Tables 3**, **4**.

DISCUSSION

The domestic epidemic had no significant (statistically) impact on the imports of the three countries. In terms of exports, it is negatively correlated with Japan, for instance. The better the epidemic is controlled in Japan, the more favorable it is for exports. Although the epidemic in China, Japan, and South Korea was generally controllable in 2020, the epidemic in Japan was significantly higher than that in China (number of infected people: 95701, infection rate: 0.68 per 10,000) and South Korea (number of infected people: 48331, infection rate: 9.3 per 10,000) in terms of both the number of infected people (193071) and the infection rate (15.3 per 10,000).

For a long time, manufacturing and international trade have been the main drivers of economic growth in China, Japan, and South Korea. However, compared with goods trade, the three countries have maintained a long-term deficit in service trade and a small share of foreign trade, especially China, whose service trade accounts for only 14.6% of foreign trade. In addition, considering the differences of influencing elements between goods trade and service trade, the study of this thesis is currently only concerned with goods trade. Only a small portion of the foreign trade in goods of the three countries is made up of primary products, with most of them industrial ones. Therefore, our study can generally reflect the situation of international trade in manufacturing industries in China, Japan, and South Korea under the impact of the epidemic. This thesis does not address the extent of the impact of the epidemic on industries such as the service sector. Xian and Zifei (21) mention that "the biggest impact of the epidemic on the U.S. was mainly in the tertiary sector, especially the restaurant, airline, retail, and hotel industries were severely damaged, while the biggest impact on Chinese industries was not the tertiary sector as perceived, but on industry, which was down 9.6% in the first quarter of 2020, far outpacing the tertiary sector's 5.2%."

Asia was the only region in the world to maintain positive growth (0.3%) in the volume of goods trade exports in 2020, and the role the three countries played as leading growth in Asian economies was an important content to examine in this thesis. Our related research will not stop there. In fact, we also prefer to study the problem from the perspective of the manufacturing industry. As time accumulates, certain available data spans will accumulate to meet our conditions for conducting regressions, and we will examine the impact of the epidemic on the manufacturing industry based on this thesis. For example, quarterly reports are available in the accounting statements of listed companies, and when a certain time span is accumulated, we intend to study the impact of the epidemic on the manufacturing industry from the aspect of manufacturing companies.

The epidemic in major trading partners is negatively correlated with Japan's imports, but the coefficient is small, implying that the impact of trading partners affects Japan's imports, but the effect is minor. On the export side, the severer the epidemic in Japan's major trading partners, the better China and South Korea's exports are. This is because their producing capacity declines due to the epidemic, with orders shifted to the two other countries, or the demand for the two countries' exports rises significantly. The epidemic kept recurring in many countries, some of the countries' factories were forced to stop production, the industry chain was broken, and some foreign trade orders from India, Bangladesh, Vietnam, and other countries were transferred to China. In addition, the demand for epidemic prevention materials such as masks, protective clothing, epidemic prevention drugs, and "home economy" products such as computers and household appliances from major trading partners also boosted the exports of both countries.

Government intervention is positively related to China's imports and also positively related to China, Japan, and South Korea's exports. It shows that government financial intervention is beneficial to the recovery of the country's international trade, especially in terms of exports. The government intervention in China has been particularly successful and has had a positive effect on imports and exports.

LIMITATIONS AND PROSPECTS

Due to the relatively short period of time (1 year) since the onset of the epidemic, the time span of the relevant data can only be accurate to the monthly level, so there are only 12 observations in the time dimension of this study, resulting in a small number of study samples. And we have selected and illustrated only the results with a high degree of creditability in the description; this also limits the use of our estimation methods. With time ongoing, more observations can be obtained, allowing us to further process these data. For example, to analyze the cointegration of the time

series data, and if the cointegration is inconsistent, we will try to use the ARDL or nonlinear-ARDL approach to analyze the endogeneity of the panel data. If there is endogeneity, we will try to analyze it by the GMM method. In addition, there are many other factors affecting the import and export trade, and this study only selected a few main variables during the epidemic period, i.e., the epidemic, trade openness, and government intervention. Considering the impact of the epidemic on import and export trade and commodity structure among China, Japan, and South Korea, we can increase the sample size and analyze other influencing factors in future studies.

CONCLUSION

Industrial structure in China, Japan, and South Korea are highly similar, but there is heterogeneity in the impact of the epidemic on imports and exports in China, Japan, and South Korea. The epidemic stimulated the demand for medical supplies and boosted export growth, and government intervention had a positive impact on imports and exports.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

Material preparation and data collection and analysis were performed by PW and CX. The first draft of the manuscript was written by PW and all authors commented on previous versions of the manuscript. All authors contributed to the study conception and design. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.682693/full#supplementary-material

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The Relationship Between "Protect People's Livelihood" and "Promote the Economy:" Provincial Evidence From China

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This study focused on medical care in a single country (China) and in regions with different economic backgrounds and different economic development levels to determine the effect of healthcare expenditure on short- and long-term economic growth. The study supported some interesting conclusions: (1) For most areas of China, increasing healthcare expenditure has a negative impact on economic growth in the short term but promotes growth in the long run; (2) Under different levels of economic development within China, there is significant heterogeneity in the interaction between healthcare expenditure and economic growth; (3) The negative effects of healthcare expenditure on short-term economic growth are greater during periods of economic turbulence than during times of stability; and (4) Healthcare expenditure has a negative effect on underdeveloped areas through the accumulation of material capital, while in economically developed areas, this channel has the opposite effect. To improve the quality of medical and health protection and the quality of life and welfare, China needs to consider the development characteristics of different economic zones and establish a multilevel, systematic and diversified medical and health protection system.

Keywords: healthcare expenditure, economic growth, time-varying, transmission channel, China

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INTRODUCTION

In early 2020, COVID-19 unexpectedly swept the world, with more than 80 million people diagnosed and nearly two million dead in less than a year. Governments worldwide launched a series of targeted measures to protect people's health and save their economies. However, it is not possible to both "protect people's livelihood" and "promote the economy." If strict isolation is implemented to prevent the further spread of the virus, it will result in a costly sharp drop in income, a soaring unemployment rate and an economic downturn. Even countries that try to maintain economic activities with the expectation that mass immunization will take effect may find that this strategy does little to maintain the normal operation of the economy. From a global perspective, with the advent of autumn and winter, the number of infected people has not decreased. Instead, the new coronavirus has mutated. The pain brought by COVID-19 may continue to affect human society well into the future. China was the first country to confront this new epidemic, but it also took the lead in restoring economic order under the epidemic, which was closely related to the anti-epidemic disaster relief provided by the government for the Chinese people regardless of the cost. China has made great efforts in the fight against COVID-19. On

June 7, 2020, the *White Paper on China's Action against the Epidemic of Coronavirus Pneumonia* published by the Press Office of the State Council of China showed that the average medical cost for confirmed patients nationally was ∼23,000 yuan, and the treatment cost of individual critically ill patients reached up to millions of yuan. All of these costs were borne by the state, and the total expenditure was well-beyond 1 billion yuan. The interaction between healthcare expenditure and economic growth is one of the key areas of public health research in China. The sudden outbreak of COVID-19 and the resulting trade-off between "protecting people's livelihood" and "promoting the economy" increase the value of discussing the impact of healthcare expenditure on the market economy. Not only China, but the whole world is facing such a test, especially at the time when the COVID-19 epidemic is raging. Is it possible to balance "protecting people's livelihood" and "promoting growth" as much as possible, directly affecting the development of a country or region's medical and health security system, people's livelihood and welfare, and long-term economic development. For the whole world, the establishment of a multi-dimensional, three-dimensional, and targeted medical and health security system is of great practical significance.

A medical and health security system can provide people with better medical care, effectively improve the health status of residents, improve life expectancy, and increase social welfare and overall safety (1, 2). However, its impact on economic growth is still subject to debate. There may be differences in the economic growth effect of healthcare expenditure given different economic contexts, and the path through which healthcare expenditure influences economic growth is not clear. Countries with different medical insurance systems have various consumption behaviors and investment concepts, and so they experience diverse effects of healthcare expenditure on economic growth, which is a topic of broad interest (3–7). However, the heterogeneity of the effect of healthcare expenditure on economic growth in distinct regions of the same country has not been discussed in depth. In a country like China, in particular, with its vast land area and great differences in development between the north and the south, different economic zones will have distinct the economic structures (8–13). Therefore, the impact of healthcare expenditure on economic growth is also likely to differ. Further comparative analysis is needed to reveal the complex mechanism through which economic growth affects healthcare expenditure in each economic zone within the same country.

From the above analysis, it can be seen that previous studies have discussed the effect of health expenditure on economic growth from various perspectives and reached many meaningful conclusions. However, there are still several research gaps to be filled. The previous literature generally studied the economic growth effect of healthcare expenditure based on the constant parameter method, but, in fact, there should be differences in the impact of healthcare expenditure on economic growth against different economic contexts, and the constant parameter model cannot describe this subtle variety. Previous research that adopted an econometric model to identify the economic growth effect of healthcare has been able to partially identify the different impacts of health expenditure on economic growth among countries with diverse economic systems but has not paid sufficient attention to the same differences in impacts across different development regions within a country. Most of these studies treat the impact of domestic healthcare expenditure on regional economic growth as homogeneous, and they do not explore the dynamic trajectory of the impact of healthcare expenditure on economic growth in different economic zones. In addition, there is no research that incorporates the numerous economic variables involved in the process through which healthcare expenditure acts on economic growth into the systematic analysis framework. The lack of important influencing variables may lead to a large deviation between the analysis results and the real economy, which is another reason why many studies fail to reach a unified conclusion on whether healthcare expenditure drives or inhibits economic growth.

In view of this gap, this paper attempts to construct a non-linear model of the dynamic time-varying relationship between healthcare expenditure and economic growth in China under a systematic analysis framework with a large number of possible economic variables and then empirically identifies the impact of medical and health spending on economic growth in China and in its distinct domestic economic regions, analyzing the possible transmission path for the impact of healthcare expenditure on economic growth. Compared with the existing literature, the marginal contribution of this paper is as follows. First, an econometric model with time-varying parameters is constructed to identify the effect of healthcare expenditure on economic growth to effectively capture whether healthcare expenditure stimulates or inhibits economic growth given different economic contexts in different periods. We also identified and distinguished the economic growth effect of healthcare expenditure in China nationally and regionally, which provides empirical evidence for the differential and comprehensive improvement in China's medical security system. Second, this paper provides not only an effectively analysis of the dynamic adjustment mechanism behind healthcare expenditures' impact on economic growth but also discusses the path through which healthcare expenditure impacts economic growth under a systematic analysis framework including a broad set of possible economic variables. This work offers a new understanding of the transmission characteristics for the effect of medical care and health on economic growth and can be regarded as a critical supplement to current research on the improvement in the medical security system.

The rest of this document is arranged as follows: the second section offers a literature review and develops the hypotheses. The third section constructs the time-varying parameter measurement model and introduces the selection of variables and data description. The fourth section analyzes the economic growth effect of healthcare expenditure, discusses the influence and transmission path between China's health expenditure and economic growth in different economic areas, and conducts a robustness test. The last section summarizes the full work and provides policy recommendations.

LITERATURE REVIEW AND HYPOTHESIS DEVELOPMENT

As a vital guarantee of national livelihood security, the medical security system plays a stabilizing role in economic development. During rapid economic development, the government can increase medical security expenditure on a large scale and improve medical security treatment to buffer the speed of economic development; when the economy is at a low, medical security expenditure can replace residents' preventive savings and stimulate domestic demand to encourage residents' consumption. In the past, most studies on the relationship between expenditure and economic growth have focused on the macro perspective (14–16). Some scholars deem that the rise of medical security expenditure will directly affect the consumption and investment tendencies of employees, effectively guarantee the quality of human capital (17), prolong life expectancy (18), and reduce infant mortality (19) to improve the savings rate, play a positive role in the growth of per capita income, and positively facilitate economic advance. However, the research of other scholars supports the completely opposite conclusion. Zhu and Hu (7) believe that healthcare expenditure will produce a negative effect on economic growth, which can be suppressed by enhancing the coverage rate of the medical security system. Likewise, Yang et al. (20) established an endogenous growth model and found that health expenditure would inhibit economic growth. According to the literature on China's health expenditures as well as economic growth, for low-income families, coverage of the medical security system is an effective guarantee of consumption. Although medical security consumption augments household expenses, it has a significantly promoting function on non-medical consumption and, in this way, influences economic growth. Tao and Wang (21) divided Chinese government health expenditure into four categories—medical and health service expenditure, medical security expenditure, administrative affairs expenditure and population and family planning affairs expenditure—and considered that only government medical security expenditure is able to promote positive economic growth. Accordingly, the first set of opposing hypotheses explored in this paper is established:

> Hypothesis 1a. China's healthcare expenditure has a positive effect on economic growth.
> Hypothesis 1b. China's healthcare expenditure has an inhibitory effect on economic growth.

Although the direction of medical and health spending on economic growth is indeterminate, a considerable number of studies have discussed this issue. In contrast, the specific mechanism through which healthcare expenditure effects economic growth has been ignored. Representative research results show that the economic growth effect from healthcare expenditure is mainly realized through the accumulation of material and human capital. Specifically, healthcare expenditure will occupy household consumption expenditures and directly affect the consumption allocation of residents. Based on precautionary savings theory, this behavior will raise household consumption and reduce savings as well as the speed of material capital accumulation (22). As a result, economic growth is slowed; however, the medical insurance system can avoid the poverty caused by illness to a certain extent and stabilize income expectations by reducing the economic risk of residents. Numerous scholars have also proven that the medical security system is a "necessity" rather than a "luxury" for most countries from mathematical and empirical perspectives (23), while the medical security system can enhance personal savings during the working span of the labor force (24, 25). Thus, it produces a positive impact on economic growth. In other words, the direction of the impact of material capital accumulation on medical expenditure on economic growth is uncertain. The research conclusions regarding the effect of human capital accumulation on healthcare expenditure and thereby on economic growth are relatively uniform. Zhu et al. (26) and Jia et al. (27) and other scholars deem that the increase in healthcare expenditures can not only reduce the newborn mortality rate and prolong the average life span but also increase investment in health and educational capital by increasing leisure time through the substitution effect, which can play a positive role in promoting the economic growth effect of healthcare expenditure. The relationship between material capital accumulation, human capital accumulation and health expenditure on economic growth can be summarized as follows.

China is a developing economy: the medical security system is not perfect, the population is large, and a considerable part of the population has little disposable income. Therefore, in the short term, healthcare expenditure creates real pressure on middle- and lower-level families, further reducing their disposable income and thereby affecting economic growth. A long-term medical insurance system can effectively alleviate the family poverty caused by illness, providing a significant umbrella for ordinary families in the face of natural and man-made disasters and preserving the time and energy of residents for investment in human capital reserves, so it may have a positive impact on economic growth. Based on this reasoning, the second assumption of this paper is proposed:

> Hypothesis 2. China's healthcare expenditure plays a role in economic growth through the accumulation of material and human capital. The material accumulation channel has a negative impact on the economic growth effect of healthcare expenditure in the short term and a positive effect in the long term. The human capital accumulation channel has a positive impact on the economic growth effect of healthcare expenditure in both the short and long term.

Few researchers have also attempted to seek the mechanism through which medical security expenditure affects economic growth considering aspects such as residents' consumption, aging, degree of economic openness, employment rate, economic development level, etc. (28–32). Taking into account the imbalance in regional economic development in China, healthcare expenditures in different regions are also significantly different. Merely considering the economic growth effect of China's healthcare expenditure from a national perspective will

not provide a comprehensive understanding; therefore, the last assumption of this article is proposed:

Hypothesis 3. The economic growth effect of China's healthcare expenditure is significantly different in different regions.

METHODS AND DATA SOURCES

To test hypotheses 1, 2, and 3, this paper designs the following research process.

Data Sources

This paper focuses on the effect of China's healthcare expenditure on economic growth and holds that healthcare expenditure will have different effects on long- and short-term economic growth. The impact of healthcare expenditure on economic growth is regulated by the medical security system and is mainly realized through the accumulation of material and human capital. In this study, China's healthcare expenditure is represented by the proportion of healthcare expenditure in GDP (%), short-term economic growth is represented by the quarterly per capita GDP growth rate (%), and long-term economic growth is represented by the 5-year per capita GDP growth rate (%). When discussing the transmission path for the effect of medical expenditure on economic growth, the accumulation of physical capital and human capital are, respectively represented by the total amount of fixed assets investment and the percentage of education expenditure in GDP (%). The specific data are described in **Table 1**.

In addition, considering that the effect of healthcare expenditure on economic growth will be influenced by many other economic factors, if the many economic variables potentially involved are not included in the systematic analysis framework, the empirical research results may deviate from the actual economic situation. Considering the latent factors that may affect the relationship between health expenditure and economic growth and the availability of data, this paper identifies and classifies 78 influencing factors, mainly related to the level of economic development, macroeconomic status, economic openness degree, population aging and so on. All data are quarterly data from the Wind database. The obvious seasonal factors are processed by X-12, the non-stationary data are processed by the ADF test, and some missing data need to be supplemented by interpolation.

Estimation Method: SV-TVP-FAVAR Model

All the factors that may impact the economic growth effect of healthcare expenditure are included in the $Database_t$. Concurrently, to eliminate the curse of dimensionality caused by including too many variables in the traditional model, we use the method of Bernanke and Boivin (33) to extract the data in the background dataset into several common factors that cannot be observed. The method is as follows:

$$Database_t = \Lambda^{\overline{ob}}\overline{ob_t} + \Lambda^{\overline{un}}\overline{Un_t} + \varepsilon_t \tag{1}$$

where $\Lambda^{\overline{ob}}$ and $\Lambda^{\overline{un}}$ are factor loading matrices. $\overline{ob_t}$ and $\overline{un_t}$ are the observable part and the unobservable part, respectively. $\varepsilon_t \tilde{} N(0, \Omega_t)$. Abstracting a large amount of information into several unobservable common factors can effectively avoid the problem of missing key data variables. However, if the economic growth effect of China's healthcare expenditure is calculated by the classical VAR model (34), it will be limited by the constant parameters of the model, with the exception of the degrees of freedom. A constant parameter model means that no part of the economic system can vary with time, and this would make it difficult to capture the effect of medical expenditure policy on economic growth in distinct economic periods. Therefore, in the above FAVAR framework, the parameters in the model are further extended to the time-varying mode:

$$\begin{cases} x_{it} = \tilde{\lambda}_i^f f_t + \tilde{\lambda}_i^l l_t + \tilde{\lambda}_i^w w_t + \zeta_{it} \\ y_t = b_{1t} y_{t-1} + ... + b_{pt} y_{t-p} + \xi_t \end{cases} \tag{2}$$

$\tilde{\lambda}_i^f$ $\tilde{\lambda}_i^l$ and $\tilde{\lambda}_i^w$ are the dynamic factor loading matrices in turn, and f_t is the extracted common factor, whose dimension is defined as (3×1)[1]; $[l_t, w_t]$ is composed of long- and short-term economic growth rate and health expenditure as observation variables and proxy variables, respectively.

i=1,...,p, $t = 1, ..., T$,$\xi_t \tilde{} N(0, \Omega_t)$,$\zeta_{it} \tilde{} N\left(0, \exp\left(h_{it}\right)\right)$.

Furthermore, let the residuals in **Equation (2)** be random walks; then, by solving the equation, we can obtain:

$$x_t = \lambda^f f_t + \lambda^l l_t + \lambda^w w_t + \Gamma(L) x_t + \varepsilon_t \tag{3}$$

$\Gamma(L) = diag\left(\rho^1(L), ..., \rho^n(L)\right)$, $\rho^i(L) = \rho_{i1}L + ... + \rho_{iq}L^q$;$\lambda^j = (I_n - \Gamma(L))\tilde{\lambda}^j$,$j = f, l, w$;$\varepsilon_t \tilde{} N(0, H_t)$,$H = diag\left(\exp\left(h_{1t}\right), ..., \exp\left(h_{nt}\right)\right)$. The form of residuals with the random walk is $h_{it} = h_{it-1} + \eta_t^h$,$\eta_t^h \tilde{} N(0, \sigma_h)$. Thus, the SV-TVP-FAVAR model is constructed and used to analyze the economic growth effect of China's healthcare expenditure.

Model Construction

Using the above framework to verify the first set of hypotheses and making full use of the advantages of MATLAB high-dimensional computing, we can draw the three-dimensional impulse response diagram for the effect of China's health expenditure on economic growth. Further exploring the transmission channel for the economic growth effect of health expenditure to test hypothesis 2, we can construct the following regression equation:

$$\begin{bmatrix} I_{short} \\ I_{long} \end{bmatrix} = \begin{bmatrix} \beta_{short,t}^K & 0 \\ 0 & \beta_{long,t}^L \end{bmatrix} \begin{bmatrix} F_K \\ F_L \end{bmatrix} + \begin{bmatrix} \beta_{short,t}^L & 0 \\ 0 & \beta_{long,t}^K \end{bmatrix} \begin{bmatrix} F_L \\ F_K \end{bmatrix} + \begin{bmatrix} e_t^{short} \\ e_t^{long} \end{bmatrix} \tag{4}$$

I_{short} and I_{long} are the short- and long-term economic growth effects of health expenditure, respectively; F_K and F_L are the effects of material capital accumulation and human capital

[1]This article also tried to extract other numbers of common factors, but these did not have a significant impact on the empirical results. The results are available on request.

TABLE 1 | Statistical description of the main variables in the article.

Var.	Var. Def.	Sam. Per.	Mean	Max.	Min.	Std. Dev	Median
HCE_CN	Healthcare expenditure in GDP (%)	2003Q1–2019Q4	4.503	7.545	0.652	0.233	4.766
GDP_S	China's quarterly per capita GDP growth rate (%)	2003Q1–2019Q4	3.004	5.611	1.548	0.130	2.607
GDP_L	China's 5-year per capita GDP growth rate (%)	2003Q1–2019Q4	12.598	17.707	8.300	0.388	12.575
PCA	Physical capital accumulation expenditure in GDP (%)	2003Q1–2019Q4	57.806	1.271	0.112	52.578	0.714
HCA	Human capital accumulation expenditure in GDP (%)	2003Q1–2019Q4	18.674	22.670	15.428	0.223	18.433

GDP, represents China's gross domestic product; Sam. Per., represents sample period; Var., variable; Max., maximum; Min., minimum; Std. Dev., standard deviation.

accumulation, respectively; $\beta^K_{short,t}$, $\beta^L_{short,t}$, $\beta^K_{long,t}$ and $\beta^L_{long,t}$ are the respective time-varying coefficients of physical capital accumulation and human capital accumulation in the effect of health expenditure on economic growth. Further referring to Primiceri (35) and Nakajima et al. (36), we can divide $\left[e_t^{short} \;\; e_t^{long}\right]'$ into lower triangular matrix A, diagonal matrix Σ and white noise sequence δ_t:

$$\left[e_t^k\right] = \alpha^{-1}\sigma\delta_t = \begin{bmatrix} 1 & \cdots & 0 \\ \vdots & \ddots & \vdots \\ a_{k1} & \cdots & 1 \end{bmatrix}^{-1} \begin{bmatrix} \sigma_1 & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & \sigma_k \end{bmatrix} \delta_t \qquad (5)$$

Following **Equation (3)**, let the model have the form of random fluctuation, and all the residuals conform to the innovative random walk. Then, this model can verify how the leading factors in the effect of health expenditure on economic growth change under diverse economic contexts. If hypothesis 2 is true, $\beta^K_{short,t}$, $\beta^L_{short,t}$, $\beta^K_{long,t}$, and $\beta^L_{long,t}$should be time-varying, and their strength will depend on the economic context. If the short-term impact of health expenditure on economic growth is mainly negative through the channel of material capital accumulation, and the long-term impact on economic growth is mainly positive through this channel, then there should be $\beta^K_{short,t} < 0$,$\beta^K_{short,t} > 0$. If, through the accumulation of human capital, the effect of health expenditure on economic growth is positive in both the long term and the short term, then $\beta^L_{short,t}$, $\beta^L_{short,t} > 0$.

In reality, China possesses a vast territory, and its economic development gap between different regions is large. To comprehensively test hypothesis 3, considering China's economic areas and data availability, we select Beijing, the capital of China; Tianjin, a municipality directly under the central government in northern China; Jilin, a representative in the northeastern part of the old industrial base; Sichuan, a representative area in southwestern China; and Inner Mongolia, a representative in the Yellow River basin, to fit the impact of health expenditure in each region on the short- and long-term growth of China's economy and transmission channels. For a description of the economic data selected in this paper, please refer to **Table 2**. If hypothesis 3 is true, $I^{EZ}_{short/long} = [I_{NMG}, I_{JL}, I_{SC}, I_{BJ}, I_{TJ}]$ should be time-varying and distinct from each other. $\beta^{EZ,K}_{short/long,t} = [\beta^K_{NMG,t}, \beta^K_{JL,t}, \beta^K_{SC,t}, \beta^K_{BK,t}, \beta^K_{TJ,t}]$ and $\beta^{EZ,L}_{short/long,t} = [\beta^L_{NMG,t}, \beta^L_{JL,t}, \beta^L_{SC,t}, \beta^L_{BK,t}, \beta^L_{TJ,t}]$ will also show different characteristics due to the difference in economic range.

EMPIRICAL RESULTS

Unit Root Test and Selection of Optimal Lag Order

Before conducting empirical research, it should be noted that all economic variables included in the systematic analysis framework should be handled as stable to avoid the problem of spurious regression. **Table 3** provides the ADF test results for health expenditure in China, Inner Mongolia, Jilin, Sichuan, Beijing, and Tianjin, as well as the short- and long-term economic growth data of the corresponding regions, all of which are consistent with first-order stationary data. Similarly, the ADF test is carried out to measure the material capital accumulation and human capital accumulation of the possible transmission path of the economic growth effect of health expenditure in different economic regions, and the consequences are also put into **Table 3**. It can be seen that material capital accumulation and human capital accumulation in diverse economic regions of China are stable data after handling.

Empirical Results of the SV-TVP-FAVAR Model

This section is based on the model in the previous section. First, the historical characteristics of the evolving effect of China's healthcare expenditure on economic growth are analyzed by the time-varying parameter method, and then the possible transmission path for the healthcare expenditure effect on short-term and long-term economic growth is discussed based on the pulse response method. Overall, the comprehensive combination of the dynamic change in the effect of China's healthcare expenditure on economic growth and its mechanism in recent years allows us to obtain some revealing findings as follows:

Figure 1 demonstrates three-dimensional impulse response diagrams of the impact of healthcare expenditure on short-term economic growth in China, Inner Mongolia, Jilin, Sichuan, Beijing and Tianjin. In this figure, the x-axis is the time dimension and reveals the time point of the impact of health

TABLE 2 | Statistical description of China's healthcare expenditure in different regions.

Var.	Var. Def.	Sam. Per.	Mean	Max.	Min.	Std. Dev	Median
HCE_NMG	Inner Mongolia's proportion of healthcare expenditure in GDP (%)	2003Q1–2019Q4	0.996	1.817	0.174	0.056	1.019
HCE_JL	Jilin Province's proportion of healthcare expenditure in GDP (%)	2006Q1–2019Q4	1.383	2.720	0.147	0.081	1.330
HCE_SC	Sichuan Province's proportion of healthcare expenditure in GDP (%)	2006Q1–2019Q4	1.564	2.241	0.160	0.072	1.701
HCE_BJ	Beijing's proportion of healthcare expenditure in GDP (%)	2009Q1–2019Q4	1.409	1.610	0.366	0.033	1.444
HCE_TJ	Tianjin's proportion of healthcare expenditure in GDP (%)	2011Q1–2019Q4	0.689	1.271	0.112	0.048	0.714

HCE, represents China's healthcare expenditure in different regions; Sam. Per., represents the sample period; Var., variable; Max., maximum; Min., minimum; Std. Dev., standard deviation.

TABLE 3 | The results of ADF unit root tests for healthcare expenditure (HCE) and GDP.

Regions	HCE		GDP_S		GDP_L	
	Level	First difference	Level	First difference	Level	First difference
CN	−1.609	−3.526**	−1.955	−8.366***	−2.804	−1.179*
NMG	−0.039	−4.433***	−1.401	−8.844***	−0.980	−8.326***
JL	−0.336	−6.520***	0.695	−8.144***	0.6334	−8.135***
SC	−2.361	−3.079**	−2.300	−8.614***	−2.018	−8.081***
BJ	−1.609	−4.496***	−1.867	−6.315***	−2.046	−8.128***
TJ	−1.492	−3.823***	0.462	−8.239***	1.462	−7.976***

, **, or * denote that the null hypothesis is rejected at the 10, 5, or 1% significance levels; HCE, represents China's healthcare expenditure in different regions; GDP_S and GDP_L, represents China's short-term economic growth and long-term economic growth in different regions, respectively.*

expenditure on the economy in the short term; the y-axis is the response dimension, showing the duration of the impact of health expenditure on economic growth; and the z-axis indicates the strength of the effect of health expenditure on economic growth. From the results of the empirical analysis, health expenditure has a significant negative effect on short-term economic growth in China. Specifically, in the short term, an increase in the proportion of health expenditure will lead to a decrease in the short-term economic growth rate. From the time dimension analysis, it can be found that during the period of global economic crisis and the new normal of the Chinese economy, the impact of health expenditure on economic growth in China, except for Tianjin, has increased significantly, which shows that the public health insurance system further inhibits the speed of economic growth when the economic system is seriously impacted. This is consistent with the economic facts, since in the period of global economic crisis included in the sampling interval, a multitude of enterprises closed down, the economy fell into stagnation, and the unemployment rate rose abruptly. These negative factors all led to weak economic growth. China's entry into the "new normal" is similar. At this stage, facing a more complex and changeable domestic and international environment, China had a slower economic growth rate, and its economic development mode changed from "quantity" to "quality." Therefore, in this economic context, enhanced health expenditure will undoubtedly increase the financial burden of the government and negatively impact short-term economic growth. Similarly, the impulse response results support the above inference. When China's economic system is affected by a negative external impact, the duration of health expenditure's impact on economic growth is extended, and the adverse effect of the increase in health expenditure on the speed of economic growth lasts longer during periods of economic fragility.

Figure 2 shows the impact of health expenditure on long-term economic growth. The x-axis and y-axis are the time dimension and response dimension, respectively, and represent the time point and duration of the impact of healthcare expenditure on long-term economic growth in China, while the z-axis is the three-dimensional impulse response amplitude of the economic growth effect of healthcare expenditure. In general, compared with the negative impact of health expenditure on short-term economic growth, the heterogeneity of health expenditure on long-term economic growth is more obvious, verifying hypothesis 3. The overall data of China show that healthcare expenditure will promote long-term economic growth. The reason may be that the establishment of the medical and health security system has greatly improved the situation of the overall population, thus increasing the effective labor supply and promoting economic growth through the accumulation of human capital in the long run. The reason may also be that from a nationwide perspective, the medical insurance system can effectively reduce the probability of poverty caused by illness and reduce the economic risk of residents, increasing personal savings in the long run and having a positive impact

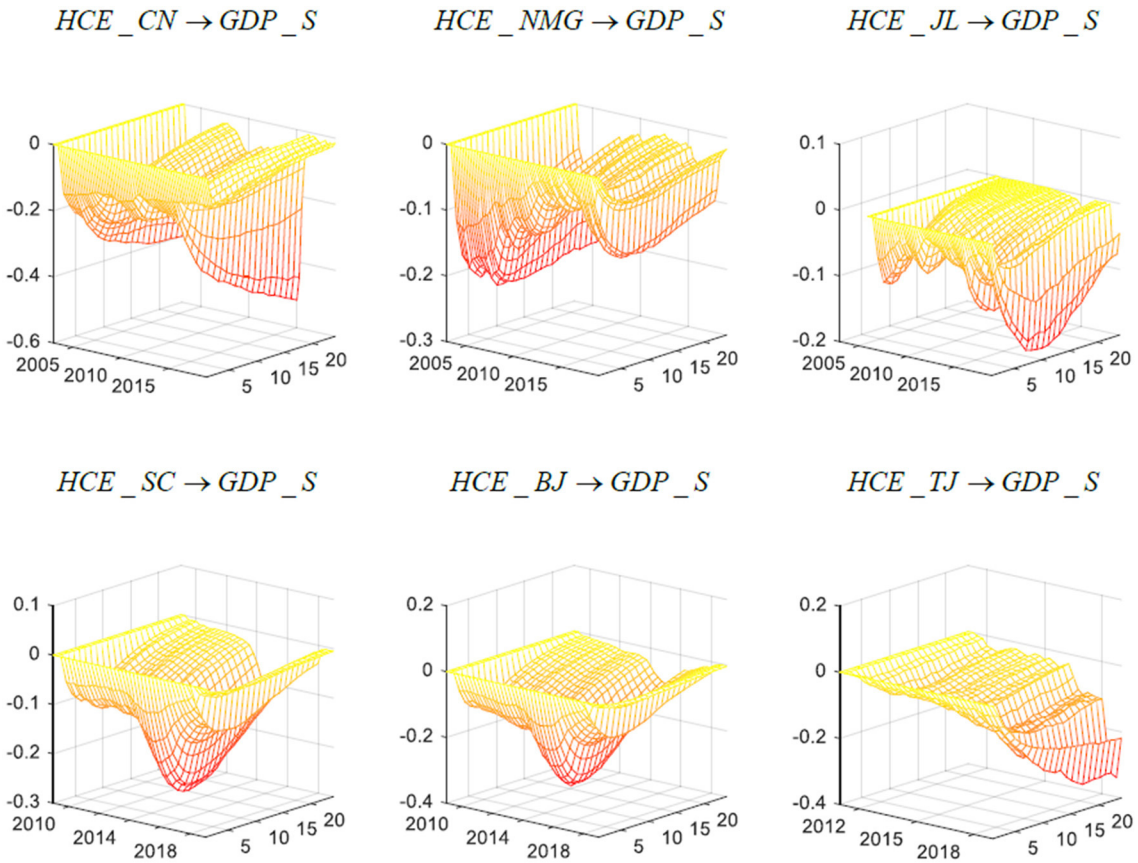

FIGURE 1 | Three-dimensional impulse response of China's short-term economic growth in different regions. Each subfigure with the title of "*X* → *Y*" demonstrates the response of variable Y to an orthogonalized positive shock to variable X. In other words, X is an impulse variable, and Y is a response variable. One period in the figure denotes one season.

on economic growth by way of material capital. Through the in-depth analysis of the impact of health expenditure on long-term economic growth in diverse economic regions of China, it can be seen that improvement in health expenditure still resists long-term economic growth most of the time for Inner Mongolia, Jilin, and other regions, and this adverse impact on long-term economic growth shows an increasing trend in the time dimension. Because both inner Mongolia and Jilin are old industrial bases with similar economic structures and are among China's relatively underdeveloped areas, their main driving force for economic growth comes from the labor-intensive secondary industry. In recent years, the economic gap between northern and southern China has gradually widened, which has also led to the further slowdown of economic growth in Inner Mongolia and Jilin. The pressure of healthcare expenditures on local finances is more apparent in these two regions, which reduces the benefits of the improved medical and health security system. Sichuan is located in the hinterland of Southwest China and is rich in resources. In recent years, a group of urban areas led by Chengdu have developed rapidly, undertaking part of the spillover capacity in the Yangtze River Delta. The increase in healthcare expenditure in Sichuan can slightly stimulate economic growth during a period of stable economic growth but will have a certain negative impact on long-term economic growth as China's economy enters the new normal. After 2018, with the improving economic development of Sichuan Province, local finance can withstand the pressure of increasing healthcare expenditures. Therefore, the long-term positive effect of the medical and health security system on the economy is obvious, showing that the impact of healthcare expenditure on long-term economic growth has increased. Beijing is the capital of China, and it thus undertakes more administrative functions. The impact of healthcare expenditure will accelerate Beijing's long-term economic growth most of the time but cause a negative response to Beijing's long-term economic growth during a period of shifting national economic growth. Tianjin, one of the municipalities directly under the central government in China, is one of the core areas of the Beijing Tianjin Hebei Economic Zone, which undertakes part of the productivity transfer in Beijing. For Tianjin, healthcare expenditure will significantly promote local economic growth, and its long-term effect on economic growth has an increasing trend over time, which indicates that the advantages of healthcare expenditure on the long-term economic growth of Tianjin are greater than the disadvantages. The results

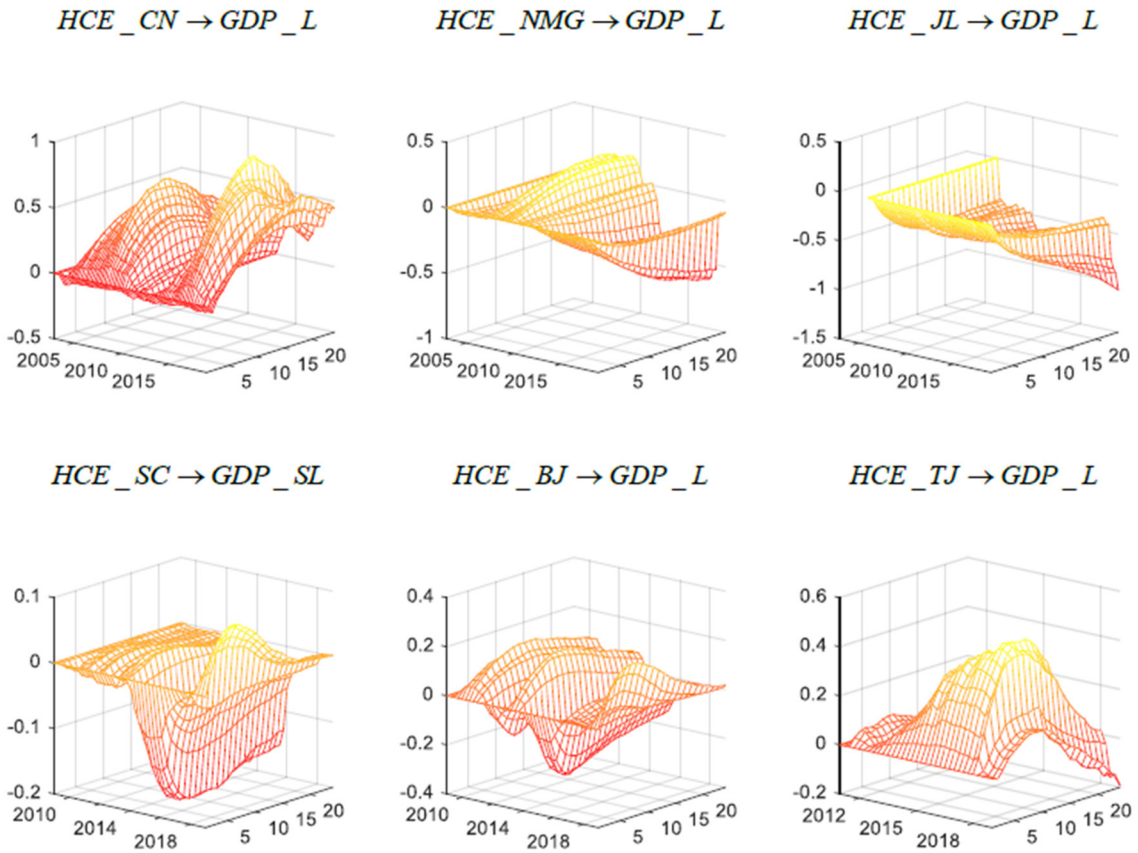

FIGURE 2 | Three-dimensional impulse response of China's long-term economic growth in different regions. Each subfigure with the title of "*X* → *Y*" demonstrates the response of variable Y to an orthogonalized positive shock to variable X. In other words, X is an impulse variable, and Y is a response variable. One period in the figure denotes one season.

are similar to the economic growth effect of national healthcare expenditure.

In conclusion, the results of the three-dimensional impulse response function illustrate the impact of health expenditure on short- and long-term economic growth and offer an initial exploration of the possible causes of heterogeneity in the effects of medical and health expenditures on economic growth in different economic contexts and different economic regions. The empirical results show that hypothesis 1 is incomplete. In the short run, increasing health expenditures will have a negative impact on economic growth, while in the long run, the benefits of increasing health expenditure gradually emerge, as reflected in the acceleration of long-term economic growth. Specifically, for distinct economic regions in China, the growth of short-term healthcare expenditures will lead to a decline in economic growth, but the corresponding results for the long-term impact of healthcare expenditure on economic growth are significantly different, so hypothesis 3 is tenable. To further test hypothesis 2 and to further explore the impact of health expenditure on economic growth, we simulated the role of the physical and human capital accumulation channels in the transmission process.

There are significant differences between physical capital accumulation and human capital accumulation. Physical capital investment has a faster effect, including it among short-term capital returns. However, human capital investment often has an exceedingly long lag before returns are realized. Whether the returns come through improving national health and then improving effective labor time or through accumulating investment in education for the next generation, they cannot be obtained in a short time. This paper investigates the role of physical and human capital accumulation channels in the economic growth effect of healthcare expenditure in China, Inner Mongolia, Jilin, Beijing, and Tianjin; the results are summarized in **Table 4**.

As shown in **Table 4**, in the short term, the material accumulation channel will have a significant negative impact on the economic growth effect of healthcare expenditure, which indicates that increasing healthcare expenditures will enhance the local financial burden in the short term, increase residents' living expenses, and thereby affect consumption, which will significantly inhibit short-term economic growth. Although the accumulation of human capital has a positive effect on the economic growth of healthcare expenditure in the short term,

the effect is smaller than that from the accumulation of material capital. There are two reasons leading to the phenomenon in which an increase in healthcare expenditure brings about a decline in short-term economic growth. In the long run, human capital accumulation channels have a positive influence on the effect of healthcare expenditure on economic growth, and this effect is higher than its short-term effect across all economic regions of China. The empirical results are consistent with the economic facts: human capital accumulation tends to take effect in the long run. The impact of material capital accumulation on the effect of healthcare expenditure on economic growth is more complex. The accumulation of material capital in the Inner Mongolia, Jilin and Sichuan regions played a negative role in the long term, with effect ranges of −0.1277, −0.0135, and −0.0027, respectively. All of China, Beijing and Tianjin were positively affected by the accumulation channels of material capital, with effect sizes of 0.0376, 0.0565, and 0.0707, respectively. This illustrates that for the material accumulation channel of China's medical expenditures, economically developed areas will benefit more in the long run because the residents in developed areas have more disposable income, and coverage from the medical security system can reduce family healthcare expenditure in the long run, thus effectively protecting families from poverty caused by illness. At the same time, personal savings can increase more quickly in economically developed areas and then promote economic growth through long-term material accumulation channels. In contrast, in economically underdeveloped areas, fiscal tension, insufficient disposable income and increased healthcare expenditures will crowd out residents' consumption and reduce savings, leading to a decline in long-term economic growth. However, for the whole country, the medical security system is undoubtedly necessary. Although the long-term economic growth of underdeveloped areas will be negatively affected by healthcare expenditures and may need certain "subsidies" from developed areas, healthcare expenditures across the country, whether through the accumulation of physical or human capital, will contribute to long-term economic growth. To a certain extent, healthcare expenditures can help to improve people's welfare and economic efficiency in the long run.

TABLE 4 | The role of physical capital accumulation and human capital channels in the economic growth effect of healthcare expenditure in China's different regions.

Regions	PCA		HCA	
	Short-term	Long-term	Short-term	Long-term
CN	−0.0916	0.0376	0.0356	0.2392
NMG	−0.0075	−0.1277	0.0074	0.0195
JL	−0.0093	−0.0135	0.0067	0.0053
SC	−0.0332	−0.0027	0.0077	0.0164
BJ	−0.0411	0.0565	0.0304	0.0138
YJ	−0.0063	0.0707	0.0031	0.0186

PCA, represents physical capital accumulation expenditure in GDP (%); HCA, represents human capital accumulation expenditure in GDP (%).

TABLE 5 | Robustness test results: change in the sampling interval.

	GDP_S	GDP_L		GDP_S	GDP_L
HCE_CN	−0.387	1.471	HCE_SC	−0.014	−0.007
HCE_NMG	−0.182	0.659	HCE_BJ	−0.039	0.384
HCE_JL	−0.078	−0.052	HCE_TJ	−0.265	0.515

Robustness Analyses

In this section, we utilize two common robustness test methods to verify the above empirical results. First, the sampling interval is replaced by other subintervals to verify whether the main conclusions we obtained are still valid in other time periods and to try to avoid the influence of the sampling interval on the main research conclusions. Second, by changing the lag order in the SV-TVP-FAVAR model, we can measure the reliability of the above empirical research conclusions from the perspective of the model.

Alternative Sample Period

In the baseline analyses, to explore the economic growth effect of national medical and health expenditure, we selected a sampling interval from the first quarter of 2006 to the fourth quarter of 2019; however, the sampling range for analyzing the economic growth effect of medical and health spending in other economic regions of China is limited by the availability of data in each economic region. The effect of health expenditure on economic growth mainly occurs through the accumulation of physical and human capital, but the effect of health expenditure on economic growth is inevitably also affected by other economic variables. To address this issue, this paper introduces the idea of factor enhancement, which abstracts major possible economic variables into three unobservable common factors to include as many factors as possible in the systematic analysis framework. However, the problem is that a longer sampling interval implies that more factors that may ultimately affect the effect of health expenditures on economic growth are included, and the sampling intervals selected in different areas are also diverse. Apart from the sampling interval selected in this paper, does the effect of medical and health expenditure on economic growth still support our main conclusions? To verify the robustness of the empirical research conclusions for other sampling intervals, we choose the first quarter of 2017 to the fourth quarter of 2019 as a new adoption interval that is unified in each region. The verification results are shown in **Table 5**, and they are analogous to the original conclusions. The results consistently support that the increase in medical and health expenditure is not conducive to short-term economic growth but can benefit long-term economic growth. For other subintervals, such as from the first quarter of 2010 to the fourth quarter of 2012 and from the first quarter of 2015 to the fourth quarter of 2017, we also verify our previous conclusions. Due to the limited space, these results are reserved for retrieval.

Alternative Selection of Variable Lag Order

In the baseline model, the first-order lag is adopted according to the AIC; thus, in this section, we change the lag order in the model. With the other conditions remaining unaltered, we change the lag order of the model and then use the second-order

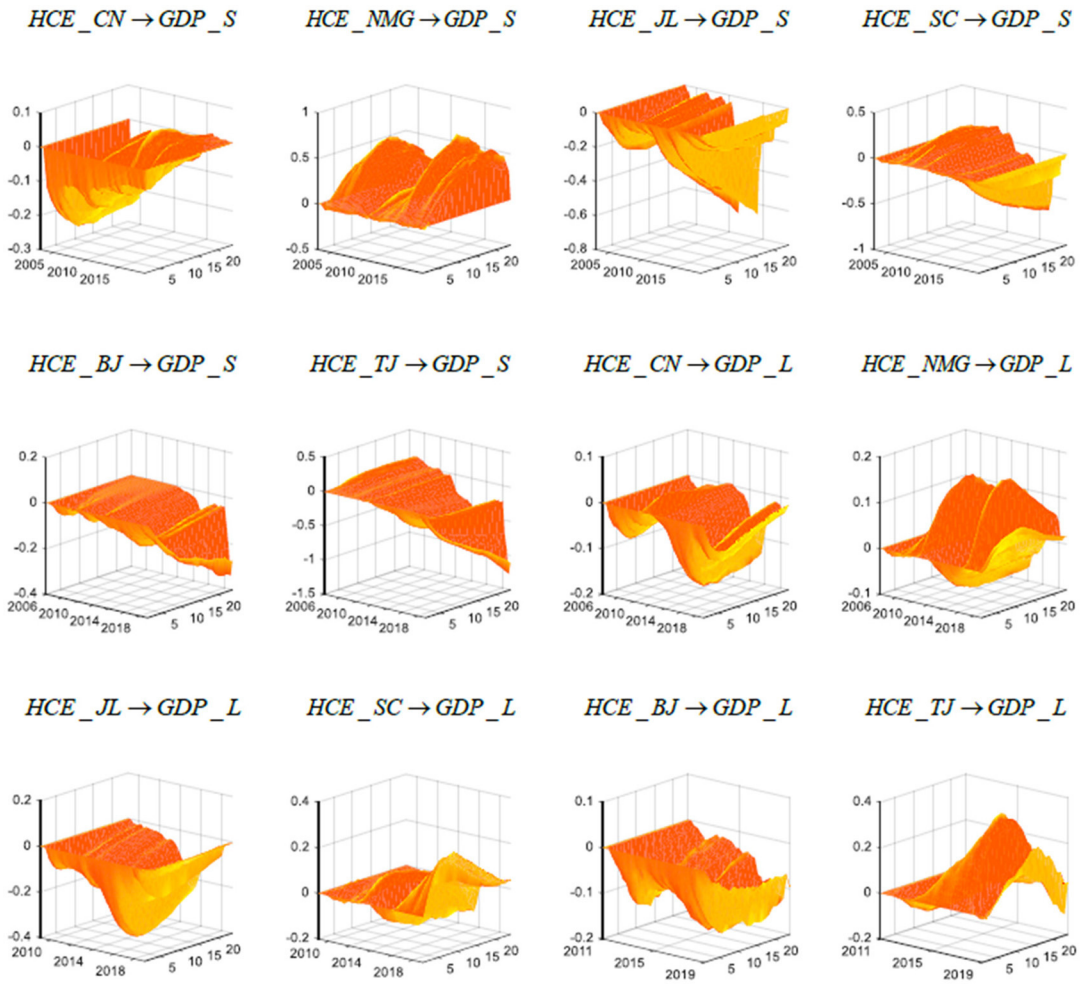

FIGURE 3 | Robustness test results: change in the selection of the variable lag order. The results shown in the figure are for the second-order lag. Due to space limitations, the empirical results of the remaining lagged orders are not listed individually but maintained for reference. Each subfigure with the title of "*X* → *Y*" demonstrates the response of variable Y to an orthogonalized positive shock to variable X. In other words, X is an impulse variable, and Y is a response variable. One period in the figure denotes one season.

lag model and the third-order lag model to analyze the effect of medical and health expenditure on economic growth. The results are shown in **Figure 3**. It can be seen that altering the lag order of the model fails to change the previous empirical results, proving that the conclusions of this paper are robust.

Alternative Number of Common Factors

This paper conducts an empirical analysis under a framework that contains many variables related to the effect of China's healthcare expenditure on economic growth. In the factor extraction section, we extracted three common factors. To further verify the robustness of the model test results, we attempt to conduct four and five common factor extractions, and the results show that changing the number of common factor extractions does not change the core conclusion of this article. Due to space limitations, the specific empirical results are not listed but have been maintained for reference.

CONCLUSIONS AND POLICY IMPLICATIONS

The coverage of the medical security system has a vital impact on people's economic ability to support their lifestyle, and medical and health expenditures also significantly affect the speed of economic growth. However, few scholars have deeply investigated the impact of medical and health expenditures on economic growth in distinct regions of the same country or explored the mechanism behind these effects. By constructing a systematic research framework, this paper analyzes the mechanism through which medical and health expenditures influence economic growth. It offers a comprehensive consideration of potential influencing factors and selects time series data of China and its different economic regions (including Inner Mongolia, Jilin, Sichuan, Beijing, and Tianjin) from the first quarter of 2006 to the fourth quarter of 2019 to empirically test the effect of medical and health

expenditure on economic growth and its internal mechanism by using a time-varying parameter model, which can capture slight dynamic changes in the economic system.

The results of the empirical research presented in this paper demonstrate that in China as a whole, increasing medical and health expenditure will produce a negative impact on economic growth in the short term, but in the long term, it will stimulate economic growth. Due to China's vast territory, the level of healthcare and economic development vary greatly for different regions, which will undoubtedly affect how medical and health expenditures influence growth in diverse economic regions within China. When our research focuses on China, we find that there are obvious differences in the effects of medical and health spending on economic growth in different regions. The increase in medical and health expenditures suppresses economic growth in Inner Mongolia and Jilin over the sampling range. It also played a negative role in the economic growth of Sichuan most of the time, though its role has become positive in recent years. Medical and health expenditures play a driving role in the economic growth of Beijing, Tianjin, and other regions, which illustrates that these are a relatively heavy burden on the local finances of subdeveloped areas in China. Due to the fragile economic environment, inadequate infrastructure and other reasons, the benefits brought by the improved medical security system are insufficient to alleviate the pressure on residents and local governments caused by increased expenditures, thereby causing the regional economic growth rate to slow down in the short and long term. For the developed areas in China, due to the high level of infrastructure construction and the high disposable income of residents, medical and health expenditures can provide more convenient health protection for residents. Through the substitution effect, residents can enhance their leisure time for health management and engage in education expenditures to promote investment and consumption, which in turn will benefit the local economy in the long run.

The empirical analysis of the effect of medical and health economic growth also reveals that the long- and short-term effects of medical and health expenditures on economic growth are achieved through the accumulation of physical and human capital. The direction of the effect of the accumulation of physical capital on the growth of medical and health economies is uncertain, but the accumulation of human capital tends to play a positive role in the short and long term. Through the in-depth analysis, it can be seen that an increase in medical and health expenditure in underdeveloped areas (Inner Mongolia, Jilin) in China plays a negative role in short-term economic growth through the channel of material accumulation, while in developed regions (Tianjin, Beijing), that same channel plays the opposite role. The effect of the transmission channel is consistent with the above empirical results in that the economic growth of underdeveloped areas is restrained by an increase in medical expenditure, and the economic growth of developed areas is restrained in the short term but significantly increased in the long term.

Not only China but the whole world is facing the need to balance between "protecting people's livelihood" and "promoting growth," especially when COVID-19 is spreading globally. Finding a balance between the two with limited resources is a momentous task. The research conclusion of this paper further verifies that the medical security system is a necessity, and its construction as well as its coverage is an important path to ensure people's livelihood and while simultaneously promoting growth. The research illustrates that a sound medical and health security system must be established, producing a positive impact on economic growth in the long run and effectively promoting economic growth through long-term material capital accumulation and human capital accumulation. Substantial economic growth can increase government revenue and provide strong support for the enrichment of livelihood projects. However, there is a major imbalance in China's internal regional development. Therefore, the construction of China's multilevel medical security system cannot be deferred, and certain policy preferences and supporting expenditures are needed for economically underdeveloped areas. The research conclusion of this paper is that a medical security system is irreplaceable for people's livelihood in China, as "ensuring the people's livelihood" is a vital way to promote long-term economic growth; the results affirm the need for the government to spare no effort to treat COVID-19 during the epidemic, motivated by the desire to restore order to the economy as soon as possible, and this need is of great significance to the establishment of a long-term sustainable medical security system in China.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found at: raw data were generated by the Wind Database. Derived data supporting this study's findings are available from the corresponding author (SW) upon request, without undue reservation.

AUTHOR CONTRIBUTIONS

SW: conceptualization, methodology, software, formal analysis, data curation, writing—original draft preparation, writing—review, and editing. BZ, SW, and ZQ: validation. BZ: investigation, resources, supervision, project administration, and funding acquisition. ZQ: visualization. All authors contributed to the article and approved the submitted version.

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COVID-19 Outbreak and Financial Performance of Chinese Listed Firms: Evidence From Corporate Culture and Corporate Social Responsibility

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This research described Chinese listed firms' COVID-19 Outbreak and financial performance using corporate culture (CC) and corporate social responsibility (CSR) evidence. The epidemic's impact on Chinese companies' profits was much less than the impact on their sales growth rates. Although the COVID-19 has had a more significant negative impact on the financial performance of Chinese listed companies in sectors that are more severely impacted, such as travel and entertainment, we believe that the financial performance of the medical industry has improved as a result of the outbreak. Meanwhile, Chinese listed companies in high-risk areas experience more significant financial losses during the epidemic, and the Hubei impact is hefty weight. Corporate social responsibility moderated the inverse relationship between this epidemic and Chinese firms' economic success. This research enhances the current literature on the effects of the COVID-19 on financial success and practical, realistic, and theoretical consequences in companies worldwide.

Keywords: coronavirus, financial performance, Chinese listed companies, corporate culture, corporate social responsibility (CSR)

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INTRODUCTION

The first cases of the Covid-19 outbreak were recorded in Wuhan, China, on December 31, 2019, marking a key turning point in the outbreak's expansion to other Chinese provinces (1). As a result of the situation, the Chinese government agreed to close Wuhan on January 23, 2020, restricting outbound and inbound travel. The Chinese economy slowed due to the extreme lockout, as shown by a drop in manufacturing outputs and retailing income and a rise in unemployment. According to Bloomberg, Chinese industrial outputs plummeted by 13.5% in January and February 2020, whereas the retailing sector's revenue declined by 20.5%, in February 2020, the unemployment rate reached 6.2%. According to the IMF, Chinese economy will cool by around 0.4% points. The financial results of Chinese listed companies are likely to suffer in the first quarter of 2020 due to this epidemic. However, the effects of the COVID-19 on firm financial results have not been investigated in Chinese literature in particular; even though assessing the outbreak's effects is crucial for firms to decide their appropriate market plans. Furthermore, there is a paucity

of literature on the effects of infectious diseases on firm financial performance since the bulk of the literature on the subject has concentrated on the effects of such diseases on stock market performance (2, 3). Scholars discovered that dangerously contagious infections harmed consumer sentiment, affecting investment decisions (4). Consequently, when the dangerously infectious epidemic erupted, equity markets displayed a greater degree of uncertainty formed by erratic investor behavior (5). Notably, the stock market can overreact to certain diseases due to herding behaviors and panic spread, and stock market performance may not accurately represent firm financial efficiency. As a result, without assessing the economic effects of such illnesses, businesses will be unable to adequately evaluate their plans for dealing with and recovering from the health crisis. This analysis aims to add to the data on the effects of the Covid-19 outbreak on Chinese firms' financial. The epidemic affected the financial performance of Chinese publicly traded companies as measured by the sales growth rate, return on assets (ROAs), return on equity (ROE), and asset turnover (ATO) (6, 7). After the epidemic began in China at the end of the fourth quarter of 2019 and deepened in the first quarter of 2020, the quarterly data more reliably represents the effect of the outbreak on firm financial results and China had successfully contained the epidemic, reducing the effects of the outbreak on businesses. Following that, China effectively handled the epidemic and, unlike other nations, did not suffer a second phase of the health crisis due to the government's tight measures and Chinese companies recovered from the recession and did well in other areas. Since this analysis uses panel results, the generalized least squares (GLS) with cross-section weights and the white cross-section covariance approach are used to deal with cross-section heteroscedasticity and residual cross-section dependency (8). In general, the Covid-19 outbreak harmed Chinese listed firms' financial results in the first quarter of 2020, as it depressed the sales growth rate, ROA, ROE, and ATO of the companies analyzed in that quarter. Furthermore, the outbreak's negative effects on Chinese firms' sales growth rate were most severe this quarter, with revenue falling by 40%. However, the epidemic had only a minor impact on Chinese listed companies' ROA, ROE, and ATO, only 0.3, 0.7, and 5.2%, respectively. The outbreak's impact on the financial performance of Chinese publicly traded companies varied by industry and businesses with various working capital management policies and capital structures. Furthermore, corporate culture (CC) and corporate social responsibility (CSR) mitigate the detrimental impact of the epidemic on Chinese firms' financial results. The rest of the analysis divides into four parts after the introduction. The research history and current results on the effects of dangerously infectious diseases on firm efficiency clarify in the literature review section. The methodology segment describes the data collection process, sampling procedure, test design, hypotheses created, and research models developed. We discussed the details of the data collection in the fourth segment, the research's accomplishments and shortcomings outlined, and recommendations to the research's related stakeholders proposed.

LITERATURE REVIEW

Firm Performance

There are different theoretical perspectives of firm performance. The shareholder theory focuses on financial performance measures to examine how healthy firms maximize their profit to satisfy shareholder's needs. Differently, the stakeholder theory considers the satisfaction of all stakeholders as an indicator of firm performance (9). The balanced scorecard measures athletic performance by four aspects—financial, customer, internal process, and learning and growth (10). According to the balanced scorecard perspective, firms with excellent knowledge, and growth performance can obtain a better internal process (11). The firms are profitable, they can offer more incentives to their employees, leading to better employee satisfaction and retention (12). Firms' financial performance refers to their effectiveness and efficiency in utilizing their assets and capital to generate revenue and profit. It measures several profitability measures (ROA, ROE, ROCE) and turnover ratios and profitability ratios measure the ability of firms to generate profit (13).

In contrast, turnover ratios measure the efficiency of firms in utilizing their assets and capital in generating revenue (14) and a turnover ratio as indicators of agency costs (15). If agency conflicts are high, the management tends to underperform (16), leading to a low ATO ratio as assets utilizes efficiently (17). On the other hand, firm performance measures by the market performance of firms' shares proxied by Tobin's Q (18). However, firms' market performance may be subjective to investor sentiment and other irrational behaviors (19). Therefore, to examine firms' performance of firms, accounting based measures are preferred since they reflect firms' intrinsic performance without influences of external factors.

Internal Determinants of Firm Performance

The literature indicates several determinants of firm performance and from the agency perspective, agency conflicts influence athletic performance as the management is self-interest-oriented (20). Hence, developing effective corporate governance mechanisms minimized agency conflicts to improve firm performance and empirically, the robust corporate governance mechanisms are not enough to justify firms' performance (21–23). Instead, other factors such as the effectiveness of business strategies and management capabilities determine how firms perform (24, 25). Besides agency conflicts, working capital strategies adopted by firms also influence their financial performance (26) and customer satisfaction increases. By contrast, the minimization of current assets, called the aggressive working capital management, minimizes costs incurred by firms since inventories are only replenished when demands emerge. Consequently, firms' profitability increases, this strategy is risky as firms may not respond effectively to customers' demands and may have to borrow additional funds to accommodate their short-term liabilities. Empirically, a large number of research studies support the trade-off between liquidity and profit as well as the negative impacts of the conservative working capital management on firm performance (27). On the other hand, the management of long-term debts is also critical

since it influences firms' profitability (28) and firms have two sources of funds—debts and equity. The ratio between debt and equity determines firms' capital structure. According to the financial leverage is a "double-edge sword" since it can provide both benefits and threats to firms. When firms increase their debts, they can gain tax shield benefit since interest expenses are tax deductible. Furthermore, with the issuance of debts, firms can avoid the dilution of their current shareholders' benefits and the production perspective, firm size is also a determinant of athletic performance. Thus, firms can improve their profitability compared to others according to Josefy et al. (29), a giant size requires extensive capital investment and a highly structured organization.

Corporate Culture and Firm Performance

Corporate culture is a collection of unique values and codes of conduct shared by a company's people. Corporate culture is the soul and core of an enterprise and it is a critical factor that determines the firm performance and sustainable development. Arogyaswamy and Byles (30) stated that when the CC had consistent values or beliefs with the corporate strategy, it positively affected its performance. Denison (31) argued that CC affected a company's financial performance: business strategy, employees' work status, innovation activities, and financial information. Argued that CC indirectly affected firm performance through the moderating role of market performance and this strength in a dynamic market.

Similarly, Flamholtz and Kannan-Narasimhan (32) also advocated that CC indirectly correlated with firms' financial performance. Molenaar et al. (33) stated the safety culture of firm had a positive correlation with the construction performance. Huhtala et al. (34) found that the ethical culture has a significant positive effect on managers' professional performance and work participation behavior. Kaptein (35) argued that the CC could promote the employees' awareness and behavior. Stated that if a company ignored the function of the CC in governance, it would cause a huge damage to the firm performance. Argued that companies with an innovative culture could promote their performance through the role of the managers with their high-level emotional intelligence. Vigolo et al. (36) found that the service-oriented CC could help to increase employee motivation and satisfaction, and thereby improved firm performance. Pinho et al. (37) argued that the different types of culture had different effects on the firm performance and Zhao et al. (38) found that CC improvements are negatively linked with firm value, and positively related to innovation outputs. In particular, CC can better affect employees' job satisfaction and strengthen their organizational commitments.

Corporate Social Responsibility and Firm Performance

Explained emerged in the 1950s by four distinct theoretical perspectives: instrumental, political, integrated, and ethical. The first theoretical perspective considers CSR a vehicle for firms to achieve their profit targets and maximize shareholders' wealth. The second advocates that CSR is needed to realize their political power and present their corporate citizenship (39–41). The third theoretical perspective argues that CSR is essential to firms since they need to discharge their accountability to different resource holders through such activities (9). Thus, firms need to integrate the demands of other stakeholders into their business strategies and performance (42). Despite their differences in explaining the role of CSR, these theories share the standard definition of CSR and environmental activities of firms that ensure their compliance with legal and ethical frameworks as well as the "self-enlightening" perspective (40). This linkage commonly agrees upon the link between CSR and firms' performance (43). The integrative theory indicates that CSR brings rewards to firms because it enables firms to satisfy the demands of different stakeholders (44) to prevent reputational risk facing firms (45), to increase employee engagement and long-run stock return (46). Differently, CSR effects on firm performance may also be neutral because its benefits offset the additional costs added to firms (47). The neutral effects of CSR on firms' market performance are also justified by the impacts of external factors on share prices, as stated by behavioral finance (48).

Dangerously Contagious Diseases and Firm Performance

Dangerously contagious diseases refer to diseases, which are highly contagious among people and require extensive healthcare resources to prevent and cure. Examples of such conditions are Spain Flu, SARS, MERS, Ebola, and COVID-19 (49). Consequently, unemployment, income decreases, consumer expenditure declines, and leading to macroeconomic headwinds (1). The literature on the impacts of such diseases on firms' financial performance is scarce since most of the existing research studies focus on examining the effects of such conditions on the stock market (2–4).

However, the heterogeneity in impacts of such diseases on the stock market found that investors of this sector expect vaccine development to maximize returns of pharmaceutical stocks in the future (4). The COVID-19 outbreak negatively influenced most stock markets in the outbreak severely infected countries (2, 3). Jung et al. (50) examined the impacts of the MERS outbreak on customer expenditures in Korea. They found that total spending reduced significantly due to this outbreak and still, the heterogeneity existed across categories Secinaro et al. (6) examined how influenced the performance of medium companies in the travel and leisure sector in Europe. This research employed the content analysis of annual reports to compare three companies' financial performance and position in 2002 and 2003 (SARS). Aifuwa et al. (7) investigated the impacts of COVID-19 on Nigerian firms' financial and non-financial performance. Hassan et al. (51) revealed that since the emergence of the Covid-19 outbreak, firms mainly were concerned with the collapse of demand, the increase of uncertainty, and the disruption of their supply chain, the reduction of capacity, closures, and employee welfare. Furthermore, many firms could also foresee business opportunities in new and disrupted markets caused by the spread of this disease and the firms, which had experience with SARS, presented their positive expectations about their ability to respond to this outbreak.

TABLE 1 | The general profile of samples by industries.

No	Industry type	Number of companies	Percentage (%)
1	Airlines	10	8.06
2	Tourism	12	9.68
3	Retailers	10	8.06
4	Healthcare	6	4.84
5	Basic materials	16	12.90
6	Automobile	1	0.81
7	Energy	5	4.03
8	Industrials	10	8.06
9	Food processing and agriculture products	9	7.26
10	Entertainment	1	0.81
11	Construction	8	6.45
12	Beverage	7	5.65
13	Textile	10	8.06
14	Paper manufacturing	5	4.03
15	Technology	9	7.26
16	Real Estate	7	4.03

RESEARCH METHODOLOGY

Data Collection Procedure

This research adopts the stratified sampling method (52) to select Chinese listed firms as samples and it divides the total population into different segments and then randomly selects selections from each piece. This method enables random samples selected across various components and in this research, the total population of Chinese listed firms divides into 16 different industries. The final sample size is 126 listed firms from both Shanghai and Shenzhen stock markets and these firms are classified into 16 sectors, as shown in **Table 1**. For each sample, the quarterly financial data gather from Wind Database from the second quarter of 2019 to the second quarter of 2020. Among quarters, Chinese firms were not affected COVID-19 outbreak Q2, Q3, and Q4 of 2019, whereas this outbreak influenced them in Q1 and Q2 of 2020.

Hypothesis Development

The COVID-19 outbreak, after its emergence in December 2019 in Wuhan, spread China nationwide rapidly. The COVID-19 attack reduced the financial performance of Chinese listed firms in the first quarter of 2020.

H_1: The COVID-19 outbreak reduced the financial performance of Chinese listed firms.

According to Donadelli et al. (4), a dangerously contagious disease may negatively affect performance. Furthermore, stated that in the context of the contagiousness of the COVID-19 outbreak, demands for commodities and manufactured products declined, whereas requests for medical supplies and food products soared and the impacts of this outbreak on the financial performance of Chinese listed firms in different industries might not be convergent.

H_2: There is heterogeneity in impacts of the COVID-19 outbreak on the financial performance of Chinese listed firms in different industries.

Under this scenario, companies in different regions shut down their production line, negatively affecting their supply chain. For the demand side, the household's consumption demand suppress by the COVID-19 outbreak (1). Thus, the impacts of this outbreak on the financial performance of Chinese listed firms in severe epidemic regions might be more potent.

H_3: The impacts of COVID-19 outbreak on the financial performance of Chinese listed firms in painful areas is substantial.

It is a psychological contract among people that enables them to have mutual recognition and understanding about the relationship and interaction between employees, managerial positions, and the entire organization in general. The CC can foster people to innovate and figure out the best way to protect themselves from this outbreak under the supports of their firms as well as to maximize firms' performance. Thus, the CC is hypothesized to have moderating effects on the relationship between the COVID-19 outbreak and Chinese listed firms' financial performance.

H_4: The corporate culture has moderated impacts of the COVID-19 outbreak on the financial performance of Chinese listed companies.

The stakeholder theory (9) and integrated theories of CSR (42) suggest that the investment in CSR enables firms to satisfy better stakeholders' demands, leading to better employee engagement, a more sustainable supply chain, and the higher reputational position. The CSR hypothesizes is to have moderating effects on the impacts of the COVID-19 outbreak on the financial performance of Chinese listed companies.

H_5: Corporate social responsibility has moderate effects on the negative impact of COVID-19 on the financial performance of Chinese listed companies.

China differentiates itself from other countries because of its political-economic model and it aims to develop the socialist market economy, in which the state's firms (SOEs) play the critical role as this economy's backbone (53). Therefore, when this outbreak spreads, SOE scan easier access to government supports to deal with this crisis than non-state own firms. The adverse effects of this outbreak on SOE's financial performance, hence, may be lessened.

H_6: Chinese SOEs experience fewer adverse effects of the COVID-19 outbreak on their financial performance than non-state own firms.

Research Models

This research develops several research models that capture the impacts of the Covid-19 outbreak on Chinese listed firms' financial performance.

$$\begin{aligned} REG/ROA/ROE/ATO &= \alpha + \beta_1 COVID19 + \beta_2 FCC + \beta_3 FCSR \\ &+ \beta_4 Liquidity + \beta_5 Efficiency + \beta_6 Leverage \\ &+ \beta_7 SO + \beta_8 Size + \beta_9 Industry + \varepsilon \end{aligned} \quad (1)$$

In which, Chinese firms' financial performance is proxy by the revenue growth rate (REG), ROA, ROE, and ATO. Revenue

growth rate measures by the logarithmic value of a Chinese firm's revenue generated in the quarter$_t$ scaled by its revenue generated in the quarter$_{t-1}$. Return on asset measures by a Chinese firm's net income generated at the end of each quarter scaled by its corresponding total assets. The measure of ROE is the ratio between a Chinese firm's net payment at the end of each quarter and its total related equity. Asset turnover measures a Chinese firm's revenue generated at the end of each quarter scaled by its corresponding total assets. While the REG is a simple measure of Chinese listed firms' ability to generate revenue, ATO measures firms' capabilities in generating income compared to their total assets (13). Asset turnover, thus, is also a proxy of agency costs (17). Differently, ROA and ROE are two measures of profitability of Chinese listed firms' payment referring to the CSR factor, and CC, referring to the CC, is constructed based on the Principal Component Analysis (PCA) method. Key variables of CSR and CC retain when their Eigenvalues are higher than 1. Subsequently, the CSR and CC indexes are constructed based on the identified weight of each variable distributed to each sample scaled by the gap between the max and min weight of all models. The name of each raw variable used to measure CSR and CC their measurement provided. On the other hand, the effect of the Covid-19 outbreak may vary across industries, state ownership, and regions classified by geographic locations, and the seriousness of the Covid-19 research models developed to test for the heterogeneity of this outbreak's effect. The effect of COVID-19 would be more significant for Chinese listed firms in the medicine/pharmaceutical industry.

$$\begin{aligned} REG/ROA/ROE/ATO &= \alpha + \beta_1 COVID-19 \\ &+ \delta_1 COVID19^{*} Medicine \\ &+ \delta_2 COVID-19^{*} ATE + \beta_2 CC \\ &+ \beta_3 CSR + \beta_4 Liquidity + \beta_5 Efficiency \\ &+ \beta_6 Leverage + \beta_7 SO + \beta_8 Size \\ &+ \beta_9 Industry + \varepsilon \end{aligned} \quad (2)$$

While β_1 measures the average effect of COVID-19 outbreak, ($\beta_1 + \delta_1$) measures the specific impact of COVID-19 on Chinese listed firms in the medicine-related industry. ($\beta_1 + \delta_2$) measures the particular impact of the COVID-19 outbreak on Chinese listed firms in related Airlines, Tourism, and Entertainment industry, named as ATE. The impact of this outbreak may vary across regions, including the dangerously unstable region and the dangerously high risky region. Therefore, several research models develop to capture the heterogeneity of such effects across regions. For the dangerously hazardous parts, research models design as follows:

$$\begin{aligned} REG/ROA/ROE/ATO &= \alpha + \beta_1 COVID-19 \\ &+ \delta COVID19^{*} DSR + \beta_2 DSR + \beta_3 CC \\ &+ \beta_4 CSR + \beta_5 Liquidity + \beta_6 Efficiency \\ &+ \beta_7 Leverage + \beta_8 SO + \beta_9 size \\ &+ \beta_{10} industry + \varepsilon \end{aligned} \quad (3)$$

DSR represents the dangerously severe regions affected by the COVID-19 outbreak, measured by the number of the confirmed COVID-19 cases/provincial (city) population; if this ratio equals 1, the number of the established cases/regional (city) population is more than the median of the country. Thus, these regions recognize as seriously affected by the COVID-19 outbreak. For the dangerously unstable areas, research models developed as:

$$\begin{aligned} REG/ROA/ROE/ATO &= \alpha + \beta_1 COVID19 + \delta\ COVID19^{*} DHR \\ &+ \beta_2 DHR + \beta_3 CC + \beta_4 CSR \\ &+ \beta_5 Liquidity + \beta_6 Efficiency \\ &+ \beta_7 Leverage + \beta_8 SO + \beta_9 Size + \varepsilon \end{aligned} \quad (4)$$

Dangerously hazardous regions (DHR) represents the high-risk regions in the COVID-19 outbreak and measures the number of COVID-19 death cases/ provincial (city) population = 1. It indicates the number of confirmed cases/local (city) population is more than the median; these regions are high-risk of the COVID-19, several regression models developed.

$$\begin{aligned} REG/ROA/ROE/ATO &= \alpha + \beta_1 COVID-19 \\ &+ \delta\ COVID-19^{*} EAST + \beta_2 CSR \\ &+ \beta_3 Liquidity + \beta_4 Efficiency \\ &+ \beta_5 Leverage + \beta_6 SO + \beta_7 Size + \varepsilon \end{aligned} \quad (5)$$

$$\begin{aligned} REG/ROA/ROE/ATO &= \alpha + \beta_1 COVID-19 \\ &+ \delta\ COVID-19^{*} CENTRAL + \beta_2 CSR \\ &+ \beta_3 Liquidity + \beta_4 Efficiency \\ &+ \beta_5 Leverage + \beta_6 SO + \beta_7 Size + \varepsilon \end{aligned} \quad (6)$$

$$\begin{aligned} REG/ROA/ROE/ATO &= \alpha + \beta_1 COVID-19 \\ &+ \delta\ COVID-19^{*} West + \beta_2 CSR \\ &+ \beta_3 Liquidity + \beta_4 Efficiency \\ &+ \beta_5 Leverage + \beta_6 SO + \beta_7 Size + \varepsilon \end{aligned} \quad (7)$$

We developed four research models to explore this outbreak's effect across the CC and CSR of Chinese state-own listed companies as following:

$$\begin{aligned} REG/ROA/ROE/ATO &= \alpha + \beta_1 COVID-19 \\ &+ \delta COVID-19^{*} DSO + \beta_2 CC \\ &+ \beta_3 COVID-19^{*} DSO^{*} CC \\ &+ \beta_4 CSR + \beta_5 COVID-19^{*} DSO^{*} CSR \\ &+ \beta_6 Liquidity + \beta_7 CCC + \beta_8 Leverage \\ &+ \beta_9 Size + \varepsilon \end{aligned} \quad (8)$$

Data Analysis Techniques

As mentioned in section Hypothesis Development, six hypotheses were developed and tested through the conduction of the cross-sectional regressions, which refer to regressions for the panel data. These regressions consider the problems of the panel data heteroscedasticity, autocorrelation, and effects of either cross-section. To determine which type of cross-sectional regressions is the best suitable for panel data gathered, firstly, the Ordinary Least Squares (OLS) perform for the developed models (54). Then, the cross-section

TABLE 2 | Descriptive statistics of variables.

	Mean	Median	Maximum	Minimum	Std. Dev.	Probability
REG	−0.151	−0.033	3.045	−4.849	0.642	0
ROA	0.005	0.007	0.097	−0.529	0.038	0
ROE	0.011	0.016	0.263	−1.09	0.085	0
ATO	0.17	0.136	0.645	−0.003	0.123	0
FCC	0.678	0.65	0.872	0.367	0.327	0
FCSR	0.589	0.557	0.883	0.252	0.213	0
Liquidity	1.735	1.253	10.903	0.222	1.557	0
Efficiency	631.324	193.925	42,145.13	−68,613.55	4,432.74	0
LEV	0.148	0.089	0.731	0.000013	0.177	0
STO	17.294	0.000002	82.3	0.000006	24.601	0
SIZE	9.814	9.634	14.545	4.435	1.94	0.002
COVID-19	0.25	0.000098	1	0.076	0.434	0

dependence test performs to figure out whether the cross-section heteroscedasticity exists. The residual tests are also committed to figuring out whether autocorrelation of residuals appears. The GLS has performed the cross-sectional weights in the contemporaneous heteroscedasticity.

RESEARCH FINDINGS AND DISCUSSIONS

Descriptive Statistics

Table 2 provides key statistics of the variables of 126 firms involved in this research. Among four past quarters, the quarter ended on March 31, 2020, witnessed the spread of the Covid-19 outbreak, whereas the three remaining quarters did not. Outbreak measured by a binary variable with one coded for the period with this outbreak and 0 for otherwise, its mean is 0.25, implying that this outbreak just existed in one over four studied quarters. Regarding the financial performance and position of Chinese firms, in four quarters (Q2, 2019 to Q1, 2020), the REG of Chinese listed firms was negative on average (−0.151). However, their ROA, ROE, and ATO were positive with 0.005, 0.011, and 0.017, respectively. Despite their average negative REGs, Chinese listed firms maintained positive profitability and ATO ratios in the past four quarters. The positive average ROA, ROE, and ATO reflect the possibility of positive gains from the COVID-19 outbreak in some industries in China. These gains offset the losses of others, leading to the slightly positive average profitability and ATO ratios of Chinese firms in the studied quarters. Chinese listed firms' CC and CSR indexes were more than 0.67 and 0.58, respectively, with a moderate standard deviation. Chinese listed firms had relatively good CC and CSR, with average CC and CSR differences among firms.

Correlation Analysis Results

Table 3 provides the bivariate associations between variables. Except for the strong positive correlation between ROA and ROE (0.95), the moderate correlation between REG and CCC (−0.544), the average correlation between size and capital structure is (0.596), and the moderate correlation between CC and CSR figure out.

However, since ROA and ROE would not be involved in the same regressions, the high degree of association between them does not matter to the regression quality. The moderate correlations found in this research would not highly likely create the multi-co linearity of regressions.

Regression Analysis

Effects of COVID-19 Outbreak on the Financial Performance of Chinese Listed Companies

Table 4 provides the GLS outcomes, using the white cross-section covariance method and Cross-section weights. This regression method adopts since the cross-section's heteroscedasticity has been detected from the Cross-section dependence test (55). In all models, coefficients of the COVID-19 outbreak variable are significant at 0.01 levels so that this outbreak can predict Chinese firms' financial performance proxy variation by four mentioned measures. Coefficients of the COVID-19 outbreak variable are −0.3994 in model-1, −0.003 in model-2, −0.008 in model-3, and −0.052 in model-4.

Thus, in the first quarter of the year of 2020, with the severe effects of the COVID-19 outbreak, Chinese firms' revenues growth rates decreased by 39.94%, whereas their ROA and ROE dropped slightly by 0.3 and 0.8%, respectively, and other variables controlled. This outbreak reduced Chinese firms' ATO ratios by 5.2%, assuming no change in other variables. In other words, the COVID-19 explosion negatively influenced Chinese listed firms' financial performance in the quarter ended March 31, 2020. Besides the negative impacts of the COVID-19 attack on Chinese listed firms' financial performance, other determinants of their financial performance figure out in four regression models. In model (1), Chinese firms' liquidity and capital structure negatively affect their REGs, although such effects were modest (−0.01 and −0.075, respectively). In the COVID-19 outbreak context, firms with one-unit higher current ratio and one-unit higher financial leverage experienced 1 and 7.5% lower REGs when the remaining variables control. The industry-specific factors, CC, and CSR positively influenced Chinese listed firms' REGs with a significant coefficient at 0.01 levels. Furthermore, Chinese firms' ROA varied across industries, but this variation was modest because the coefficient of the industry variable was small (0.0004).

Effects of COVID-19 Outbreak on the Financial Performance

Table 5 provides outcomes of tests for the industry heterogeneity in impacts of the Covid-19 outbreak on Chinese firms' financial performance. The coefficient of the Medical industry was significant and positive in all models, so in the context of this outbreak, Chinese medical firms obtained higher financial performance, which is similar to the results of Sun et al. (56).

By contrast, the coefficient of the ATE variable was significant and negative, so Chinese travel, entertainment, and airline firms obtained lower financial performance than others in this outbreak. The interaction terms between the Covid-19 attack and medicine were significant and positive in all models, the harmful effects of this outbreak on firms' financial performance in the medical industry reduce (56). Differently, the interaction terms

TABLE 3 | Correlation analysis results all variables.

	REG	ROA	ROE	ATO	COVID-19	LIQ	Eff	LEV	STO	SIZE	CC	CSR
REG	1											
ROA	0.186***	1										
ROE	0.151***	0.959***	1									
ATO	0.314***	0.130***	0.121***	1								
COVID-19	−0.380***	−0.006*	0.004*	−0.215***	1							
LIQ	−0.083**	0.061**	0.022*	−0.160***	0.017*	1						
Eff	−0.544***	−0.033**	−0.017**	−0.196***	0.133***	0.193***	1					
LEV	−0.011*	0.037*	0.085*	−0.178***	0.011*	−0.300***	0.004*	1				
STO	−0.006*	0.061*	0.082*	0.081*	−0.003*	−0.146***	−0.052*	0.187***	1			
SIZE	0.042*	0.127***	0.173***	0.085*	0.005*	−0.382***	−0.063*	0.596***	0.366***	1		
CC	0.068**	0.054**	0.053**	0.061**	−0.052**	0.001*	0.049*	0.0002*	−0.034*	0.004*	1	
CSR	0.089**	0.072**	0.075**	0.081**	−0.078**	0.019*	0.066**	0.011*	−0.024*	0.352***	0.532***	1

*** *is significance level at 0.01,* ** *is 0.05 significance level;* * *is 0.1 significance level.*

TABLE 4 | Generalized Linear Regression (GLR).

Dependent variable	REG	ROA	ROE	ATO
C	0.007002	−0.021072	−0.057966	0.104588
COVID-19	−0.399433***	−0.003005***	−0.007744***	−0.052164***
CC	0.004927***	0.003433***	0.002093***	0.001077***
CSR	0.002372***	0.003412***	0.002109***	0.015577***
Liquidity	−0.00156	0.002067*	0.001078*	−0.000905
CCC	0.000001*	0.00000101	0.000001	0.000025*
Capital structure	−0.004837	−0.002184*	−0.003275*	−0.004159***
State ownership	0.000585*	0.00000035	0.0000002	0.000257
Size	0.001328	0.002298*	0.006062*	0.001277
F-statistics	86.32963***	22.31128***	44.03888***	91.45425***

*** *significance level is at 0.01;* * *is 0.1 significance level (Cross-section weights and white cross-section variance method).*

TABLE 5 | Generalized linear regression with medicine and ATE industry.

Dependent variable	REG	ROA	ROE	ATO
C	0.004821	−0.013052	−0.066109	0.002817
COVID-19	−0.009374***	−0.005529***	−0.004138***	−0.005244***
Medicine	0.001352***	0.000511***	0.001258***	0.001169***
COVID-19*Medicine	0.004662***	0.001493***	0.001152***	0.001519***
ATE	−0.023942***	0.001449***	0.003028***	0.002685***
COVID-19*ATE	−0.014384***	−0.009186***	−0.000229***	−0.002356***
CC	0.003284***	0.002458***	0.002173***	0.001592***
CSR	0.001092**	0.0021817**	0.001302**	0.008309**
Liquidity	−0.002319	0.001173*	0.001083*	−0.001358
CCC	0.000013*	0.0000002*	0.000001*	−0.000036*
Capital structure	−0.062169	−0.002109*	−0.001752*	−0.252419
State ownership	−0.001056*	0.00000021*	0.0000012*	0.000107
Size	0.001263	0.001018*	0.001253*	0.000789
F-statistics	78.24398***	19.31872***	52.14027***	87.28372***

*** *is 0.01 significance level;* ** *is 0.05 significance level;* * *is 0.1 significance level (cross-section weights and white cross-section covariance method).*

between this outbreak and ATE were significantly negative in all models, It confirms that Hypothesis 2. **Table 6** provides outcomes of the tests for the regional heterogeneity in impacts of the Covid-19 outbreak on Chinese listed firms' financial performance. The coefficients of DSR in all models were significant and negative, meaning that the Covid-19 attack negatively reduced the financial performance of firms located in the dangerously severe risky regions, although such adverse effects were modest.

Moreover, **Table 7** provides the outcomes of tests for the heterogeneous impacts of the Covid-19 outbreak on Chinese firms' financial performance across DHR. The interaction terms between the Covid-19 attack and DHR were significant and negative in all models, so Chinese firms experienced the more severely damaging impacts of the COVID-19 outbreak than others in DHRs.

The coefficient of interaction terms between the Covid-19 attack and DHR are stronger and the death cases of COVID-19 in different provinces and cities have substantial adverse effects on the financial performance of Chinese listed companies. Furthermore, **Table 8** provides outcomes of tests for impacts of the Covid-19 outbreak on Chinese firms' financial performance across regions in China. The interaction terms between the Covid-19 attack and each area were negative and significant in all models. These terms were most important for the central region, so Chinese listed firms in the mid regions experienced the more substantial negative impacts of the COVID-19 outbreak on their financial performance than others. Compared with east and west, Hubei, an essential province in Central China, has been severely impacted by the attack. Overall, Hypothesis 3 is confirmed.

To explore the most potent effects on the central region in China, **Table 9** provides outcomes of tests for impacts of the Covid-19 outbreak on firms' financial performance in 6 provinces around the Hubei province, where the outbreak emerged. The interaction terms between the Covid-19 outbreak and DHB were significant and negative, so Chinese listed firms' financial

TABLE 6 | Generalized linear regression in serious regions.

Dependent variables	REG	ROA	ROE	ATO
C	0.002923	−0.082392	−0.012693	−0.001927
COVID-19	−0.004335***	−0.003532***	−0.002245***	−0.003544***
DSR	−0.001432**	−0.001930**	−0.002804**	−0.001082**
COVID-19*DSR	−0.003193***	−0.002291***	−0.002192***	−0.004138***
CC	0.002720***	0.001933***	0.001381***	0.001318***
CSR	0.001752**	0.001429**	0.001093**	0.001029**
Liquidity	−0.00226	0.001072*	0.001108*	−0.003025
CCC	−0.000902*	−0.004072	0.000003	−0.000712*
Capital structure	−0.001933	−0.001651*	−0.001523*	−0.000492
State ownership	−0.001923*	0.0000023	0.0000013	0.00000028
Size	0.002837	0.000184*	0.001224*	0.003717
F-statistics	96.44512***	35.82471***	47.90162***	95.24629***

*** *is 0.01 at significance level;* ** *is 0.05 at significance level;* * *is 0.1 at significance level (cross-section weights and white cross-section covariance method).*

TABLE 7 | Generalized linear regression in high-risky regions.

Dependent variable	REG	ROA	ROE	ATO
C	0.001038	0.018164	−0.012264*	−0.0031527
COVID-19	−0.045867***	−0.006243***	−0.072545***	−0.005436***
DHR	−0.008682**	−0.004853**	−0.004421**	−0.001488**
COVID-19*DHR	−0.005859***	0.004915***	0.004926***	0.005387***
CC	0.003120***	0.002384***	0.002819***	0.002072***
CSR	0.001942*	0.001209*	0.002247*	0.001529*
Liquidity	−0.00193	0.002742*	0.000450*	−0.000556
CCC	−0.001134*	−0.001787	−0.002452	−0.001249*
Capital structure	−0.000133	−0.000329*	−0.002246*	−0.001397
State ownership	−0.002019*	−0.001292	0.000329	0.002417
Size	0.001324	0.000412*	0.000412*	0.000513
F-statistics	97.43421***	39.98565***	58.26957***	95.67289***

*** *is 0.01 significance level;* ** *is 0.05 significance level;* * *is 0.1 significance level (Cross-section weights and white cross-section covariance method).*

TABLE 8 | Generalized linear regression in Chinese different zones.

Dependent Variable	REG	ROA	ROE	ATO
C	0.002453	0.002454	0.004549	0.001782
COVID-19	−0.003428***	−0.002143***	−0.001334***	−0.002446***
Coast	−0.001342*	−0.001729*	−0.001533*	−0.001619*
COVID-19*East	−0.002817*	−0.003569*	−0.002926*	−0.002871*
Mid	−0.000938**	−0.000193**	−0.00184**	−0.000748**
COVID-19*Central	−0.002342**	−0.001239**	−0.001286**	−0.002394**
West	−0.000221*	−0.000185*	−0.000153*	−0.000169*
COVID-19*West	−0.001329*	−0.000928*	−0.000712*	−0.001895*
CC	0.001668***	0.001367***	0.001768***	0.001352***
CSR	0.000832*	0.000287*	0.000432**	0.000513**
Liquidity	−0.003228	0.001039*	0.001543*	−0.001457
CCC	−0.000352*	−0.00239	−0.001325	−0.000847*
Capital structure	−0.001029	−0.001028*	−0.001392*	−0.000869*
State ownership	−0.002329*	−0.001918	−0.001303	−0.001836
Size	0.001129	0.001348*	0.001980*	0.001762
F-statistics	128.39173***	61.29183***	69.42754***	96.30183***

*** *is 0.01 significance level;* ** *is 0.05 significance level;* * *is 0.1 significance level (cross-section weights and white cross-section covariance method).*

TABLE 9 | Generalized linear regression in Hubei effects.

Dependent variable	REG	ROA	ROE	ATO
C	0.001244	−0.001048	−0.002693	−0.001257
COVID-19	−0.004351***	−0.002538***	−0.002713***	−0.000144***
DHB	−0.000676**	−0.000530**	−0.000354**	−0.00472**
COVID-19*DHB	−0.005134***	−0.003976***	−0.002628***	−0.004751***
CC	0.000385**	0.000279**	0.000281**	0.000298**
CSR	0.000152*	0.000169*	0.000193*	0.0000129*
Liquidity	−0.001926	0.001123*	0.001186*	−0.001174
CCC	−0.001134*	−0.001422	−0.002242	−0.001327*
Capital structure	−0.002681	−0.001917*	−0.001638*	−0.002438
State ownership	−0.000334*	0.00223	0.000192	0.000539
Size	0.002431	0.001354*	0.000847*	0.001182
F-statistics	99.83116***	58.64263***	53.03872***	97.34183***

*** *is 0.01 significance level;* ** *is 0.05 significance level;* * *is 0.1 significance level (cross-section weights and white cross-section covariance method).*

performance around the Hubei province were most severely affected by this outbreak than others.

Moderating Effects of Corporate Social Responsibility

Table 10 provides outcomes of tests for the moderating role of CC and CSR for the relationship of Covid-19 outbreak and Chinese firms' financial performance. In four models, the interaction terms the Covid-19 attack and CC. As the moderating role of CSR for Covid-19 attack and CSR is significant and positive, so it confirms the Hypothesis 5–6. Corporate culture and CSR reduced the negative impacts of the COVID-19 attack on Chinese firms' financial performance. However, such moderating effects were modest (coefficients of the interaction terms were extremely small in four models).

We test the interactions COVID-19 outbreak, the medicine industries, and the CC test. These interaction terms were significant and positive, so Chinese medical firms with good CC could reduce the negative impacts of the Covid-19 outbreak on their financial performance. For ATE industry interaction terms between this industry, the Covid-19 attack and CC added, coefficients of these terms were significant and positive so that CC could reduce the negative impacts of this outbreak. Similarly, CSR reduces the harmful effects of the COVID-19 spell on the financial performance of both the medicine and ATE. Moreover, CC is significant and negatively influences the relationship between the Covid-19 outbreak and firms' financial performance in serious regions. However, the moderating role of CSR for the negative relationship between the Covid-19 outbreak and firms' financial performance in this region confirms. To the

TABLE 10 | Generalized linear regression with CR and CSR.

Dependent variable	REG	ROA	ROE	ATO
C	0.001426	−0.001048	−0.001423	−0.001374
COVID-19	−0.002314***	−0.001258***	−0.001353***	−0.001685***
CC	0.002382***	0.001349***	0.001831***	0.001991***
COVID-19*CC	0.000120***	0.000096***	0.000104***	0.000112***
CSR	0.001228**	0.001029**	0.001038*	0.0000129*
COVID-19*CSR	0.000082*	0.000043*	0.000035*	0.000057*
COVID-19*Medicine*CC	0.008230***	0.005282***	0.004982***	0.005872***
COVID-19*ATE*CC	0.006831**	0.004338**	0.003281**	0.004482**
COVID-19*DSR*CC	−0.000827**	−0.000429**	−0.000381**	−0.000608**
COVID-19*DHR*CC	−0.001182*	−0.001093*	−0.000812*	−0.0001042*
COVID-19*East*CC	−0.000128*	−0.000127*	−0.000138*	−0.000192*
COVID-19*Central*CC	−0.003621**	−0.001823**	−0.001338**	−0.002142**
COVID-19*West*CC	−0.000372*	−0.000239*	−0.000216*	−0.000182*
COVID-19*DHB*CC	0.000225*	0.000142*	0.000129*	0.000231*
COVID-19*Medicine*CSR	0.002982**	0.002392**	0.002426**	0.001093**
COVID-19*ATE*CSR	0.002938*	0.002178*	0.001982*	0.000128*
COVID-19*DSR*CSR	−0.000292*	−0.000224*	−0.000183*	−0.000198*
COVID-19*DHR*CSR	−0.000394*	−0.000242*	−0.000221*	−0.000128*
COVID-19*East*CSR	−0.000117*	−0.000087*	−0.000079*	−0.000126*
COVID-19*Central*CSR	−0.000382**	−0.000212*	−0.000192*	−0.000223**
COVID-19*West*CSR	−0.000115*	−0.000098*	−0.000079*	−0.000143*
COVID-19*DHB*CSR	0.000213*	0.000168*	0.000192*	0.000179*
Liquidity	−0.000382	0.000283*	0.000155*	−0.002564
CCC	−0.000313*	−0.002556	−0.001426	−0.000455*
Capital structure	−0.002861	−0.000496*	−0.000835*	−0.002863
State ownership	−0.000230*	0.000289	0.000232	0.000736
Size	0.000134	0.000692*	0.000324*	0.000122
F-statistics	129.82463***	82.98143***	86.82736***	117.98133***

*** *is 0.01 significance level;* ** *is 0.05 significance level;* * *is 0.1 significance level (cross-section weights and white cross-section variance method).*

TABLE 11 | Generalized linear regression in state-ownership list companies.

Dependent variable	REG	ROA	ROE	ATO
C	0.027817	−0.022708***	−0.056606***	0.108270***
COVID-19	−0.003135***	−0.002306***	−0.002418***	−0.003216***
DSO	0.000343***	0.000221***	0.000127***	0.000259***
COVID-19*DSO	0.001431***	0.001325***	0.001164***	0.001273***
CC	0.000832***	0.000563***	0.000329***	0.000664***
COVID-19*DSO*CC	0.000272*	0.000118*	0.000105*	0.000198*
CSR	0.000629**	0.000483**	0.000276**	0.000489**
COVID-19*DSO*CSR	0.000517*	0.000386*	0.000281*	0.000392*
Liquidity	−0.001323	0.001124*	0.001273*	−0.009049
CCC	−9.05E-05*	−4.04E-07	2.48E-07	−2.78E-06*
Capital structure	−0.084562	−0.001925*	−0.001341*	−0.25172
Size	0.002324	0.002461	0.005835	0.015371
F-statistics	155.7781***	21.30743***	46.73687***	72.72873***

*** *is 0.01 at significance level;* ** *is 0.05 at significance level;* * *is 0.1 at significance level (cross-section weights and white cross-section covariance method).*

high risky regions, the interaction terms between the Covid-19 attack, DHR, and CC and the interaction terms between this outbreak, DHR, and CSR were significant and negative in all models. **Table 11** provides outcomes of tests for the moderating role of Chinese state-owned listed companies' CC and CSR for the relationship between the Covid-19 outbreak and financial performance. The state ownership moderated the relationship between the COVID-19 outbreak and Chinese firms' financial performance. The SOEs experienced fewer negative effects of the COVID-19 outbreak on their financial performance than non-SOEs. Regarding the moderating effects of CC and CSR, the interaction terms between these variables, the COVID-19 outbreak, and DSO were positive and significant in all models.

CONCLUSIONS AND RECOMMENDATIONS

This study found that after controlling for firms' particular characteristics and industry-specific conditions, the COVID-19 epidemic harmed Chinese listed companies' financial efficiency, as their sales growth rate, ROA, ROE, and ATO decreased dramatically in the first quarter of 2020. As a result, the first hypothesis (H1) is accurate. However, aside from the significant impact on sales growth, the COVID-19 epidemic had only minor adverse effects on ROA, ROE, and ATO, with only 0.3, 0.08, and 5.2%, respectively. Hassan et al. (51) found that the effects of the COVID-19 epidemic on Chinese listed companies' financial results are not uniform, confirming the second hypothesis (H2). Furthermore, this study found that companies with a conservative working capital management approach could reduce COVID-19's adverse results. In terms of the moderating influence of CC and CSR, this study discovered that CC and CSR mitigated the negative effects of the Covid-19 epidemic on Chinese firms' financial results, confirming the H4 and H5 hypotheses. The H6 supports this study, which found that state ownership moderated the relationship between the COVID-19 and economic consequences of Chinese listed companies. Since the relationship terms between the COVID-19 outbreak and state ownership is favorable, state ownership minimized the severity of the outbreak's negative impact on the financial output of Chinese listed companies. In other words, SOEs' sales growth rate, ROAs, ROE, and stock turnover was less affected by the epidemic than others. The ability to generate revenue from the Travel and Leisure, Retailer, Healthcare, and Basic Materials industries was highest in ATO, while the ability to generate revenue from assets of Technology, Paper manufacturing, and other sectors was lowest.

SUGGESTIONS FOR FUTURE RESEARCH

Despite the accomplishments of this study and its essential contribution to the literature, it nevertheless has two significant flaws. The results of the study point to several practical

consequences for clinicians related to improvements in market practices. Firms should use a cautious working capital management approach rather than an offensive working capital management strategy in the event of a viral epidemic. In the light of supply chain delays triggered by the health crisis, the traditional working capital management approach also works.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

YS: data analysis, writing, and supervision. YL: writing, discussion, and analysis. All authors contributed to the article and approved the submitted version.

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The Impact of Family Income on Body Mass Index and Self-Rated Health of Illiterate and Non-illiterate Rural Elderly in China: Evidence From a Fixed Effect Approach

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Background: Rural communities worldwide are experiencing the most significant levels of aging. Most rural elderly have no stable pension, and leading family income plays an indispensable role in the life security of rural elderly. This study aims to investigate whether the association between annual family income per capita and body mass index (BMI) and self-rated health (SRH) in rural elderly is moderated by education during fast economic development.

Methods: We chose the fixed-effects model to analyze the impact of the annual family income per capita change on BMI and SRH based on a large, nationally representative longitudinal dataset of rural respondents aged above 60 of the China Family Panel Studies (CFPS) from 2010 to 2018.

Results: Six hundred and fifty-eight were eligible for inclusion in our analysis in CFPS. The median age of participants was 65 years in 2010, and 379 (57.60%) participants were male. Self-rated health increased with higher the logarithmized family income per capita among the rural illiterate elderly ($\beta = 0.0770$; 95% CI = 0.0065–0.1473). Body mass index increased with higher the logarithmized family income per capita among the rural elderly ($\beta = 0.1614$, 95% CI: 0.0325–0.2903), and it was more evident among the illiterate elderly ($\beta = 0.2462$, 95% CI: 0.05519–0.4372).

Conclusion: Family income has an impact on BMI and SRH moderated by education level among rural elderly in China. These results contribute to developing more targeted strategies in the context of a developing country. In addition, it also reminds us to consider the differences in the educational level of the elderly in rural areas when examining the relationship between family income and health.

Keywords: rural elderly, family income, body mass index, self-rated health, fixed effects

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INTRODUCTION

With the decline of fertility and mortality, the number of elders continues to increase rapidly. It is estimated that between 2017 and 2050, the proportion of the world's population aged 60 and above will nearly double from 926 million to 2.1 billion (1). The problem of aging is particularly evident in Asia. From 2015 to 2050, the total number of people aged 80 and above in 23 Asian countries is expected to quadruple (2).

Rural communities worldwide are experiencing the most significant levels of aging in place, including many developed countries and developing countries, such as China, India, Japan, Indonesia, Australia, the United States (3–7). Compared with the urban elderly, the rural elderly have limited economic and material resources (8, 9). Under the background of economic and social transformation and rural structural adjustment, the rural economy of many developing countries has developed rapidly (10–13). Some developing countries, such as Brazil, South Africa, Mexico, and China, have launched government transfer or social pension programs for elderly who have not previously covered pensions (14). Nevertheless, the elderly in rural areas, especially in less developed regions, is expected to receive less pension than those in urban counterparts (15). Therefore, family income has played an indispensable role in life support for the rural elderly.

Previous studies confirmed a relationship between family income and health (16, 17). The reason may be that income affects health through quality housing, social networks and relationships, health-related knowledge, diet choices, and sports activities in safe communities (18). Most previous studies of the association between family income and health have used regression modeling applied to cross-sectional data (19–22). We cannot be confident that the associations uncovered in these studies are not spurious by this methodological approach. In addition to methods, the choice of outcome indicators will also affect the results. Veenstra and Vanzella-Yang found that the change of family average income impacted health (18), but it only takes self-rated health (SRH) as an outcome indicator and lacks the objective outcome indicator to evaluate health.

The outcome indicators used in this study were body mass index (BMI) and SRH. Body mass index was regarded as an objective indicator of health outcomes. Moreover, the health burden of obesity has been widely recognized, and it is the leading risk factor for many adverse health consequences, such as cardiovascular disease, diabetes, and depression. Therefore, it has been the focus of many researchers in social science and public health to clarify the reasons for weight gain (23, 24). Self-rated health was used as an outcome indicator to evaluate the subjective health of the elderly. It is also a concise and straightforward public health indicator to evaluate the overall health status in epidemiological studies (20), and it is also can be used as a predictor of subsequent mortality and health issues (25, 26). This study aims to find the relationship between the growth of family income and the health changes of the elderly in rural areas based on a large, nationally representative longitudinal dataset of rural respondents aged above 60 from three waves of the China Family Panel Studies (CFPS) from 2010 to 2018. Because the education level of the elderly did not change, this study hopes to focus on whether annual family income per capita has different effects on BMI and SRH of the elderly with different educational levels.

METHODS

Sample and Data Collection

The data were derived from the CFPS. China Family Panel Studies is a biennial longitudinal survey conducted by the Institution of Social Science Survey at Peking University. This investigation launched in 2010 with five waves of publicly released datasets. The samples covered 25 provinces, accounting for 95% of the total population of China. The contents of CFPS are rather typical, covering the demographics, socioeconomic condition, education, and health of respondents.

The Biomedical Ethics Review Committee of Peking University approved CFPS, and all participants were required to provide written informed consent. The ethical approval number was IRB00001052-14010.

Since the fixed-effect regression studied the relationship between the change in dependent variables and those independent variables across each wave, we selected 658 participants according to the following criteria: (1) aged 60 and above in 2010, (2) rural elderly (respondents were categorized into urban and rural residents according to their household living regions defined by National Bureau of Statistics of the People's Republic of China), and (3) had not missing values of dependent or independent variables in all three waves (2010, 2014, and 2018).

Variables

Dependent Variable

The health outcomes selected in this paper are SRH and BMI, considered from subjective and objective aspects.

The dependent variable was SRH. Respondents were asked, "in general, would you say your health is excellent, very good, good, fair, or poor?" We coded this variable as 5 = excellent, 4 = very good, 3 = good, 2 = fair, and 1 = poor.

Body mass index, a continuous measure of body weight relative to height, was calculated as body weight in kilograms divided by squared height in meters (kg/m^2).

Independent Variable

Family income was measured by annual family income per capita (taking the natural log and deflating based on the 2010 CPI). Family income of CFPS included wage income, business income, transfer income, property income, and other income. Then, we divided the family income by the family size to get the family per capita income.

Control Variable

Socio-demographics included sex, age, marital status, and the number of years of education. Age and the number of years of schooling were continuous variables. Marital status and chronic diseases weredefined as binary variables. Marital status was divided into married and divorced/widowed/unmarried, and chronic disease was divided into with and without.

Illiterate refers to the older adults who have not received a formal education, that is, the number of years of education was 0. Non-illiterate refers to the older adults who have received a formal education, that is, the number of years of education was more than 0.

Analysis Strategy

Fixed effect model and random effect model can explain the estimation error caused by concrete variables. The main difference between the two models is that the fixed effect model

TABLE 1 | Characteristics of the respondents.

Variable	2010		2014		2018	
	n (%)	*M* (*SD*)	*n* (%)	*M* (*SD*)	*n* (%)	*M* (*SD*)
SRH		2.16 (1.17)		3.54 (1.25)		3.54 (1.28)
BMI		21.89 (3.28)		21.93(3.97)		22.52 (4.05)
The annual family income per capita		5401.40 (7137.36)		6902.47 (7832.86)		6090.83 (8717.06)
Age		65.00 (4.35)		69.00 (4.35)		73.00 (4.35)
The number of years of education		3.22 (3.84)		3.22 (3.84)		3.22 (3.84)
Gender						
Female	279 (42.40)		279 (42.40)		279 (42.40)	
Male	379 (57.60)		379 (57.60)		379 (57.60)	
Marital status						
Married	561 (85.26)		527 (80.09)		503 (76.44)	
Divorce/Separate/Widowed	97 (14.74)		131 (19.91)		155 (23.56)	
Chronic disease						
Yes	144 (21.88)		191 (29.07)		192 (29.33)	
No	514 (78.12)		466 (70.93)		465 (70.67)	

treats the unobserved differences between individuals as fixed parameters. In contrast, the random effect model treats the missing variables as random variables with a special probability distribution and assumes they are unrelated to the observed variables. This assumption of the stochastic model is generally challenging because the missing variables are usually associated with other explanatory variables in the model. The Hausman test testifies the null hypothesis that the random effects coefficients are identical to the fixed effects coefficients. The test produced $P < 0.001$ for both SRH/BMI, indicating that fixed effect models were appropriate.

To address the potential endogeneity, one of the best methods for addressing confounding in observational research are fixed effect models applied to longitudinal data containing repeated measures of both income and health (27). In this study, a longitudinal linear fixed-effects regression model was employed to estimate the association between changes in annual family income per capita and changes in SRH/BMI during three waves in older adults. The fixed effect model could effectively eliminate the influence of missing variables on dependent variables and the interference between independent and dependent variables. Meanwhile, the model also allows us to control time-variant factors that do not vary across individuals.

Specification of our model was as follows:

$$\mathrm{SRH}_{it} = \beta_0 + \beta_1 \text{ Annual family income per capita}_{it} + \beta_2 \text{ Control A}_{it} + \beta_3 \text{ Control B}_i + \varepsilon_{it}$$

$$\mathrm{BMI}_{it} = \beta_0 + \beta_1 \text{ Annual family per capita}_{it} + \beta_2 \text{ ControlA}_{it} + \beta_3 \text{Control B}_i + \varepsilon_{it}$$

SRH_{it} refers to SRH for individual i at time t, and BMI_{it} refers to BMI for individual i at time t. Similarly, Annual family income per capita$_{it}$ denotes the explanatory variable, the annual family income per capita for individual i at time t. Control A_{it} represents the time-varying control variable, including age, marital status, and chronic disease. Control B_i represents the non-time-varying control variable, including gender and the number of years of education. ε_{it} is the error term.

RESULTS

Basic Characteristics of the Respondents

Table 1 shows descriptive statistics separated by sample wave. Overall, the SRH increased significantly from 2010 to 2014, and the average value in 2018 was the same as that in 2014. For BMI, the rural elderly had a slight increase with age.

The annual family income per capita we used was comparable with that in 2010. The revenue increased significantly from 2010 to 2014 and decreased slightly in 2018.

Regression Results of the Effect of Annual Family Income per Capita on SRH and BMI

Model 1 (**Table 2**) summarized the modeling results of SRH changes in 2010, 2014, and 2018 and changes in equivalized annual family income per capita in 2010, 2014, and 2018, controlling for survey year, age, and marital status. The annual family income per capita was not significantly associated with SRH in model 1. Model 2 and 3 summarized the changes in SRH and equivalized per capita family income between illiterate and non-illiterate in 2010, 2014, and 2018, controlling for age, marital status, chronic diseases, and survey year. Interestingly, with the increase of annual family income per capita of the rural illiterate elderly, their SRH level improved significantly ($\beta = 0.0770$; 95% CI = 0.0065–0.1473), but for the non-illiterate elderly, there was no significant correlation between their SRH and annual family income per capita.

Model 4 (**Table 3**) summarized the modeling results of BMI health changes in three waves and changes in equivalized annual family income per capita in three waves. The time-varying factors of survey year, age, and marital status were controlled. The annual

TABLE 2 | Fixed effect modeling of changes in SRH and the annual family income per capita between 2010, 2014, and 2018.

	Model 1: Whole sample		Model 2: illiteracy		Model 3: non-illiteracy	
	β	95% CI	β	95% CI	β	95% CI
Ln (The annual family income per capita)	0.0338	−0.0182 0.0858	0.0770**	0.0065 0.1473	−0.0252	−0.1018 0.0514
Age	0.0132	−0.0957 0.1220	0.0210	−0.0919 0.1338	−0.1099	−1.0305 0.8107
Marital status	−0.2139	−0.5313 0.1035	−0.0189	−0.4267 0.3889	−0.4830	−0.9976 0.0223
Chronic disease	−0.3433**	−0.4782 −0.2082	−0.4844***	−0.6712 −0.2976	−0.1711*	−0.3643 0.0222
Intercept	1.5333	−6.4315 9.4982	0.5044	−7.7907 8.7996	11.1732	−55.8225 78.1689
R^2: within	0.4110		0.3837		0.4614	

*Regression coefficients are unstandardized and unweighted; ***P < 0.01; **P < 0.05.*

TABLE 3 | Fixed effect modeling of changes in BMI and the annual family income per capita between 2010, 2014, and 2018.

	Model 4: Whole sample		Model 5: illiteracy		Model 6: non-illiteracy	
	β	95% CI	β	95% CI	β	95% CI
Ln (The annual family income per capita)	0.1614**	0.0325 0.2903	0.2462**	0.05519 0.4372	0. 0470	−0.1173 0.2113
Age	0.0357	−0.5257 0.5970	−0.0275	−0.6770 0.6220	1.0642	−0.8962 3.0246
Marital status	0.1061	−0.6935 0.9057	−0.0014	−1.1382 1.1354	0.3011	−0.7952 1.3973
Chronic disease	0.1246	−0.2116 0.4607	0.0252	−0.4806 0.5311	0.2436	−0.1769 0.6640
Intercept	18.4295	−22.5309 59.3897	22.1391	−25.3525 69.6306	−55.2547	−197.8846 87.3751
R^2: within	0.0241			0.0237	0.0362	

*Regression coefficients are unstandardized and unweighted: **P < 0.05.*

family income per capita was significantly associated with BMI in model 4. Income increased corresponded to increases in BMI (β = 0.1614; 95% CI = 0.0325–0.2903).

Model 5 and 6 (**Table 3**) summarized BMI changes and equivalent annual family income per capita between illiteracy and non-illiteracy in three waves. Compared with the overall rural elderly, the increase in BMI of the elderly in illiterate rural areas was more prominent (β = 0.2462; 95% CI = 0.05519–0.4372), and there was not significantly associated with BMI for non-illiteracy.

DISCUSSION

This study used a nationally representative dataset to investigate annual family income per capita on BMI and SRH among rural older adults in China. We found that, for SRH, with the increase of the annual family income per capita, the better results of SRH only existed in the illiterate elderly. However, for BMI, annual family income per capita had a positive correlation with the BMI of the rural elderly, that is, with the increase of income, the BMI of the rural elderly also increased. Meanwhile, in the illiterate elderly, with a rise in income, BMI was more prominent. Our application of dynamic panel models with fixed effects on the Chinese rural old adult population provided a unique chance to uncover the association between annual family income per capita and SRH and BMI in a society undergoing the rapid development of the rural economy.

In previous studies, the relationship between income and SRH was not consistent. Our research found that the increase of income among the rural elderly did not cause significant changes in SRH, and these changes only existed in the illiterate elderly after the stratification of education level. Gunasekara et al. analyzed 13 studies and five longitudinal surveys from four different countries. They came to a general conclusion: in most cases, there was a slight positive correlation between the increase of income and SRH, but these four countries were developed countries and did not consider developing countries (27). By analyzing the panel data of Canada, Veenstra et al. found a weak negative correlation between family income and self-health (18). However, the difference between our study results and the above is probably due to the different study objects. The population of our study is the elderly in rural areas. We can use resource substitution (28) to explain our results. When resources replace each other, the existence of one resource will reduce the harm caused by the lack of another resource. On the contrary, the less one resource, the more influential the other. Income and education are two kinds of resources. Using the resource substitution perspective, we can argue that more substantial health-protective effects of income among disadvantaged populations (rural illiterate elderly) because they have fewer alternative health-promoting resources, especially in rural areas. The increase of family income can increase their economic resources, better access to medical care, and more extensive social networks that promote healthier lifestyles that helps rural illiterate elderly to avoid poor health. Chronic diseases pose a great health threat to the rural elderly, reducing SRH,

especially for the illiterate rural elderly. It can be explained that chronic diseases can lead to the decline of physical function of the elderly, affect their mental health, and reduce their quality of life (29).

The BMI of rural elderly increased significantly with the increase of income, but there is no such relationship among the non-illiteracy elderly. Our study differs from the conclusion of Deuchert et al., who found that obesity was a problem that focuses on the social and economic elites in developing countries, such as high-income groups (30). The previous explanation was that the relationship between income and BMI is related to nutrition change. The shift in nutrition refers to the change in eating habits with the development of the economy (31). Through the China Health and Nutrition Survey (CHNS) panel data, Ren found that rising income increased the adults' BMI and the propensity to be overweight. From the perspective of nutrition, there are five potential channels: nutritional intakes, dietary diversity, dietary knowledge, food preference, and dining out, among which dietary diversity plays the most significant role in explaining the income impact (32). It is also helpful to explain the relationship between family income and BMI in rural elders by nutritional change. Because for the rural elderly, higher family income means more food choices and dining out, increasing their extra energy intake. However, we were surprised to find that education seems to be alleviating this relationship, and the educated rural elderly do not increase BMI due to the increase of income. This result can explain the associations between levels of education and nutrition knowledge and concern with weight control (33).

Three limitations of this study must be noted. Firstly, because our BMI and SRH are self-reported—the prevalence of obesity would be overestimated when using self-reported height and weight (34), recall bias may exist in this study, affecting the accuracy of the estimation. Future research should consider other indicators, such as body fat percentage and waist-hip ratio, to better measure body fat and subjective health. At the same time, more perfect scales can be used to measure health status. Secondly, fixed effects analysis controls time-invariant confounding factors at the individual level. There may be unmeasurable or unmeasurable time-varying variables in this study. Third, our sample is restricted to better observe the changing process of the health impact of family income among the rural elderly in China. A threat to representativeness pertains to the high attrition rate experienced by the CFPS from wave one to wave three, although we control for marital status, gender, and age in our models. The existence of missing independent and dependent variables of the CFPS compromises the generalizability of our results, given that rural older are not well-represented by our study. Overall, our study has selection bias.

CONCLUSION

Few studies measured the association between annual family income per capita between BMI and SRH in rural elderly using fixed effects analysis that rules out the potential endogeneity to the best of our knowledge. At the same time, this study considers the gap between illiteracy and non-illiteracy to adapt to the high illiteracy rate in rural areas. In this study, the illiteracy rate is as high as 55.47%.

Self-rated health increased with higher the logarithmized family income per capita among the rural illiterate elderly. Moreover, BMI increased with higher the logarithmized family income per capita among the rural elderly, especially the illiterate elderly.

In rural economic development, the impact of family income on the rural elderly is undeniable. It is worth noting that the health status of the rural illiterate elderly needs particular attention, because first of all, they have lower education levels and lack health knowledge. Second, most of them have lower insurance levels and lower ability to resist disease risk. At the same time, the average BMI of the rural non-illiterate elderly was 22.56 $\pm$ 3.67, while the average BMI of the rural illiterate elderly was 21. 75 $\pm$ 3.85. The family income of the illiterate elderly in rural areas also needs to be paid attention to because the increase of average family income can improve their BMI, which is likely to be reasonable. Theoretically and methodologically, we need more research to understand the relationship between socioeconomic status and the health of the elderly and its internal mechanism. It also reminds us to consider the educational differences in rural areas when investigating causal relationships further, which may help develop more targeted strategies in a developing country.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

YX: methodology, software, and writing—original draft. XR: writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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Impact of Internet Use on Multi-dimensional Health: An Empirical Study Based on CGSS 2017 Data

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Based on the data of the Chinese General Social Survey (CGSS) in 2017, the paper divides overall health into physical, mental, and social health, using the ordered probit model to examine the impact of Internet use on multi-dimensional health. It then discusses the possible heterogeneity in different groups and underlying mechanism. Results found that using the Internet can improve the health level in multiple dimensions. After endogenous and robustness tests, the results remain robust. Heterogeneity analysis shows that Internet use has more obvious effects on the health of senior high school education or above, the elderly, and men. Further analysis of the mediating effect model found that information, leisure, and social preferences are important path mechanisms for Internet use to promote physical, mental, and social health, respectively.

Keywords: internet use, multi-dimensional health, heterogeneity analysis, mediating effect, endogenous test

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INTRODUCTION

With the implementation of the "broadband China" strategy, China's Internet industry has developed rapidly in recent years. According to the 47th China Statistical Report on Internet Development issued by the China Internet Network Information Center in February 2021, by December 2020, the scale of Chinese netizens has reached 989 million, and the main netizens have begun to transform from youth groups to minors and "silver netizens." The overall Internet penetration rate has reached 70.4%, the number of mobile Internet users has reached 986 million, and the proportion of netizens using mobile phones to access the Internet is as high as 99.7%. The popularization of the Internet is slowly affecting and changing people's thinking habits and lifestyle. The important manifestation is Internet plus Healthcare. According to the 44th China Statistical Report on Internet Development, as of December 2016, the number of Internet users using Internet medical services has reached 194.76 million, with a utilization rate of 26%.

Health is not only the eternal theme pursued by all mankind but also the cornerstone and destination of high-quality economic and social development. In fact, the Chinese government has constantly attached profound importance to health. The Fifth Plenary Session of the 18th CPC Central Committee clearly proposed to promote the construction of "healthy China;" the "healthy China 2030 plan" officially promulgated by the CPC Central Committee and the State Council pointed out that "people's health should be given priority to the strategic layout of development" in October 2016. The report of the 19th National Congress of the Communist Party of China further emphasizes the significance of the era and strategic significance of the "Healthy China Strategy." Driven by the dual strategies of "broadband China" and "healthy China," the Internet

is providing more and more people with employment, medical, and other information support, especially the disadvantaged groups. In this context, exploring the relationship between Internet use and residents' health has important policy implications for promoting the development of health.

LITERATURE REVIEW

What Is Health?

Health seems to be a mirage. We find difficulty establishing precise definitions when we are in close contact; but when we are far away, we can clearly "see" health (1). Many scholars are concerned with objective health indicators, such as growth and development, prevalence rate, and ADL, among others (2). With the rise of social medicine, subjective health indicators are increasingly proven to be able to successfully predict mortality and disability rate (3). The World Health Organization in 1948 defined health as not only the absence of disease or weakness but also satisfying the need to achieve the perfect state of physical, mental, and social adaptation. Therefore, the complete connotation of health should include multiple dimensions such as physical health, mental health, and good social adaptability (4). However, the current literature mostly focuses on a single dimension of health and lacks a comprehensive investigation of the connotation of health.

Can Internet Use Affect Individual Health?

At present, two seemingly opposite arguments exist. One is the theory of health promotion which holds that healthy individuals are likely to use the Internet to search for relevant health information (5). In addition, Internet use has a positive role in promoting individual self-reported health (6). By contrast, the theory of technological pressure holds that the Internet popularity has brought negative effects on individual health. Its prominent manifestations are Internet addiction, unreasonable use of the Internet, and excessive dependence on social networking, which will increase the health risk of Internet users (7). How does the Internet affect individual health? First is the mechanism for accessing health information from the Internet. Access to health information through the Internet and online health services can improve individual health literacy and strengthen self-health management (8). The Internet has been said to have become an effective means to obtain health information and prevent various diseases (9, 10). Second is the interpersonal emotional interpretation mechanism of the Internet (11). The mechanism accepts as true that the Internet, as a medium of social communication, can alleviate users' loneliness and anxiety and then improve their health (12). Social networking can also relieve pain and reduce the probability of depression (13, 14). Apart from physical and mental health, the Internet can also improve residents' enthusiasm to participate in community activities (15). This idea means that Internet use can have a positive impact on individual social adaptability or social health, but only a small amount of literature has explored this assumption.

Which Groups Are More Affected by Internet Use?

From the perspective of age, adolescents, and the elderly are the focus of literature. The study found that approximately 14.5% of Chinese young netizens have ever caused property loss or physical and psychological injury due to false information on the Internet; some young people have also suffered varying degrees of personal and behavioral injuries due to excessive addiction to online games. Internet use time affects the health status of adolescents by changing their life time allocation (16). For example, with the increase in online time, teenagers' sleep and exercise time are often squeezed out (17). In addition, the Internet has begun to play an increasingly important role in the lives of the elderly. People aged 60–70 with higher socioeconomic status are more likely to use the Internet (18, 19). The elderly keep close contact with their children, relatives, and friends mainly through e-mail and other forms (20). In general, Internet use not only can improve the physical health of the elderly but also increase their subjective well-being (21, 22).

A Brief Review

To sum up, from the perspective of academic research, it still requires improvement from the following aspects. First of all, the literature mostly focuses on a single dimension of health and lacks multi-dimensional consideration of health connotation. Second, given the possible reciprocal cause–effects between Internet use and individual health, we should further consider the endogenous problem. Regular or moderate Internet use can improve health. For example, it can relax oneself, relieve anxiety and so on. But excessive addiction to the Internet will lead to decline in health. In reverse, anxiety, loneliness, and other factors can also affect Internet use, especially the Internet addiction. That is to say, there is a causal endogeneity between them. Therefore, an instrumental variable model is necessary for correction. Third, the formation mechanism of social health may be ignored due to the single research dimension.

The purpose of this paper is to explore the effects of Internet use on Multi-dimensional health. First, the study divides the overall self-reported health into three dimensions: physical, mental, and social health, and then examines the impact of Internet use on health in each dimension. Second, Eoprobit model is used to test endogeneity, and substitution variables, linear regression model, and Heckman model for the robustness test. Third, considering the heterogeneity of the sample, we use the interaction term model to test the impact of Internet use on the health of different groups. Fourth is through the mediating effect model to explore the underlying mechanism of Internet use affecting physical, mental, and social health.

DATA SOURCES AND ECONOMETRIC MODELS

Data Sources

The data used in this paper are from the CGSS. This database was completed by the Department of Social Sciences, Renmin University of China in cooperation with the Survey Research

Center of the Hong Kong University of Science and Technology. Five-year (2003–2008, excluding 2007) high-quality survey data have been completed in the first phase. Then, seven surveys were conducted in the second phase (2010–2019, excluding 2014). This survey item mainly focuses on the major theoretical and practical problems in the change of China's social structure and comprehensively collects some basic information about residents' behavior mode, thinking mode, lifestyle, and social change. At present, this database has become an important reference for academic research and policy formulation. The CGSS questionnaire includes questions on individual health and Internet use. According to the respondents' answers, we can measure these variables. Considering the timeliness and availability of the data, this paper uses the 2017 CGSS data. Following the purpose of the research, 9,808 samples were retained by deleting missing values and outliers.

Variable Selection

Dependent Variable

According to the ideas of Rosini (4) and Wang (23), the paper uses the self-reported health indicator to measure general health; the items of "health affects the frequency of work and life," "the frequency of depression or depressed," and "the frequency of participating in social activities or visiting in free time" in the questionnaire are, respectively, used to measure physical, mental, and social health. According to the respondents' answers, health status is divided into five levels with values ranging from 1 to 5. The higher the value, the higher the level of health.

Independent Variable

The independent variable is Internet use. According to the respondents' answers in the 2017 CGSS, we assign 1 to "never," 2 to "rarely," 3 to "sometimes," 4 to "often," and 5 to "always."

Control Variables

Including two types of control variables at the individual and family levels. The former includes gender, age, marital cohabitation, party member status, education, and physical exercise. The latter includes family economic status and household register. Considering that anxiety and other health problems are often closely related to emotional and financial support of family members, especially spouses (couples). Therefore, we design the variables of marital cohabitation according to whether they live together or not, which is different from most previous literature. We assigned 0 to the four situations of "unmarried," "separated without divorce," "divorced," and "widowed" in the questionnaire which are regarded as "divorced;" and 1 to other situations, which means "married."

Mediating Variables

This paper argues that Internet users have different preferences. For example, some people prefer watching movies on the Internet, while others may prefer to search for relevant information. According to the three dimensions of physical, mental, and social health, this paper proposes three corresponding mediating variables: information, leisure, and social preferences. Information preference is expressed by "the frequency of online access to information in the past year," leisure preference is expressed by "the frequency of online participation in leisure entertainment (games, music, video, etc.) in the past year," and social preference is expressed by "the frequency of online participation in social activities in the past year." The three variables are all five-level sequence category variables. 1 means "never," 2 means "little," 3 means "sometimes," 4 means "often," and 5 means "always." **Table 1**. shows the specific variable settings.

Empirical Model

Two types of empirical models are involved in this paper. One is the regression of ordered probit model on health, and the other refers to the three mediating effect models based on information, leisure, and social preferences.

First, we set up the following ordered probit model about health for ordered categorical variables. Assuming that the healthy value range is 1, 2,..., m, then, the ordered probit model can be set as follows:

We assume that $Y_i = j$.when we satisfy

$$u_{j-1} < Y_i^* \leq u_j, j = 1, 2, ..., m. \tag{1}$$

Y_i^* is the latent variable of the ordered categorical variable Y_i and is affected by the Internet use $Inter_i$ and the control variable X_i. It can be expressed as follows:

$$Y_i^* = \beta Inter_i + \gamma X_i + u_i. \tag{2}$$

When we satisfy$u_j \leq u_{j+1}, u_0 = -\infty, u_m = +\infty$, the probability of$Y_i = j$ can be expressed as follows:

$$\begin{aligned} pr(Y_i = j) \; = \; & \Phi(u_j - \beta Inter_i - \gamma X_i) \\ - \; & \Phi(u_{j-1} - \beta Inter_i - \gamma X_i). \end{aligned} \tag{3}$$

Φmeans the cumulative density function that obeys the standard normal distribution and satisfies $j = 1, ..., 5$.

Second, according to information, leisure, and social preferences, we set up the following three mediating effect models.

According to the mediating effect test procedure proposed by Wen et al. (24), this paper uses the following Equations (4)–(6). For convenience, the control variables are omitted here, and only social preference is used as an example.

$$Y_i = c \times Inter_i + \varepsilon_i, \tag{4}$$

$$socialprefer_i = a \times Inter_i + \mu_i, \tag{5}$$

$$Y_i = c^{'} \times Inter_i + b \times socialprefer_i + \nu_i. \tag{6}$$

In Equation (4), c is the total effect of the independent variable $Inter_i$ (Internet use) on the dependent variables Y_i(health); in Equation (5), a is the effect of the independent variable $Inter_i$(Internet use) on mediating variables Socialprefer (Social preference); in Equation (6), b is the effect of mediating variable Socialprefer (Social preference) on dependent variable

TABLE 1 | Descriptive statistics of samples.

Variables	Mean value	Standard deviation	Minimum value	Maximum value	Explain
Physical health	4.027	1.072	1	5	Ordered classification variables, assigned to 1–5
Mental health	3.809	0.990	1	5	Ordered classification variables, assigned to 1–5
Social health	2.745	1.022	1	5	Ordered classification variables, assigned to 1–5
General health	3.6037	1.073	1	5	Ordered classification variables, assigned to 1–5
Internet use	3.173	1.679	1	5	Always = 5, often = 4, sometimes = 3, rarely = 2, never = 1
Gender	0.467	0.499	0	1	Male = 1, female = 0
Age	44.813	13.180	18	65	Survey year minus birth year
Marital cohabitation	0.800	0.400	0	1	Unmarried, separated without divorce, divorced, and widowed = 0, others = 1
Party member status	0.093	0.290	0	1	Party membership = 1, others = 0
Education	9.705	4.093	1	15	No formal education = 1, primary school = 6, junior high school = 9, senior high school = 12, junior college or above = 15
Physical exercise	2.505	1.555	1	5	The frequency of participating in physical exercise is 1–5
Household register	0.361	0.480	0	1	Agricultural household registration = 0, Non-agricultural household registration = 1
Family economic status	2.564	0.738	1	5	Family economic status level, assigned to 1–5
Information preference	3.550	1.069	1	5	Five level sequence category variable
Leisure preference	3.349	1.107	1	5	Five level sequence category variable
Social preference	3.705	1.074	1	5	Five level sequence category variable

Y_i (health), and c' is the direct effect of the independent variable$Inter_i$ (Internet use) on the dependent variable (health) after controlling Social preference. Following the idea of Wen et al. (24), we first test whether the regression coefficient c is significant. If significant, it should be judged according to the mediating effect; otherwise, it should be judged according to the masking effect. Second, we judge the significance of regression coefficients a and b; if they are both significant, the indirect effect is significant. We then further test the significance of the direct effect c' of Social preference on Y_i (health). If the coefficient c' is significant, a partial mediating effect possibly exists. Otherwise, a complete mediating effect is considered to exist.

The above basic model may evidently cause inconsistent and biased estimates due to the sample self-selection bias or mutual causality between Internet use and individual health. Later, We will use the Heckman model and Eoprobit model to solve these problems.

EMPIRICAL RESULTS

Impact of Internet Use on Individual Multi-Dimensional Health

The general, physical, mental, and social health are divided into five ordered levels, i.e., 1, 2, 3, 4, 5, while controlling many variables such as individuals and family characteristic and using the regression of ordered probit model to investigate the impact of Internet use on individual's multi-dimensional health. **Table 2** shows the results.

From the control variables, marital cohabitation, age, gender, and household register have different directions and degrees of influence on individual multi-dimensional health. Compared with women, men's general, physical, and mental health levels are higher, but women's individual social health level is higher than men's. Overall, the regression coefficients of gender are significant at the level of 0.01. With the growth of age, the health level of each dimension begins to decline, but age had no significant effect on the latter two types of health. The regression coefficients of married cohabitation are all positive in the four regression equations and are significant at the level of 0.01, implying that cohabitation can improve the general health and the health levels of all dimensions. In fact, living together with a spouse or couple can provide emotional or financial support for each other, which will somewhat reduce anxiety and relieve stress. Party member status only has a certain positive impact on the general, physical, and mental health. The higher the education, the higher the level of general, physical, and mental health. However, a negative relationship exists between the education and social health levels, which may mean that the higher the education level, the lower the possibility of participating in social activities and visiting. In addition, the frequency of participating in physical exercise is positively correlated with the level of health in all dimensions. At the same time, the higher the family's

TABLE 2 | Ordered probit estimation of Internet use on individual multidimensional health.

Variables	General health	Physical health	Mental health	Social health
Internet use	0.0752***	0.0949***	0.0403***	0.0392***
	(0.00928)	(0.00964)	(0.00937)	(0.00917)
Gender	0.0833***	0.0738***	0.0931***	−0.110***
	(0.0220)	(0.0229)	(0.0221)	(0.0216)
Age	−0.0251***	−0.0135***	−0.00108	−0.00157
	(0.00115)	(0.00119)	(0.00114)	(0.00112)
Marital cohabitation	0.137***	0.155***	0.217***	0.0915***
	(0.0293)	(0.0304)	(0.0291)	(0.0286)
Party member status	0.109***	0.117***	0.112***	0.0505
	(0.0395)	(0.0423)	(0.0401)	(0.0385)
Education	0.0281***	0.0372***	0.0265***	−0.00805**
	(0.00379)	(0.00390)	(0.00379)	(0.00373)
Physical exercise	0.0747***	0.0593***	0.0666***	0.0616***
	(0.00757)	(0.00789)	(0.00763)	(0.00745)
Household register	−0.0356	0.0660**	0.0845***	−0.105***
	(0.0265)	(0.0278)	(0.0266)	(0.0260)
Family economic status	0.00296**	0.00505***	0.00422***	0.000347
	(0.00148)	(0.00166)	(0.00153)	(0.00144)
Pseudo-R^2	0.0737	0.0606	0.0224	0.0508
Observations	9,808	9,808	9,808	9,808

*The parentheses are standard errors. ***, **, and * indicate significance at 1, 5, and 10% levels, respectively. Owing to space limitation, the estimation of cut-off points is omitted here.*

TABLE 3 | The marginal effect of oprobit model.

Variables	$Y = 1$	$Y = 2$	$Y = 3$	$Y = 4$	$Y = 5$
Internet use	General health				
	−0.0051***	−0.0113***	−0.0094***	0.0063***	0.0196***
	(0.0006)	(0.0014)	(0.0011)	(0.0007)	(0.0024)
	Physical health				
	−0.0054***	−0.0103***	−0.0120***	−0.0060***	0.0338***
	(0.0006)	(0.0010)	(0.0012)	(0.0006)	(0.0034)
	Mental health				
	−0.0016***	−0.0051***	−0.0079***	0.0014***	0.0132***
	(0.0003)	(0.0012)	(0.0018)	(0.0003)	(0.0030)
	Social health				
	−0.0071***	−0.0082***	0.0031***	0.0087***	0.0034***
	(0.0016)	(0.0019)	(0.0007)	(0.0020)	(0.0008)

*Delta-method standard error in parentheses. ***, **, and * indicate significance at 1, 5, and 10% levels, respectively.*

economic status, the higher the health level except social health. Non-agricultural household registration individuals show higher physical and mental health levels. Meanwhile, agricultural household registration has a higher social health level, showing certain "optimistic" characteristics.

Table 2 also shows that the regression coefficients of Internet use on general health, physical health, mental health, and social health are all positive and significant at the level of 0.01, which means that Internet use can improve the health level in multiple dimensions. Because multi-dimensional Health are ordinal categorical variables, the regression coefficients in **Table 2** only reflect their effective degree on health, not marginal effects. Therefore, the marginal effect of Internet use on multi-dimensional health was investigated based on the estimates of each cut-off points. **Table 3** shows the results. Taking general health as an example, when Internet use increases by one unit, the probability of overall health status as "very unhealthy," "relatively unhealthy," and "average" will decrease by 0.51, 1.13, and 0.94%, respectively. The probability of being "healthier" and "very healthy" increased by 0.63 and 1.96%. Similar explanations can be made for physical, mental, and social health.

As the research literature points out, excessive use of the Internet may have a negative impact on health. This paper takes the mental health dimension as an example to discuss the relationship between the time spent on the Internet and the "frequency of individual's depression or depressed." We consider "never" and "little" as "healthy" and assign them to 1, but we deem other cases "unhealthy" and thus assign them to 0. By estimating the predicted probability that the mental health level is "healthy," a significant inverse U relationship is found between the predicted probability value and the logarithm of the number of online hours per week as shown in **Figure 1**. With the increase in Internet use time, the degree of individual psychological depression will be significantly reduced or the probability of individual self-reported as "health" will increase. However, when the logarithm of the number of online hours per week exceeds a certain threshold, it will have a negative impact on individual's mental health, and the probability of individual self-reported as "health" will continue to decline.

Endogenous Test

The impact of Internet use on health status is investigated above, but other influencing factors may be present because of the availability of data. At the same time, Individual with good health status may have more energy and time to surf the Internet. Therefore, this study may face an endogeneity problem caused by an omitted variable and reciprocal cause–effects relationship. The instrumental variable is an effective method for endogeneity problems. Theoretically, effective instrumental variables must be uncorrelated with random disturbances. Meanwhile, they must be highly correlated with endogenous variables. According to the CGSS 2017 data, we use other family members' Internet access in the past 6 months, referred to as Family internet use as an instrumental variable. Firstly, Family internet use is closely related to individual Internet use. After all, online communication is an important way for family members to maintain affection in the Internet age. Secondly, the health status of an individual depends mainly on self-responsible factors, and has little to do with the frequency of Internet access of other family members. Specifically, this variable is assigned to 1 when other family members have used Internet in the last 6 months, and 0 otherwise.

Since Internet use is a discrete variable, the traditional instrumental variable model cannot solve this problem. For this

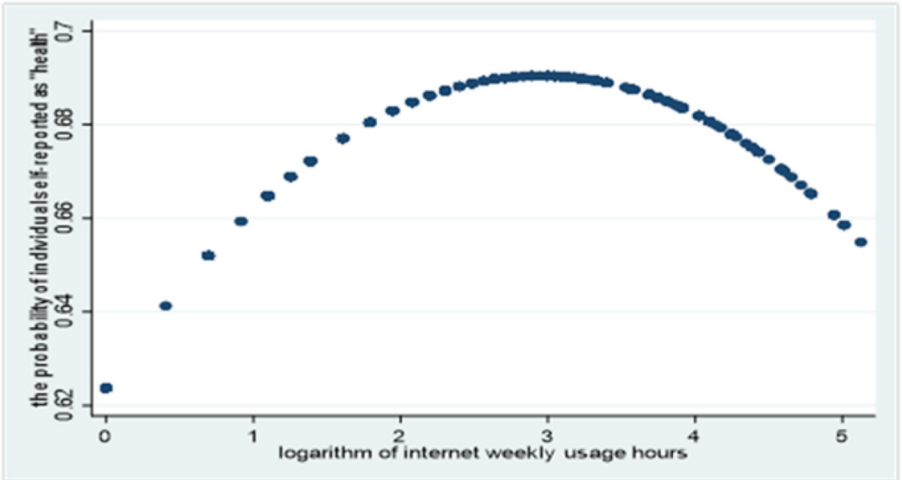

FIGURE 1 | Relationship between the logarithm of Internet weekly usage hours and the degree of depression.

TABLE 4 | Results of endogenous test.

Variables	General health	Internet use
Gender	0.0845***	0.0147
	(0.0221)	(0.0235)
Age	−0.0143***	−0.0526***
	(0.00240)	(0.00108)
Marital cohabitation	0.0750**	0.209***
	(0.0318)	(0.0314)
Party member status	0.0628	0.262***
	(0.0409)	(0.0415)
Education	0.00326	0.126***
	(0.00620)	(0.00379)
Household register	−0.120***	0.444***
	(0.0306)	(0.0276)
Physical exercise	0.0693***	
	(0.00752)	
Family economic status	0.00254*	
	(0.00146)	
Internet use	0.246***	
	(0.0335)	
Family internet use		0.859***
		(0.0327)
Observations	9,683	9,683
Corr (e.general health, e.internet use)	−0.2082***	
	(0.0396)	

*The parentheses are standard errors. ***, **, and * indicate significance at 1, 5, and 10% levels, respectively. Owing to space limitation, the estimation of cut-off points is omitted here.*

reason, the paper uses the Eoprobit regression model in extended regression models (ERMs) to solve the endogeneity problem when the independent variable is discrete variable in ordered probit model. Limited by space, here only lists the test results of the general health. **Table 4** shows the results.

On the one hand, the regression coefficient of Internet use to general health is 0.246 and significant at the level of 0.01 in the main regression equation. On the other hand, the regression coefficient of Family internet use to Internet use is 0.859 in the auxiliary regression equation, which is significant at the level of 0.01. The correlation coefficient of the residuals of the two equations is −0.2082 and significant at 0.01 level, which means Internet use is an endogenous variable and the unobservable factors that affect Internet use reduce an individual's health level. But why? As shown in **Figure 1**, excessive addiction to the Internet will lead to decline in health. Some unobservable factors such as doldrums and loneliness related to Internet addiction may have greater negative effects on health. So, the negative sign maybe expected. The above results indicate that Internet use is an endogenous variable. Family internet use has strong explanatory power to Internet use. The findings that Internet use improves general health status remained robust after accounting for endogeneity.

Robust Test

In this section, substitution variables, linear regression model, and Heckman model were used to test the robustness. Again, take general health as an example. In the first method, Frequency of surfing the Internet in free time is used as a substitute variable for Internet use. According to the item in the CGSS data in 2017, "never," "Several times a year or less," "Several times a month," "Several times a week," and "Every day" were assigned a value of 1–5, respectively. It can be seen from the first column of **Table 5** that frequency of surfing the Internet in free time has a significant positive impact on general health. If we use linear regression instead of ordered probit model, Internet use remains a significant impact on overall health. In the Heckman two-step selection model, the first stage is to establish the Internet use decision equation, the outcome equation in the second stage examines the effect of

TABLE 5 | Results of robust test.

Variables	Substitution variable	Linear regression	Heckman model
Internet use		0.0730***	0.0575***
		(0.0083)	(0.0127)
Frequency of surfing the Internet in free time	0.0690***		
	(0.0082)		
R^2/Pseudo-R^2	0.0739	0.1950	
Rho			−0.1458***
			(0.0462)
LR test			10.05***

*The parentheses are standard errors. ***, **, and * indicate significance at 1, 5, and 10% levels, respectively. Owing to space limitation, the estimation of cut-off points is omitted here.*

Internet use on general health. The results of selection equation are not presented in the **Table 5** due to lack of space. As shown in the third column, rho = −0.1458 and LR test = 10.05, indicating that the null hypothesis that the correlation coefficient between selection and outcome equation is equal to 0 should be rejected. Thus, the two equations are related. There will be sample selection bias if we don't estimate two equations simultaneously, so the Heckman model is effective and necessary. Based on the selection equation, the regression coefficient of the Internet use is 0.0575, which means that as the frequency of Internet use increases, so does the general health level.

Heterogeneity Analysis

As emphasized in the research literature, Internet use may have different effects on adolescents and the elderly, which means there may be heterogeneity in the health effects of Internet use. This section only takes the general health as an example and adds the interaction items of Internet use and education, age, and gender into the basic model to study the heterogeneity of Internet use affecting general health. For comparison between groups, education and age are treated as binary dummy variables. That is, education is assigned to 1 when the level of education is higher than high school, otherwise, it is 0; Age is assigned to 1 when individual biological age is between 36 and 65 years old, it is 0 when individual biological age is between 18 and 35 years old. When the ordinal regression model incorrectly assumes that error variances are the same for all groups in the population, the parameter estimates will be biased. Different age, education and gender groups may have different health outcomes. So, we use the heteroskedastic ordered models proposed by Williams (25) for research. This models simultaneously fit two equations, one for the means model and one for the residual variance, thereby allowing the variance to differ across all groups in the population. **Table 6** shows the results.

As seen from the upper part of the **Table 6**, also controlling the relevant variables, the interaction items between Internet use and education, age, and gender are 0.157, 0.0066, and 0.171, respectively, and they are significant at the 0.01 level. The lower part of the **Table 6** shows these variables proved to be statistically significant determinants of the residual variance—e.g., the level of education is higher than high school (reduced variance), biological age is between 36 and 65 years old (increased variance), and being male (increased variance)—these include our variable of interest. A certain degree of heterogeneity is indicated to exist in the general health effects of Internet use on individuals with different characteristics. Specifically, the effect of Internet use on health promotion of high school or above education group is significantly greater than that of groups with a degree below high school, and Internet use has a greater role in promoting the general health level of the elderly and male groups.

TABLE 6 | Heterogeneity of Internet use affecting general health.

	Control variable	Controlled	Controlled	Controlled
Means model	Internet use × education	0.157***		
		(0.0267)		
	Internet use × age		0.0066***	
			(0.000790)	
	Internet use × gender			0.171***
				(0.0281)
Variance model	Education	−0.163***		
		(0.0194)		
	Age		0.00487***	
			(0.000781)	
	Gender			0.0541***
				(0.0183)
	Pseudo-R^2	0.0712	0.0454	0.0725
	LR test	69.26***	38.52***	8.75***
	Observations	9808	9808	9808

*The parentheses are standard errors. ***, **, and * indicate significance at 1, 5, and 10% levels, respectively. Owing to space limitation, the estimation of cut-off points is omitted here.*

Mediating Effect of Internet Use Preference

The above results show that Internet use has a significant promoting effect on each dimension of health, and heterogeneity exists among different groups. Furthermore, how does Internet use affect health in all dimensions? In fact, different individuals have different Internet usage preferences, which may lead to different health outcomes. Combined with the CGSS data in 2017, this paper argues that Internet use preference is an important path mechanism for Internet use to promote health. It also attempts to test the mediating effect of Internet use preference on the relationship between Internet use and health. For physical health, the Internet is an important health information dissemination channel, which can improve the personal health literacy and quality of life. Therefore, the paper uses Equations (4)–(6) to test the mediating effect of information preference between Internet use and physical health. Similarly, we examine the mediating effects of leisure

and social preferences between Internet use and mental or social health.

Table 7 reports the mediating effects of information, leisure, and social preferences in three parts. The results of the first part show that the regression coefficient of Internet use to information preference is 0.3462, and it is significant at the level of 0.01. This finding indicates that the two are highly correlated. Furthermore, when Internet use and information preference are simultaneously included in the regression equation, the direct impact of Internet use on physical health is found to be 0.0420 and significant at the level of 0.1. Meanwhile, the regression coefficient of information preference is 0.0880 and significant at the level of 0.01. Combining the results of the total effect of Internet use on physical health in the second column of **Table 2**, information preference is considered to play a partial mediating role in the relationship between Internet use and physical health. The mediating effects of leisure and social preferences can undergo similar analysis, which will not be repeated here.

TABLE 7 | Test results of mediating effect.

Variables	Dependent variable: information preference	Dependent variable: physical health
Mediating effect of information preference		
Information preference		0.0880***
		(0. 0258)
Internet use	0.3462***	0.0420*
	(0.0244)	(0. 0262)
Other variables	controlled	controlled
Observations	2247	2247
Pseudo-R^2	0.0997	0.0324
Mediating effect of leisure preference		
Main variables	**Dependent variable: leisure preference**	**Dependent variable: mental health**
Leisure preference		0.0386*
		(0. 0221)
Internet use	0.2447***	0.0526**
	(0.0241)	(0.0237)
Other variables	controlled	controlled
Observations	2247	2247
Pseudo-R^2	0.0629	0.0072
Mediating effect of social preference		
Main variables	**Dependent variable: social preference**	**Dependent variable: social health**
Social preferences		0.1107 ***
		(0.0233)
Internet use	0.3458***	0.0520 **
	(0.0243)	(0. 0247)
Other variables	Controlled	Controlled
Observations	2,247	2,247
Pseudo-R^2	0.0770	0.0129

*The parentheses are standard errors. ***, **, and * indicate significance at 1, 5, and 10% levels, respectively. Owing to space limitation, the estimation of cut-off points is omitted here.*

CONCLUSION AND ENLIGHTENMENT

On the bases of the data of the 2017 CGSS, this paper examines the impact of Internet use on general, physical, mental, and social health. It then explores the heterogeneity of the impact among different groups and its underlying mechanism. The results show that Internet use has a significant positive impact on all dimensions of health. After endogenous and robustness tests, the results confirm the robustness of the conclusion that Internet use can improve health level.

Through the analysis of the possible heterogeneity in different groups, the results show that the impact of Internet use on individual health varies significantly among different educational background, age, and gender. Internet use has more obvious health effects on senior high school education, the elderly, and the males. Furthermore, the analysis of the mediating effect model identifies information, leisure, and social preferences as the important path mechanisms for Internet use to promote physical, mental, and social health.

In view of the above conclusions, this paper puts forward the following policy recommendations. First is the need to further improve Internet penetration. Although the overall Internet penetration rate in China has reached 70.4% by December 2020, differences persist between urban and rural areas and regions. According to the 2017 CGSS data, among the 1,789 individuals who did not surf the Internet, 32.03% did not know how to surf the Internet, 2.96% had no equipment or place to surf the Internet, and 26.33% could not surf the Internet. Therefore, we should further strengthen the construction of Internet infrastructure, increase the access opportunities of the entire society, and lay the foundation for improving the health effect of the Internet. Second is to provide differentiated and high-quality Internet services. In view of the heterogeneity of Internet health effects, the government should establish health information platform for adolescents, middle-aged, and elderly people and implement "Internet plus precision health" to provide differentiated high-quality health information for different social groups. At the same time, we should further enrich the content of Internet services, appropriately increase Internet entertainment and leisure functions, and then meet diversified needs. Third is to cultivate a good network culture and enhance the comprehensive scientific literacy of netizens. In the Internet age, all kinds of "fresh" information emerge endlessly. Different Internet usage preferences may lead to different health outcomes. Therefore, we should cultivate a healthy, green, civilized, and harmonious Internet culture in the entire society to promote individuals' formation of a good healthy choice mechanism. We must also enhance the individual's comprehensive ability to "access the Internet" and minimize the negative effects of Internet use.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This date can be found here: http://cgss.ruc.edu.cn.

AUTHOR CONTRIBUTIONS

JH: research conceptualization, methodology, validation, resources, data curation, writing—original draft preparation, supervision, project administration, and funding acquisition. XZ: software, formal analysis, investigation, writing—review and editing, and visualization. All authors have read and agreed to the published version of the manuscript.

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Estimating the Cost of the Design, Production, and Dissemination of Social Media Videos for Social and Behavioral Change: Evidence From Merci Mon Héros in Niger and Côte d'Ivoire

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Merci Mon Héros (MMH) is a youth-led multi-media campaign in Francophone West Africa seeking to improve reproductive health and family planning outcomes using radio, television, social media, and community events. One component to this project is the development of a series of youth-driven videos created to encourage both youth and adults to break taboos by talking to each other about reproductive health and family planning. A costing study was conducted to capture costs associated with the design, production, and dissemination of 11 MMH videos (in French) on social media in Côte d'Ivoire and Niger. The total costs to design, produce and disseminate 11 of the campaign videos for MMH in both Côte d'Ivoire and Niger were $44,981. Unit costs were calculated using three different denominators, resulting in average unit costs of $0.16 per reach, $1.29 per engagement, and $4.27 per video view. These findings can be useful for future studies of SBC interventions using social media for framing the analysis and selecting the appropriate metrics for the denominator, as well as for budgeting and planning SBC programs using social media.

Keywords: reproductive health, family planning, social media, videos, social and behavior change, unit cost

INTRODUCTION

Francophone West Africa continues to experience challenges in reproductive health and family planning (RH/FP), including high levels of maternal and child mortality, high unmet need for FP, and high fertility rates (1, 2). Adolescent pregnancy contributes to these poor health indicators by perpetuating intergenerational cycles of poverty and poor health (3). An increase in modern contraceptive prevalence rate (mCPR) among women in West Africa could help improve these health measures, however, uptake of FP has been low in this region, particularly among adolescents (4, 5). There are several factors driving the high fertility rate and low levels of FP use in the region, including poor access to FP services, negative attitudes toward FP, and religious and social norms surrounding fertility and early marriage (6–8). Due to cultural norms and taboos around RH,

adolescents in sub-Saharan Africa typically do not have access to RH information via open dialogue with their parents, elders, or partners, which can improve knowledge and influence attitudes and behaviors (9).

A literature review of SBC strategies for improving RH/FP outcomes among youth ranging from adolescence to early adulthood in West Africa found evidence on the use and impact of traditional mass media interventions (e.g., radio and television), but limited evidence on interventions using social media platforms (10). Social media as a tool to convey (i.e., obtaining, sharing, or exchanging) information to the public can help inform or motivate health-related behavior change and/or influence health decision making as well as allow targeted messaging with hard-to-reach groups (11).

To fill this research gap, the United States Agency for International Development (USAID) is working in West Africa through the Breakthrough RESEARCH project to evaluate a mass multi-media campaign called Merci Mon Héros (MMH), which means "thank you, my hero" in French, being conducted through its sister project, USAID-funded Breakthrough ACTION. The MMH campaign includes radio, television, social media, and community events. One important component of MMH was the development of a youth-led campaign, beginning with a youth design challenge (YDC) at the Francophone SBC Summit in Abidjan, Côte d'Ivoire in February 2019. From this challenge evolved the "Merci Mon Héros" campaign wherein youth thank their parents, other family members, friends, teachers, and partners for communicating with them about RH and family planning (FP), and helping or supporting them when they had difficulty accessing RH/FP information or services (12). To help develop the campaign, the YDC winning team participated in a video production and dissemination-specific hands-on training on filming the videos (in French) with smartphones, interviewing, and post-production. Videos are not the MMH campaign's sole social media content, also included screenshots with key video quotes or messages as static visuals posted on social media to help increase the likelihood that key messages, themes, or ideas are captured. However, these components were not included in this analysis as the focus of the study was solely to capture costs associated with the design, production, and dissemination of the MMH videos on social media.

During the timeframe of the analysis, 11 MMH videos were disseminated via social media (e.g., Facebook, Twitter, YouTube, Instagram) and via radio, television, and community-based events in nine countries (Burkina Faso, Côte d'Ivoire, Togo, Niger, Democratic Republic of Congo, Guinea, Mali, Benin, and Senegal). The videos consisted of individuals recounting their experiences when someone in their life shared information about reproductive health issues and how this information helped them better understand their health and options. This study examines the cost of designing and disseminating the MMH videos via social media, with a focus on the videos' dissemination in Niger and Côte d'Ivoire. These two countries were selected for analysis because: (1) The YDC that sparked the original MMH campaign idea was held in Côte d'Ivoire, and (2) Niger has the highest total fertility rate in the world and high levels of adolescent pregnancy (13, 14). The results from this study will help fill important knowledge gaps on the costs of digital SBC interventions for health to improve coordinated investments in SBC for family planning and reproductive health (15).

The primary purpose of this study was to estimate the total design, implementation, and unit costs associated with the MMH videos. Many SBC costing studies neglect estimating the design costs of SBC interventions, and even less is known regarding design costs associated with RH/FP SBC programming with and for youth (15). Thus, these results will address this gap and help assist program planners considering similar approaches in the region.

A second objective was to examine the unit costs of MMH in Niger and Côte d'Ivoire. There are several potential program unit costs to examine with digital media, where the denominators of the unit costs (i.e., SBC campaign "reach") are currently being discussed and conceptualized in the literature (16, 17). Unit costs are critical for budgeting and planning and defining unit costs has important implications for comparing costs across interventions (18–20). The different unit costs, based on different measures of reach, that can be used for SBC interventions delivered through social media are explored here to contribute to this new area of research.

MATERIALS AND METHODS

Protocol and Data Collection Tool Development

The study protocol and data collection instruments were developed by Breakthrough RESEARCH and led by Avenir Health with support from MMH key country stakeholders. The data collection questionnaire was developed based on the SBC costing guidelines (21). Before data collection commenced, a series of web-based consultations were conducted with the Breakthrough ACTION team in Niger and Côte d'Ivoire, designed to gather their inputs and to evaluate whether the study instruments captured all relevant data. Feedback was documented and the data collection tool was subsequently revised and finalized.

Approach and Cost Components

This costing study primarily took an economic costing approach, focusing on the resources needed to replicate the development of videos delivering SBC messaging through social media platforms in a similar setting. Included in the costs are those associated with in-kind contributions, such as donated personnel time and meeting space, which were valued at the expected costs based on information on the value of the donation provided by Breakthrough ACTION country teams. Broader societal costs were not included, such as the costs associated with the time for the intended audience to view the videos or the cost of internet access for users of social media.

Table 1 details the cost components included in this study from the time of conceptualization in late 2018 to dissemination through October 2020. Design costs included those associated with the YDC, training and production. The first set of costs includes personnel costs associated with preparing for and attending the February 2019 Abidjan SBC Summit, where the

TABLE 1 | Cost components included in MMH video costing analysis.

Cost category	Included components	Time frames
Start-up and Youth Design Challenge	• Personnel time in preparation of the YDC (including donated time) • Personnel time at the YDC (including donated time) • Travel to the YDC, per diems, lodging • Conference and workshop costs (e.g., rooms, catering) • Stipends for youth	November 2018–February 2019
Training and production	• Personnel time (including donated time) • In-kind contributions • Travel and transport, per diems, lodging • Training venue and catering • Equipment	June 2019 and February 2020
Dissemination	• MMH launch cost • Personnel costs (youth consultants, influencers) • Social media advertising	November 2019–October 2020
Overhead	• Breakthrough ACTION overhead, including personnel not directly engaged in SBC activities (e.g., finance, human resources)	November 2019–October 2020

YDC committee selected the winning team, who were later invited to be co-creators of the resulting MMH campaign. Costs associated with the YDC include personnel and consultant time, travel, conference fees, room and catering fees, and stipends for 18 youth consultants/trainees who attended the summit. Since the attendees to the summit were not there exclusively to participate in the YDC, only a portion of the total conference costs were attributed to the campaign design, based on interviews with key staff.

Subsequently, there was a workshop to strengthen capacity of the winning youth consultants, plus nearly a dozen additional young activists, journalists, and other young people working in the RH space in Francophone African countries for 2 weeks in June and July 2019. In addition, there was a 1-week refresher training on video production and dissemination for a group of paid youth consultants in February 2020. The costs associated with training and production were primarily the personnel time associated with staff and consultant trainers, travel, lodging and catering, car hires, and equipment. Equipment costs were relatively low as the videos were filmed using smart phones and open-source software; the costs of four smartphones purchased by Breakthrough ACTION and used for MMH were included in the analysis.

The first MMH video was posted on Facebook in November 2019. Dissemination costs associated with the core MMH videos include personnel costs associated with social media influencers/bloggers paid to disseminate and promote the videos, social media paid advertising, and costs associated with the MMH launch in each country (e.g., equipment rental, services). While the dissemination of the videos and production of new videos continues at the time of this manuscript, the data collection for the dissemination phase reported here includes costs from November 2019 through October 2020 only.

Finally, a portion of the overhead costs associated with Breakthrough ACTION's oversight of the production and dissemination of the videos were included. These include rent and support personnel (e.g., finance, human resources) costs to support activities for the purpose of planning, coordinating, and managing youths' technical work on MMH video production.

Data Collection

Because of the ongoing COVID-19 pandemic, the costing team worked remotely with Breakthrough ACTION headquarters and the Côte d'Ivoire and Niger teams to collect the data using the data collection instrument. Despite the communication challenges of remote data collection, in-country stakeholders' engagements commenced via a series of calls and web consultations in July 2020 to review the questionnaire and discuss the required data. The web consultations also familiarized the country teams with the data collection tool and the informed consent form. Verbal informed consent was obtained from key informants, which primarily included in-country SBC program and financial managers for Breakthrough ACTION.

Starting in September 2020, the team conducted extensive in-country stakeholder engagements via a series of phone calls, emails, and web consultations to review the data provided. Where data were incomplete, the research team requested clarifications from MMH stakeholders, both at headquarters as well as in-country.

Data on the reach of the MMH videos were captured via social listening reports conducted by Breakthrough RESEARCH in partnership with M&C Saatchi Intelligence (22). Their final campaign summary report captured social media engagement with MMH videos from November 1, 2019 through October 20, 2020 and included the number of persons reached, video views, likes, retweets, shares, and other forms of engagement by country, based on user IP addresses.

Analysis

Cost data obtained from the data collection instruments were entered into a Microsoft Excel workbook for analysis. The total design and production costs were captured and allocated to the two study countries using the proportion of the level of effort the production team (youth consultants) and the in-country Breakthrough ACTION team spent on the conceptualization, production, and review of the videos during the analysis period. Because of the potential recall bias for respondents to accurately estimate their level of effort to support the different stages of design, production, and dissemination of MMH videos, a

sensitivity analysis around this estimate was carried out by varying the level of effort in both direction by ± 5%, that is if the level of effort was estimated to be 10%, for example, the sensitivity analysis examines a range from 5 to 15%.

Costs allocated to the design and production of the videos include costs associated with the YDC and trainings for creating the videos, including personnel costs for these activities. To apportion the design and production costs for Côte d'Ivoire and Niger from the total costs of the overall MMH program, the percentage of the overall design and production costs allocated to each of the two countries was based on the relative reach to these countries, based on the social listening dissemination report, with 18% in Côte d'Ivoire and 6% in Niger.

The apportioned design and production costs were added to the total dissemination costs for each country. Dissemination costs include costs associated with the in-person campaign launch events, social media advertising, social influencers/bloggers, and program personnel for these activities. The launches were in-person but meant to drive interest in the broader campaign as well as the digital campaign. As such, only a portion of the launch costs were attributed to the dissemination of the videos, based on input from key staff. For costs listed in local currency, the average exchange rate for 2019/2020 of 552.47 FCFA = US$1 was used (23).

Unit costs were calculated using an ingredients-based costing approach, where all inputs were listed, their costs collected, and the contribution of these costs to the overall cost were quantified. For SBC disseminated *via* social media, measuring cost per exposure is particularly interesting due to the nature of social media platforms, which measures exposure differently from other SBC approaches, such as mass media and interpersonal communication. Three different program output denominators that measure exposure were used to calculate unit costs for Côte d'Ivoire and Niger:

- **Reach**—the number of people who saw MMH posts at least once; meaning any content from the MMH page entered their screen, including when people scroll past the post quickly.
- **Engagements**—the number of times people engaged with MMH posts through reactions, comments, shares, retweets, mentions, and likes.
- **Views**—the number of times the eleven videos were viewed for at least 30 s, where each video was at least 2 min long (max four and half minutes).

To calculate the number for each denominator for Côte d'Ivoire and Niger, the breakdown in Facebook users who have engaged with MMH content by location was used to best approximate country-specific denominators.

RESULTS

The total cost to design, produce and disseminate the 11 core videos for MMH in both Côte d'Ivoire and Niger from November 2018 through October 2020 was $44,981, as shown in **Table 2**. Among the categories shown, the highest proportion of costs across both countries are for overhead and consultants (each 35% for a total of 70%). The distribution of costs was mostly consistent between Côte d'Ivoire and Niger. Costs can also be disaggregated into two categories: (1) design and production and (2) implementation and dissemination (see **Table 3**). For both Côte d'Ivoire and Niger, ∼60% of the costs went into design and production and 40% went into dissemination.

TABLE 2 | Total design, production, and dissemination costs.

	Côte d'Ivoire		Niger	
Cost Category	**USD**	**Percentage**	**USD**	**Percentage**
Personnel	3,105	10	1,072	8
Consultants	10,206	33	5,422	39
Travel and transport	903	3	213	2
Social media advertising	2,633	8	827	6
Campaign launch	899	3	1,079	8
Training (non-personnel)	2,511	8	549	4
Overhead	11,076	35	4,586	33
Total	31,592	100	16,707	100

TABLE 3 | Costs, denominators, and unit costs (USD).

	Côte d'Ivoire	Niger
Costs		
Design and production	18,840	8,173
Implementation	12,394	5,575
Total	31,233	13,748
Denominators		
Reach	206,645	73,802
Engagements	26,074	9,312
Views	7,890	2,818
Unit costs		
Cost per reach	0.14	0.18
Cost per engagement	1.12	1.45
Cost per view	3.75	4.79

Unit costs are presented using three different denominators in **Table 3**. The average unit cost per person reached via social media across both countries was $0.16 (Côte d'Ivoire $0.14 and Niger $0.18), while the average unit cost per engagement was $1.29 (Côte d'Ivoire $1.14 and Niger $1.45). Finally, the average unit cost per 30+ second view was $4.27 (Côte d'Ivoire $3.75 and Niger $4.79). **Figure 1** further shows the unit costs for each country in graphical format.

Results of the sensitivity analysis around the respondent estimated level of effort by either a unilateral increase or decrease by 5% in the level of effort allocated to MMH videos are shown in **Table 4**. Based on the sensitivity analysis, the average unit cost ranged from $0.15 to $0.17 per reach, $1.23 to $1.36 per engagement, and $4.06 to $4.48 per view.

Since the total costs of the design and production of the MMH videos were captured for all the West African core countries, the aggregate unit costs associated with design and production can also be examined using data capturing outcomes across all

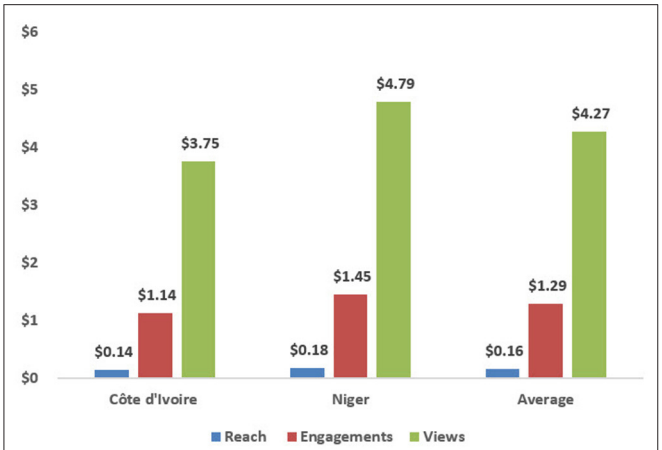

FIGURE 1 | MMH video unit cost by exposure level.

TABLE 4 | Unit costs range of MMH videos.

Denominator	Côte d'Ivoire	Niger	Average
Reach	$ 0.14–0.15	$ 0.17–0.19	$ 0.15–0.17
Engagements	$ 1.08–1.19	$ 1.38–1.52	$ 1.23–1.36
Views	$ 3.57–3.94	$ 4.55–5.03	$ 4.06–4.48

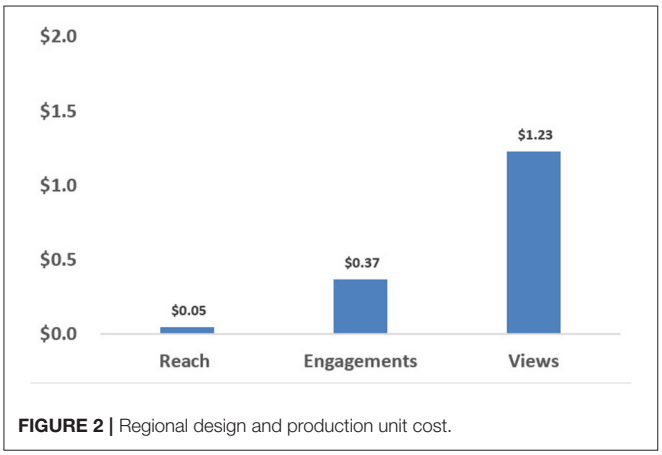

FIGURE 2 | Regional design and production unit cost.

of the countries where MMH was disseminated. This total unit design and production cost was $57,525. When divided by the total outcome variables, the unit costs for design and production were $0.05 per reach, $0.37 per engagement, and $1.23 per view (see **Figure 2**).

DISCUSSION

The use of social media for disseminating SBC messages has greatly increased in recent years, with many publications describing the uses, benefits, and limitations of social media for achieving public health objectives (16). Few studies, however, have examined the measurement of reach and/or costs when using social media. Researchers have considered different measures of social media and have acknowledged that there are a variety of outcome metrics available and a lack of agreement on which is the most appropriate for gauging the impact of a social media campaign (16, 17). In a literature review on SBC costs, no studies were identified that examined the unit costs associated with SBC campaigns using social media (15). As such, it is difficult to benchmark the unit cost findings from this research to other SBC campaigns on social media; however, it is useful to think about the results and their implications for SBC costing.

Approximately one third of the costs associated with MMH was spent on design and production and two thirds on dissemination in Côte d'Ivoire and Niger. The $57,525 total spent on design and production for the region was apportioned to Niger and Côte d'Ivoire based on country specific program reach. As such, it is important to consider the total costs for design/production when considering the findings for budgeting and planning purposes, as country-specific costs can contain efficiencies from having a regional program or approach. As dissemination continues over time and as more videos are produced leveraging the ever-deepening knowledge from the original training sessions, the design and production costs per output will decrease as these initial fixed costs are spread over more persons engaging with and viewing the videos. One of the novel approaches undertaken by MMH is the collaboration with youth in the design, production, and dissemination of the MMH videos. While the counterfactual of what it would cost to design and produce MMH without the involvement with youth was not assessed in this analysis, any additional costs associated with youth-led SBC should be weighed against the economic benefits of building capacity in the next generation of SBC professionals in the region. These benefits are not captured in this analysis but have important implications for potential societal returns on investment.

The unit costs for Côte d'Ivoire and Niger are very similar, with slightly higher unit costs in Niger due to the lower reach of the MMH videos in Niger compared to Côte d'Ivoire. While the design and production costs were allocated based on country reach, dissemination costs had fewer people reached, engagements, and views to be spread over. This is apparent in the higher proportion of total costs in the campaign launch costs in Niger vs. Côte d'Ivoire. The lower reach of SBC via social media in Niger is likely a function of more limited internet connectivity in Niger relative to Côte d'Ivoire and other countries in the region, where only 2% of the population is on Facebook in Niger compared to 18% in Côte d'Ivoire (24).

Finally, the unit cost results using the three different denominators highlight the different potential approaches for assessing social media costs. The cost per reach denominator measures the cost to have the MMH videos appear on an individual's screen. By "reaching" an individual, one may scroll past the video without absorbing the content; however, by having the message on their social media feed, they have the opportunity to further engage with the content. The "engagement" denominator indicates an individual is noticing the content based on likes, shares, and comments. Finally, the

"view" denominator examines how many times the video was viewed for longer than 30 s.

The unit cost results indicate that the MMH videos were inexpensive to reach people with an average of $0.16 per person reached. This is comparable to the median unit costs for traditional SBC mass media campaigns per person exposed ($0.17 for television, $0.26 for radio, $0.25 billboards/flyers) (15). In the world of social media, however, reaching someone's screen is not likely sufficient for a person to absorb and process the campaign's message, as social media feeds are abundant with other content simultaneously competing for one's attention.

The second measure is the $1.29 average cost per "engagement," which reflects the cost to get people to acknowledge the MMH campaign by either sharing, liking, or commenting. While "engagement" can capture a range of intensity from a simple "like" to a more participatory conversation through comments, this aggregated measure appears to be a more accurate gauge of campaign exposure. A remaining question is whether individuals who are engaging with the MMH content without fully watching the videos are still receiving the basic messages of MMH around destigmatizing and normalizing conversations about RH. Thus, future SBC impact analysis could investigate to what extent "engagement" is associated with improved knowledge, beliefs, and attitudes that the videos are addressing.

Finally, the $4.27 per video view is the most expensive outcome; the unit costs are comparable to SBC unit costs for group interpersonal communication (15). The higher cost per video view, compared to reach and engagements, is driven by the lower number of "views" for at least 30 s. In the West Africa context, this may be due to the fact that viewers usually have out-of-pocket costs on internet credit to access social media video content. Most individuals need to pre-purchase internet bundles for viewing videos and other media and watching videos can quickly drain internet credit. As such, after getting a sense of the primary message of the campaign without watching them for long, viewers may be stopping the videos early to conserve internet credit or because the videos are not engaging their attention.

Limitations

While efforts were made to produce a comprehensive cost analysis of SBC, several limitations to this analysis should be noted. First, the cost data on the MMH videos were aggregated with costs from the broader MMH campaign and estimates of level of effort were used to isolate the costs of the MMH videos' design, production, and dissemination for the two focal countries of Côte d'Ivoire and Niger. However, these estimates may lack precision and have the potential for error. Contributing to potential imprecision is the possibility of recall bias. Staff supporting the MMH activities do not work solely on this program; respondents needed to accurately estimate their level of effort to support the design, production, and dissemination of MMH videos. Because no time-motion study was carried out to assess how staff and youth consultants spent their time on the MMH videos, a sensitivity analysis was used to explore this imprecision and found the 5% variability did not have substantial impact on the unit costs.

Second, this study is novel in that no prior research was identified quantifying the unit costs associated with SBC via social media. As such, it is impossible to benchmark these results against the costs of other SBC campaigns via social media studies. The costs presented here are unique to this particular social media campaign, and a different set of videos with a different subject matter, length, or use of professionals would likely vary greatly from those presented in this analysis. While the unit costs described here can be considered against the backdrop of other SBC interventions such as "per person exposed" for mass media or "per person participating" for IPC, these unit costs are not directly comparable since they have different denominators. More research is needed on the effectiveness, costs, and cost-effectiveness of SBC using social media to appropriately benchmark MMH to similar programs. Only when several studies emerge on the costs of SBC interventions disseminated via social media, will there be enough information to properly gauge how the costs of SBC vary when using social media vs. more traditional forms of SBC dissemination.

A third limitation is that this analysis is narrowed to include only the MMH videos where there is denominator data to generate unit costs. However, MMH is not exclusively a digital campaign nor are the videos the campaign's sole digital content, but rather has complementary mass media and community-based activities. While neither the cost nor the reach of these non-digital activities is included in the analysis, there are potential areas where synergies between these program components are not being captured. For example, if the videos are screened at a community event, the number of people who viewed the videos during that event are not being captured in the analysis.

CONCLUSION

This study examining the cost of designing, production and disseminating the core MMH videos via social media in Niger and Côte d'Ivoire is the first to examine the unit costs of an SBC social media campaign and can be used by future research to compare findings from similar approaches, despite the above limitations. The variety of available denominators makes this a particularly interesting area for new research; thus, this study suggests that the selection of denominator is critical in determining unit cost estimates. Looking forward, SBC programmers should investigate which denominator(s) (e.g., reach, engagement, views) provide the best measure to capture based on the program objectives. Additionally, future research that pairs effectiveness and cost studies on SBC via social media are essential to better understand the utility of this channel for promoting positive behavior change.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

NB and MT conceptualized and designed the study, conducted the literature search, and wrote the original manuscript. MT, NB, EP, ZL, AD, MS, and LB had roles in the questionnaire design. MT conducted data collection virtually, data analysis, and data interpretation. EP, ZL, AD, and JH critically reviewed the data collected. All authors contributed to the writing and improvement of the data interpretation of the manuscript, read, and approved the final version.

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Cost-Effectiveness Analysis of Tyrosine Kinase Inhibitors in Gastrointestinal Stromal Tumor: A Systematic Review

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Background: The introduction of tyrosine kinase inhibitor (TKI) therapy has dramatically improved the clinical effectiveness of patients with locally advanced and/or metastatic gastrointestinal stromal tumors (GIST), and this systematic review was conducted aiming at the cost-effectiveness analysis of TKIs in GIST.

Methods: A thorough literature search of online databases was performed, using appropriate terms such as "gastrointestinal stromal tumor or GIST," "cost-effectiveness," and "economic evaluation." Data extraction was conducted independently by two authors, and completeness of reporting and quality of the evaluation were assessed. The systematic review was conducted following the PRISMA statement.

Results: Published between 2005 and 2020, 15 articles were incorporated into the systematic review. For advanced GIST, imatinib followed by sunitinib was considered cost-effective, and regorafenib was cost-effective compared with imatinib re-challenge therapy in the third-line treatment. For resectable GIST, 3-year adjuvant imatinib therapy represented a cost-effective treatment option. The precision medicine-assisted imatinib treatment was cost-effective compared with empirical treatment.

Conclusion: Although identified studies varied in predicted costs and quality-adjusted life years, there was general agreement in study conclusions. More cost-effectiveness analysis should be conducted regarding more TKIs that have been approved for the treatment of GIST.

Systematic Review Registration: https://www.crd.york.ac.uk/, PROSPERO: CRD42021225253.

Keywords: cost-effectiveness, economic evaluation, gastrointestinal stromal tumor, systematic review, TKI - tyrosine kinase inhibitor

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INTRODUCTION

Gastrointestinal stromal tumors (GIST) are rare mesenchymal tumors that predominantly originate from the gastrointestinal tract, mainly in the stomach (60%) and small intestine (30%) (1). Around 85% of GIST harbor gene mutations in stem cell factor receptor (KIT), and another 5–10% of GIST have a mutation in the gene encoding the platelet-derived growth factor receptors-α (PDGFRA) (2–5). Since the development and application of tyrosine kinase inhibitor (TKI) therapy that inhibits KIT and PDGFRA kinase activity and then intercepted the signal transduction pathways related to tumor proliferation and apoptosis, the therapeutic effects of locally advanced and/or metastatic GIST has achieved a revolutionary breakthrough.

The first TKI *imatinib mesylate* was approved in February 2002, for the treatment of KIT-positive metastatic and/or locally advanced GIST (6, 7). Treated with initial dose at 400 mg/day of imatinib, patients with metastatic or unresectable GIST reached median progression-free survival (mPFS) at 18 months, median overall survival (mOS) at 55 months (8–10). Other phase III studies have assessed the efficacy of imatinib at two initial dose levels (400 vs. 800 mg daily, given as 400 mg twice a day), showing equivalent response rates and OS for both dose levels (10–12). For resectable GIST patients, imatinib has been used in both pre- and post-operative therapy as several prospective studies have demonstrated the safety and efficacy of preoperative imatinib in patients undergoing surgical resection (13–15), while other studies revealed adjuvant imatinib therapy was associated with longer relapse-free survival (RFS) (16–18) and a longer duration (36- vs. 12-month group) of postoperative imatinib therapy improved RFS and OS for patients with a high risk of recurrence (19, 20).

Resistance to imatinib therapy is categorized into two situations. A small number (<15%) of patients have primary resistance to imatinib therapy (21), which is a disease that cannot be stabilized or progress within 6 months of initiation of treatment. The majority of patients (50%) develop secondary resistance characterized by an initial response or stable disease but subsequent progression, which is the result of acquired mutations generated during the course of treatment (22). For patients with imatinib-resistant or intolerant GIST, *sunitinib* was approved and recommended in January 2006, as it significantly improved median time to tumor progression (mTTP) (27.3 weeks in patients receiving sunitinib vs. 6.4 weeks in patients on placebo) and estimated OS (23). An recent study suggested that via sunitinib therapy, GIST patients after imatinib failure could reach the mTTP at 8.3 months and median mOS at 16.6 months (24).

In patients with metastatic or unresectable GIST progressing after the failure of imatinib and sunitinib, *regorafenib* was approved and regarded as the preferred option for third-line therapy, as it provided a significant improvement in PFS compared with placebo (4.8 months for regorafenib vs. 0.9 months for placebo) and higher disease control rate (DCR; 53 vs. 9%) (25).

Concerning rational decision making in health care, a major challenge in pharmacoeconomic evaluation is to make full use of cost-effectiveness data to optimize clinical practice and allocation of healthcare resources. This review was conducted aiming at the cost-effectiveness analysis of TKIs in GIST.

MATERIALS AND METHODS

This systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement (26). PICOS criteria (population, intervention, control, outcomes, and study design) was used to guide the development of the search strategy. A thorough literature search of the following online databases was performed: PubMed, Web of Science, and Embase. Medical Subject Heading (MeSH) terms were individually selected using the National Library of Medicine controlled vocabulary thesaurus used for indexing articles: gastrointestinal stromal tumor or GIST, cost, cost-effectiveness, economic evaluation, economics, monetary, reimbursement, insurance. Searches were conducted on December 9, 2020 and all studies published before this date will be investigated.

Eligibility criteria were published studies in English evaluating the cost-effectiveness of any of the TKIs in GIST. Care was taken to ensure that the inclusion criteria were sufficiently broad so that possibly pertinent publications could be assessed by individual screening. Given the heterogeneity of available studies, we were not able to perform a meta-analysis.

Study data extraction was conducted independently by two authors (M.F., Y.Y.) and was extracted using a data extraction form, which included author, published year, country, study population, study design, intervention and comparison, model type, perspective, time horizon, discount rate, sensitivity analysis, threshold, sponsors, cost-effectiveness outcomes, and conclusions. To allow direct comparisons across countries, all costs were converted to US dollars, then inflated to December 2020 using the country-specific Consumer Price Index (CPI) (https://www.bls.gov/data/inflation_calculator.htm).

Completeness of reporting was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist, which provides 24 items and accompanying recommendations to optimize reporting of health economic evaluations (27). The quality of the evaluation was assessed using the quality of health economic studies (QHES) instrument, which is designed to discriminate higher-quality cost-effectiveness information to enhance decision making (28). The QHES instrument was a quantitative and weighted scoring approach to appraise health economic evaluations, consisting of 16 items and each of them has a weighted point value ranging from 1 to 9. The sum of the weights of a study ranges between 0 (means extremely poor quality) and 100 (means excellent quality). Both checklists were completed independently by two authors (M.F., Y.Y.), and disagreements were resolved by discussion and arbitration (W.L.) where necessary.

This review has been registered with PROSPERO (CRD42021225253).

RESULTS

Based on the initial searches, a total of 1,440 articles were identified, which were independently screened by two reviewers (M.F., Y.Y.). Of these, 606 were removed as duplicates. Of the 834 publications remaining, 777 records were excluded via reading abstracts and titles with reasons for exclusion: case reports, reviews, and non-original research (e.g., letters or commentaries). Unpublished abstracts and meeting conferences were not included owing to the inability to completely assess quality. Then, 57 full-text articles were assessed for eligibility by two reviewers independently (M.F., Y.Y.). Disagreements were resolved by discussion and arbitration (W.L.) where necessary.

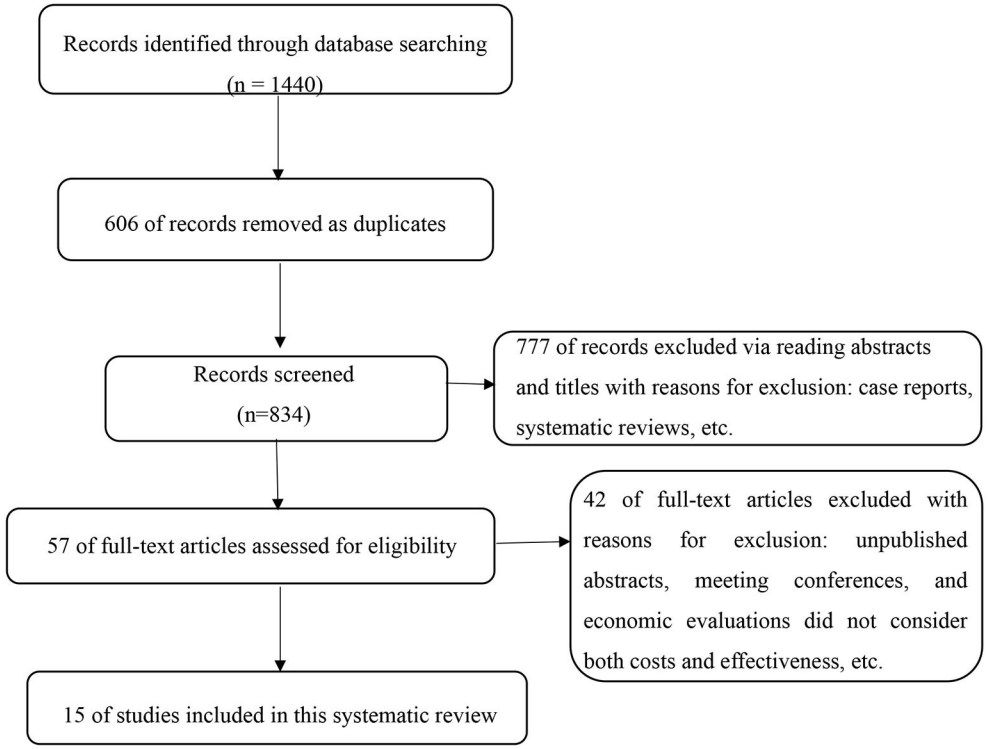

FIGURE 1 | The process of selecting eligible articles for further research.

Finally, 15 original investigations were found to have sufficient focus and relevance to be incorporated into the systematic review (**Figure 1**).

Study Design and Structural Assumptions

The 15 identified studies were published between 2005 and 2020, **Tables 1**, **2** illustrates the general information, information of economic analysis, and outcomes and findings. Most studies were set in the European countries (n = 7), with three from the United States, two from Canada, and one each from Thailand, Mexico, and Singapore. Five studies were sponsored by the pharmaceutical industry (30, 32, 37, 40, 41), two declared there was no resources of funding (36, 43), four was funded independently (29, 35, 39, 42), and two did not include declarations of funding (31, 38). Besides, there were two study that did not specify the source of funding but the authors worked for pharmaceutical industry at the time of study (33, 34).

Most studies (n = 8) used a Markov modeling approach (32–35, 39–42). Two study used a Markov decision-analysis model (36, 43), two used a partitioned survival model (37, 38), and the modeling approach was not clearly specified in one study (30). Five study used the conventional three-health state model of PFS, progressive disease, and death (33, 34, 37, 40, 42). One study determined seven clinically plausible pathways based on three-state model structure (35). One study encompassed four-health states: free of recurrence, first recurrence, second recurrence, and death (41). Another study constructed the model that simulated treatment outcomes following the treatment algorithm defined by the National Comprehensive Cancer Network (NCCN) guideline (39). One study used modified Novartis model, which contained two- and three-state transition model, and four-state probability Markov model (29). Another study performed a retrospective medical record review without applying any model (31).

The perspective of institution or healthcare system was most common (n = 7) (29, 31–33, 35, 36, 41), while one of them merely include the cost of drug acquisition, supply and labor and did not include surgery or radiotherapy costs, health care visits, or costs related to supportive care or adverse events (AEs) (31). Five studies were performed from the healthcare payer's perspective (34, 37, 39, 40, 43). Three studies claimed they provided the societal perspective (30, 38, 42), whereas two of them did not include indirect costs in the analysis (30, 38) and should be classified as healthcare system's perspective instead.

Varied from 5 years to lifetime, time horizons were clearly specified in most studies (n = 14), except in the one that was a retrospective review (31). Time horizons were put in sensitivity analysis in six studies (30, 34, 35, 37, 39, 41). Lifetime was the most frequently used time horizon option (n = 6) (32, 36, 37, 40–42).

All studies specified a discount rate in their analysis. The discount rates of cost varied from 3 to 6% and benefits varied from 1.5 to 5%. Three studies applied different discount rates to

TABLE 1 | Summary of included economic evaluations for advanced GIST.

General information				Economic analysis				Outcomes and key findings	
Author, year, country, QHES score	**Study population**	**Intervention**	**Comparator**	**Model type**	**Perspective, sponsor**	**Time horizon, discount rate, threshold**	**Sensitivity analysis**	**Cost effectiveness, 2020 US$**	**Conclusions**
Wilson (29), 2005, UK, 88	Unresectable and/or metastatic, KIT-positive GIST	IM 400 or 600 mg/day	BSC (Historical controls)	Two-state, three-state transition model, and four-state probability Markov model	UK NHS, NICE HTA programme	10 years, Costs: 6%, Benefits: 1.5%, NS	Sensitivity analysis, Monte Carlo simulation	2 years: $203,514/QALY; 5 years: $98,431/QALY; 10 years: $71,136/QALY	NS.
Huse (30), 2007, US, 89	Unresectable or metastatic GIST	IM 400 mg/day	Untreated (palliative and supportive care)	NS	US societal, Novartis Pharmaceuticals	10 years, 3%, $50,000/QALY	Sensitivity analysis	$51,619/QALY	IM 400 mg/day is cost-effective.
Mabasa (31), 2008, CA, 82	Advanced GIST	IM 400 mg/day, increased to 600–800 mg/day with PD	Historical controls	No economic model was used	BCCA, NS	NA, 3 and 5%, $50,000/QALY	Sensitivity analysis	$18,293/LYG	IM for advanced GIST seems cost-effective.
Chabot (32), 2008, CA, 89	Unresectable or metastatic GIST intolerant or resistant to IM	SU plus BSC	Placebo plus BSC	Markov model	Provincial health ministry, Pfizer Canada Inc.	Lifetime, 5%, $132,166/QALY	Sensitivity analysis	$86,900/QALY $54,202/LYG	SU is cost-effective for patients with unresectable, recurrent, or metastatic GIST and have failed or are intolerant to IM.
Paz-Ares (33), 2008, Spain, 93	Unresectable or metastatic GIST intolerant or resistant to IM	SU plus BSC	Placebo plus BSC	Markov three-state	Spanish National Health System, NS	6 years, 3.5%, $50,000/QALY	Sensitivity analysis, Monte Carlo simulation	$83,094/QALY $51,190/LYG	SU should be considered a cost-effective alternative for the second-line treatment of GIST.
Contreras-Hernande (34), 2008, Mexico, 97	Advanced GIST	High dose IM 800 mg/day or SU	Palliative care	Markov three-state	IMSS, NS	5 years, 5%, $51,300/QALY	Sensitivity analysis, Monte Carlo simulation	SU vs. palliative care, $54,601/LYG; SU vs. high dose IM, dominant	SU would be cost-effective in second-line treatment.
Hislop (35), 2011, UK, 96	Unresectable and/or metastatic GISTs progressed on treatment with IM at 400 mg/day or intolerant to IM	Path-2 IM 600–800 mg to SU; Path-3 IM 600 mg to SU; Path-4 IM 600 mg; Path-5 IM 800 mg to SU; Path-6 IM 800 mg; Path-7 SU	Path-1 BSC	Markov model	UK NHS, NICE HTA programme	10 years, 3.5%, variable threshold	Sensitivity analysis, Monte Carlo simulation	Path-1: reference; Path-7: $545,724/QALY; Path-4: $54,708/QALY; Path-3: $143,708/QALY; Path-6: dominated; Path-5: dominated; Path-2: $88,880/QALY	If society's WTP is ~£25,000/QALY, BSC is cost-effective; when WTP is £25,000–£45,000/QALY, IM 600 mg/d is cost-effective; when WTP is £45,000/QALY~, IM 600 mg/d to IM 800 mg/d to SU is cost-effective.

(Continued)

TABLE 1 | Continued

General information				Economic analysis				Outcomes and key findings	
Author, year, country, QHES score	**Study population**	**Intervention**	**Comparator**	**Model type**	**Perspective, sponsor**	**Time horizon, discount rate, threshold**	**Sensitivity analysis**	**Cost effectiveness, 2020 US$**	**Conclusions**
Nerich (36), 2016, France, 96	Advanced GIST	Strategy 2: IM 400 mg/day–IM 800 mg/day-BSC; Strategy 3: IM 400 mg/day-SU-BSC; Strategy 4: IM 400 mg/day–IM 800 mg/day-SU-BSC	Strategy 1: IM 400 mg/day-BSC	Markov decision-analysis model	French Public Healthcare System, None	Lifetime, 4%, €50,000/LYG	Sensitivity analysis, Monte Carlo simulation	S3 vs. S1: $72,096/LYG; S2 vs. S3: dominated; S4 vs. S3: $542,574/LYG	IM in first-line treatment, followed by SU in second-line treatment strategy may be considered as the best cost-effective strategy.
Tamoschus (37), 2017, Germany, 100	Unresectable or metastatic GIST patients who have progressed on, or are intolerant or resistant to IM and SU	Regorafenib 160 mg/day	IM rechallenge 400 mg/day	Partitioned survival model	German payer, Bayer Pharmaceuticals	Lifetime, 3.5%, €50,000/QALY	Sensitivity analysis, Monte Carlo simulation	$25,394/QALY $17,229/LYG	Regorafenib is cost-effective compared with IM rechallenge in Germany.
Zuidema (38), 2019, Netherlands, 93	Unresectable or metastatic GIST	TDM-guided dosing IM	Fixed dosing IM	Partitioned survival model	The societal perspective, NS	5 years, costs: 4%, benefits: 1.5%, €80,000/QALY	Sensitivity analysis, Monte Carlo simulation	$71,453/QALY $67,756/LYG	TDM-guided dosing may be a cost-effective intervention.
Banerjee (39), 2020, US, 96	Metastatic GIST	TGT- and variation-directed first-line therapy: KIT exon 9 variations: high-dose IM-SU-BSC	Empirical imatinib therapy (IM 400 mg-IM 800 mg-SU-BSC)	Markov model	US payer perspective, Surgical Society of the Alimentary Tract Mentored Research Award	10 years, 3%, $100,000/QALY	Sensitivity analysis, Monte Carlo simulation	$93,501/QALY	TGT-directed therapy is cost-effective compared to empirical IM.

QHES, quality of health economic studies; GIST, gastrointestinal stromal tumors; BSC, best supportive care; NHS, national health service; NICE, national institute for health and clinical excellence; HTA, health technology assessment; IM, imatinib; NS, not specified; QALY, quality-adjusted life-year; PD, progressive disease; BCCA, British Columbia Cancer Agency; LYG, life year gained; SU, sunitinib; IMSS, Instituto Mexicano del Seguro Social; WTP, willingness to pay; TDM, Therapeutic drug monitoring; TGT, targeted gene testing.

TABLE 2 | Summary of included economic evaluations for resectable GIST.

General information				Economic analysis				Outcomes and key findings	
Author, year, country, QHES score	**Study population**	**Intervention**	**Comparator**	**Model type**	**Perspective, sponsor**	**Time horizon, discount rate, threshold**	**Sensitivity analysis**	**Cost effectiveness, 2020 US$**	**Conclusions**
Sanon (40), 2013, US, 96	Resected primary GIST	3-year adjuvant IM 400 mg/day	1-year adjuvant IM 400 mg/day	Markov 3-state	A third party payer, Novartis Pharmaceuticals	Lifetime, 3%, $100,000/QALY	Sensitivity analysis, Monte Carlo simulation	$74,792/QALY $68,102/LYG	Treating surgically resected GIST patients with 3 years adjuvant IM is cost-effective.
Majer (41), 2013, Netherlands, 100	Resected primary GIST patients who have high risks of tumor recurrence	3-year adjuvant IM 400 mg/day	1-year adjuvant IM 400 mg/day	Multistate Markov model	Dutch healthcare provider, Novartis Oncology	Lifetime, costs: 4%, benefits: 1.5%, €50,000/QALY	Sensitivity analysis, Monte Carlo simulation	$49,894/QALY $36,520/LYG	Longer-term (3 years) adjuvant IM therapy represents a cost-effective treatment option.
Bussabawalai (42), 2019, Thailand, 96	Localized GIST patients who underwent complete resections and had a high risk of recurrence	Option 2: Recurrence during therapy: BSC; after therapy: IM 400 mg/day-BSC; 2.1: adjuvant IM 400 mg/day for 1 year; 2.2: for 3 years; Option 3: Recurrence during therapy: SU-BSC; after therapy: IM 400 mg/day-SU-BSC; 3.1: adjuvant IM 400 mg/day for 1 year; 3.2: for 3 years; Option 4: No adjuvant IM-IM 400 mg/day-SU-BSC	Option 1: No adjuvant IM-IM 400 mg/day-BSC	Markov 3-state	The societal perspective, National Health Security Office	Lifetime, 3%, 160,000 THB/QALY	Sensitivity analysis, Monte Carlo simulation	Option 2.1, 3.1, 4 were dominated by 2.2; Option 2.2 vs. 1: $55,463/QALY; Option 3.2 vs. 2.2: $87,737/QALY	Adjuvant IM treatment improved the health benefits of patients with high risk of GIST recurrence. However, in the Thai context, it was not cost-effective at the current price.
Farid (43), 2020, Singapore, 96	Rectal GIST patients requiring abdominoperineal resection following neoadjuvant IM	UAPR	CIUP	Markov decision model	Healthcare payers' perspective, None	20 years, 3%, 50,000 SGD/QALY	Sensitivity analysis, Monte Carlo simulation	UAPR dominates CIUP being both more effective (8.66 QALYS vs 5.43 QALYs) and less expensive ($241,499 vs $261,881).	UAPR is more effective and less costly than CIUP.

QHES, quality of health economic studies; GIST, gastrointestinal stromal tumors; IM, imatinib; QALY, quality-adjusted life-year; LYG, life year gained; BSC, best supportive care; SU, sunitinib; UAPR, upfront abdominoperineal resection; CIUP, continued IM until progression.

costs and benefits (29, 38, 41) and the remaining studies applied the same rate to both costs and outcomes.

Four studies estimated model costs in USD (30, 34, 39, 40), two each in GBP (29, 35) and CAD (31, 32), five in EUR (33, 36–38, 41), and one each in THB (42) and SGD (43). Threshold was specified in most studies ($n = 14$).

Most studies focused on cost-effectiveness of TKIs used in patients with unresectable and/or metastatic GIST ($n = 11$) (29–39). Three studies focused on cost-effectiveness of adjuvant imatinib therapy after resection (40–42). Another study focused on rectal GIST patients requiring abdominoperineal resection following neoadjuvant imatinib (43).

Five studies used evidence from a single phase II/III clinical trial and include only one comparator (30, 32, 33, 40, 41). For the remaining studies, approaches to evidence synthesis were varied and included a systematic review to identify clinical inputs (29, 35, 36, 42), from previously published studies (38, 39, 43), comparison between uncontrolled trials and historical control patients (29), Bucher indirect comparison (37), comparisons via reviewing retrospective medical record (31, 34), and comparison between two RCTs by using the indirect treatment comparison program developed by the Canadian Agency for Drugs and Technologies in Health (CADTH) (42).

Most commonly, PFS and OS outcomes from clinical trials were the source of treatment effects in the studies, while one study also used the data of time to treatment failure (TTF) (29). In most cases, it was necessary to extrapolate the data to the time horizon of the model, except in a pragmatic, population-based review (31). Parametric extrapolation methods were the most common, and two studies had used several extrapolation methods, including Gompertz, Weibull, and log-logistic, and chose the best fitted parametric model (37, 41). Transition probabilities were calculated using the Declining Exponential Approximation of Life Expectancy (DEALE) method in another study (36), which is an approximation of life expectancy by using a simple exponential function for survival. Extrapolation of OS curves used external data sources [i.e., retrospective studies or databases like Surveillance, Epidemiology, and End Results (SEER)] in some studies to simulate the natural disease history (35, 38–40, 43). In addition, patients' data in the real world were collected in several studies (30, 42), due to the lack of clinical or cost data.

Most identified studies ($n = 12$) were cost-utility analyses. Utility values were sourced from a mapping of Eastern Cooperative Oncology Group (ECOG) performance status from pivotal clinical trials to EuroQol-5 Dimensions (EQ-5D) scores (29, 30), obtained from EQ-5D scores directly collected in clinical trials (32, 33, 37), comprehensively extracted from previously published economic evaluations (35, 38–41, 43), or use the EQ-5D-3L questionnaire to interview local hospital's patients and convert the quality of life scores into utility values (42). Two studies applied a utility improvement during the treatment off period (32, 33), and two studies applied a utility decrement for AEs (40, 41), while one study claimed that aggregate utility values had already included any disutilities associated with AEs (37).

The estimation of costs varied in the studies. Drug acquisition costs mostly come from public institutional databases, except for one study that drug was not available in the market at the time of the analysis, so its cost information was provided by pharmaceutical manufacturer (34). Management of AEs related costs were calculated in several studies ($n = 8$) (29, 32, 33, 35, 38, 40–42), while one study only include direct drug acquisition costs (37). Costs of genetic testing were included in two studies (36, 39). Costs of other cancer types (i.e., pancreatic cancer and ovarian cancer) were used as models to estimate the costs of medical management due to the lack of GIST cost data in two studies (30, 33). End-of-life costs were included in only one study (32).

Model Outcomes

TKIs in Advanced GIST

Imatinib was firstly compared with best supportive care (BSC) or historical controls in unresectable and/or metastatic, KIT-positive GIST in three studies (29–31), and was associated with an increase in costs and QALYs compared to BSC in all studies. The predicted QALYs associated with imatinib varied from 4.15 QALYs (30) to 4.85 QALYs (29) in 10 years' time horizon, while a retrospective medical record indicated that imatinib therapy was associated with 5.56 life years gained (LYGs) (31). The predicted total costs ranged from $91,950 (31) to $554,880 (30). In the earliest economic analysis of imatinib we included, the authors calculated incremental cost-effectiveness ratio (ICER) in different time horizons at $203,514/QALY (2 years), $98,431/QALY (5 years), and $71,136/QALY (10 years), respectively (29) in UK, claiming that the estimates after 2 years were of great uncertainty because they were based on the extrapolation beyond the trial data. Another study calculated ICER at $51,619/QALY, and concluded that the findings suggested imatinib was cost-effective in the US according to NCCN guidelines (30), the other study calculated ICER at $18,293/LYG and concluded that imatinib seemed cost-effective at willingness-to-pay (WTP) threshold of $50,000/QALY in Canada (31).

For unresectable or metastatic GIST patients who were intolerant or resistant to imatinib, sunitinib was compared with BSC in two studies (32, 33) based on the results of the pivotal phase III trial (23), and both studies predicted that sunitinib was associated with an increase in costs and QALYs and were likely to be cost-effective at the WTP thresholds. They were associated with costs ranging from $39,370 (33) to $50,176 (32) and QALYs ranging from 0.97 QALYs (32) to 1.00 QALYs (33), resulting in ICER at $86,900/QALY (32) and $83,094/QALY (33), respectively. For patients who were intolerant or resistant to both imatinib and sunitinib, regorafenib ($26,566, 1.691 QALYs) was compared with imatinib re-challenge therapy ($16,021, 1.275 QALYs) using a partitioned survival model, resulting in ICER at $25,394/QALY and was thought to be cost-effective in Germany (37).

Several other articles have constructed a variety of treatment pathways to carry out an economic evaluation of treatment methods for advanced GIST. One study compared high-dose imatinib, sunitinib, and BSC in the second-line treatment of advanced GIST (34). In this study, sunitinib was dominant of high-dose imatinib, because it costed less ($21,085 vs. $41,713) and produced more effectiveness (1.4 LYGs vs. 1.31 LYGs).

Compared with BSC, sunitinib was associated with an ICER of $54,601/LYG and was considered the most cost-effective option. Another study constructed seven clinical treatment pathways for advanced GIST patients who had progressed on treatment with regular-dose imatinib or were intolerant to imatinib (35). Total costs ranged from $185,961 to $344,932 and QALYs ranged from 2.397 QALYs to 4.803 QALYs among the seven pathways. The BSC was considered as the most cost-effective when WTP was under £25,000/QALY, while imatinib 600 mg/day was the most cost-effective when WTP was during £25,000–£45,000/QALY and "imatinib 600 mg/day followed by imatinib 800 mg/day followed by sunitinib" was the most cost-effective when WTP was above £45,000/QALY. Similarly, another study constructed four clinical treatment pathways using the Markov decision-analysis model and concluded imatinib 400 mg/day in first-line treatment, followed by sunitinib in second-line treatment strategy may be considered as the best cost-effective strategy (36).

The cost-effectiveness of therapeutic drug monitoring (TDM) guided dosing imatinib was investigated in comparison with fixed dosing imatinib (38). The TDM-guided dosing imatinib was associated with an increase in costs ($182,901 vs. $130,050) and QALYs (3.54 QALYs vs. 2.80 QALYs) compared with fixed dosing imatinib, producing an ICER at $71,453/QALY which was considered cost-effective. Another study (39) assessed the cost-effectiveness of targeted gene testing (TGT) directed therapy (TGT means if KIT exon 9 variations is positive, then directly use imatinib 800 mg/day) was compared with empirical therapy (imatinib 400 mg/day to imatinib 800 mg/day to sunitinib to BSC). The TGT-directed therapy was associated with an increase in cost, from $476,242 with the empirical imatinib approach to $485,900 with TGT-directed therapy. QALYs increased by 0.10, from 4.88 with empirical imatinib to 4.98 with TGT-directed therapy, so TGT-directed therapy yielded an ICER of $93,501/QALY which was considered cost-effective at a WTP threshold of $100,000/QALY.

TKIs in Resectable GIST

For patients with resected primary GIST, the cost-effectiveness of 1- vs. 3-year adjuvant imatinib 400 mg/day treatment after resection was compared in two studies (40, 41) based on the data of SSGXVIII/AIO clinical trial (19). They found that 3-year adjuvant therapy was associated with increased costs and QALYs, thus resulting in ICER at $74,792/QALY (40) and $49,894/QALY (41), respectively. Both studies concluded that 3-year adjuvant therapy was a cost-effective treatment option under the WTP threshold.

For patients with resected localized GIST and had a high risk of recurrence, clinical treatment pathways of four alternative treatment options were constructed (42). In the study, option 2.2 (adjuvant imatinib 400 mg/day for 3 years) was most likely to be the cost-effective option as it was dominant to other three options, but was not cost-effective at the current price in the authors' country. Another economic evaluation (43) was conducted from a novel perspective: for rectal GIST patients requiring abdominoperineal resection following neoadjuvant imatinib, upfront abdominoperineal resection (UAPR) was compared with continued imatinib until progression (CIUP). The author concluded that UAPR dominates CIUP for being more effective (8.66 QALYS vs. 5.43 QALYs) and less expensive ($241,499 vs. $261,881).

Reporting and Quality Assessment

The CHEERS checklist was used to review completeness of reporting of the evaluation. Compliance with the CHEERS checklist was variable. Two studies were found to have perfect compliance with the CHEERS reporting requirements (37, 42). Seven studies were assessed as having only one non-compliance (29, 35, 36, 39–41, 43), two each were found to have two non-compliances (33, 38), three non-compliances (30, 32), and four non-compliances (31, 34). Many studies ($n = 7$) did not describe the population and methods used to elicit preferences for outcomes. Most studies ($n = 13$) reported the dates of the estimated resource quantities and unit costs and described methods for converting costs into a common currency, except in two studies (29, 34).

The QHES instrument was used to assess of the quality of the economic evaluation. The mean QHES score was 93.8 ± 4.9 (range 82–100). Two studies were found to have perfect compliance with the QHES instrument (37, 41). Most studies ($n = 11$) did not clearly state the reason why the perspective of the analysis were chosen. Systematic reviews and quality assessment were performed in only three studies (35, 36, 42).

The complete tables of the CHEERS checklist and QHES instrument could be found in **Supplementary Materials**.

DISCUSSION

Almost every new drug is associated with better clinical benefits in patients and higher costs, posing challenges to cost-effectiveness and affordability, and results of economic evaluations have become increasingly important as criteria for the allocation of health care resources. In our study, there were major differences in the structural assumptions in the identified studies, including in the model types, study perspectives, time horizons, discount rates, assumption of utility, and extrapolation of survival. Therefore, there were large variations in the predicted costs and QALYs associated with each treatment, for example, the predicted QALYs of advanced GIST treated with imatinib varied from 2.96 to 4.85. Variations in QALYs could be explained by the use of utility values derived by different methods, different time horizons, and alternative approaches to survival extrapolation. Variations in total costs could be explained by different healthcare resource use and costs across jurisdictions. Moreover, the different study perspectives would significantly affect total costs. It may also be accounted for by different approaches to capturing costs of post-progression treatment, where some studies assumed no post-progression drug costs while others (35, 36, 42) constructed a series of pragmatic clinical treatment pathways and clearly calculated the costs of each treatment path.

Despite these variations, there was consistency in the conclusions across most of the studies. For patients with advanced/metastatic GIST, all publications agree that TKIs are associated with higher costs and effectiveness than placebo or empirical treatment. Some articles (29–31) concluded that imatinib 400 mg/d in first-line therapy was cost-effective, but

these economic analyses were carried on between 2005 and 2008, and some model parameters they used may not be fully standardized. Other studies confirmed the cost-effectiveness of sunitinib in second-line therapy (32–34), and regorafenib was cost-effective compared with imatinib re-challenge in the third-line therapy in Germany (37). Two other studies simulated the most cost-effective medication plan by constructing multiple clinical pathways (35, 36), and based on these results, we suggest for advanced GIST, the treatment of imatinib in first-line, followed by sunitinib in second-line, and regorafenib in third-line was cost-effective.

For patients with resectable GIST, several studies (40, 41), respectively, investigated the 3- vs. 1-year adjuvant imatinib therapy in resected GIST, and both confirmed the cost-effectiveness of the longer-term (3-year) therapy. Another study (43) illustrates the necessity of surgery in rectal GIST patients requiring abdominoperineal resection following neoadjuvant imatinib. Most of the identified studies were conducted in high-income and developed countries, including European and American countries, and most studies had positive conclusions regarding the cost-effectiveness of the interventions except one study (42) taking into account the country's context.

Another two recent economic evaluations carried out by Banerjee et al. (39) and Zuidema et al. (38), respectively, are not limited to a fixed-dose of medication but are concerned about individualized medication methods that guide the use of TKIs in advanced GIST, such as TDM (38) and TGT (39), which are both considered cost-effective. It is known that mutational status has a dramatic impact on response to imatinib or sunitinib in patients with advanced or metastatic GIST. The presence of a KIT exon 11 mutation was associated with better response rates, PFS, and OS compared to KIT exon 9 mutations or wild-type GIST (44–46). In patients whose tumors expressed a KIT exon 9 mutation, high-dose imatinib (800 mg/d) resulted in a significantly superior PFS (44, 45) and increased response rates (46, 47) compared to those treated with imatinib 400 mg/d. And the cost-effectiveness analysis (39) focusing on TGT-guided therapy was performed based on this setting. Another study (38) focused on the TDM-guided dosing imatinib. Therapeutic drug monitoring is a technique used to determine the plasma exposure levels of certain drugs and enable to ensure the GIST patients redistributed with adequate imatinib concentrations in plasma (48, 49). By performing an economic evaluation between TDM-guided and fixed-dose imatinib, the results are a valuable addition to the investigation of the effect of dose optimization. It is foreseeable that with the further development of molecular oncology, there would be more novel economic evaluations.

At the same time, there existed other new TKIs that have been approved by the food and drug administration (FDA) and endorsed by NCCN guidelines, for instance, avapritinib for PDGFRA D842V-mutant GIST as first-line therapy (50), and ripretinib for the progressive disease after imatinib, sunitinib, and regorafenib as fourth-line therapy (51). Nevertheless, sorafenib, nilotinib, dasatinib, and pazopanib have also shown activity in patients with GIST resistant to imatinib and sunitinib. However, much of the data on these TKIs came from phase II studies or retrospective analyses, which lack high-quality clinical evidence. The cost-effectiveness of these TKIs still needs to be measured.

There exist some limitations in this study. First, the QHES instrument employs yes or no responses rather than a continuous scale for each criterion, which would lead to inaccuracy when a study actually partly meets the criteria but is appraised with zero points. Therefore, the CHEERS checklist was applied to cross-evaluate the quality of the literature. But the CHEERS statement is an assessment of reporting, not methodological quality, and failure to follow all the requirements in the CHEERS statement is not indicative of a poor-quality study. Second, our systematic review excluded conference abstracts, unpublished studies (gray literature), and studies that lack full-text resources, which may also introduce some bias.

In conclusion, our systematic review identified 15 economic evaluations of TKIs used in patients with GIST and demonstrated several important findings. First, for patients with advanced GIST, imatinib in the first-line treatment, followed by sunitinib in the second-line treatment was considered cost-effective, and regorafenib was cost-effective compared with imatinib re-challenge in the third-line therapy. Second, for patients with resectable GIST, 3-year adjuvant imatinib therapy represented a cost-effective treatment option compared with 1-year therapy. Third, the precision medicine-assisted imatinib treatment plan represented by TDM- and TGT-guided imatinib therapy was cost-effective compared with empirical fixed-dose treatment.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

MF: material preparation, data acquisition, and wrote the first draft of the manuscript. YY: material preparation and data acquisition. The revised draft of the manuscript was written by MF and YY. All authors contributed to the conception and design of the study, commented on previous versions of the manuscript, read, and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.768765/full#supplementary-material

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Assessment of Financial Toxicity Among Patients With Advanced Lung Cancer in Western China

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Background: Lung cancer is the leading source of cancer-caused disability-adjusted life years. Medical cost burden impacts the well-being of patients through reducing income, cutting daily expenses, curtailing leisure activities, and depleting exhausting savings. The COmprehensive Score for Financial Toxicity (COST) was created and validated by De Souza and colleagues. Our study intends to measure the financial burdens of cancer therapy and investigate the link between financial toxicity and health-related quality of life (HRQoL) in an advanced lung cancer population.

Methods: Patients aged ≥ 18 years with confirmed stage III to IV lung cancer were eligible. The COST questionnaire verified by de Souza et al. was used to identify financial toxicity. Multivariable linear regression analysis with log transformation univariate analysis and Pearson correlations were used to perform the analysis.

Results: The majority of the patients (90.8%, $n = 138/152$) had an annual income of $50,000 ($7,775). The cohort's insurance situation was as follows: 64.5% of the cohort had social insurance, 20.4% had commercial insurance, and 22.0% had both. Patients who were younger age (50–59, $P < 0.001$), employed but on sick leave, and had lower income reported increased levels of financial toxicity ($P < 0.05$). The risk factors for high financial toxicity: (i) younger age (50–59), (ii) <1 month of savings, and (iii) being employed but on sick leave. Increased financial toxicity is moderately correlated with a decrease in QoL.

Conclusion: Poorer psychological status and specific demographics are linked to increased financial toxicity (lower COST). Financial toxicity has a modest relationship with HRQoL and may have a clear link with HRQoL measurements.

Keywords: financial burden, financial toxicity, medical cost, health-related quality of life (HRQL), lung cancer

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INTRODUCTION

In most nations, lung cancer is the primary reason for cancer-caused disability-adjusted life years (DALYs) (1, 2). Patients with lung cancer face considerable medical costs and service utilization (3–5). The financial burden on patients with lung cancer includes both direct costs and indirect expenditures, such as transportation and lost income (out of work or on sick leave) (3, 6). Medical cost burden has an influence on the well-being of patients through reducing income, cutting daily spending, leisure activities, and eliminating savings. Financial hardship has been identified as an independent risk factor for mortality since it might lead to bankruptcy (7).

The phrase financial toxicity was coined in order to draw attention to financial stress and its detrimental implications. It refers to a side effect of cancer treatment that is comparable to nausea and alopecia (8). The COmprehensive Score for Financial Toxicity (COST) was then developed and validated by De Souza et al. (9, 10). The COST questionnaire has 11 elements with values ranging from 0 to 44. They validated it using a population from North America. Lower COST ratings in De Souza's study indicated a higher degree of financial toxicity. Then, studies on financial toxicity revealed that increased financial toxicity was connected with a lower Health-Related Quality of Life (HRQoL) and increased psychological distress. Meanwhile, it has an effect on cancer therapy. To cut expenses, patients take less medication than advised, use over-the-counter medications, and take medicine prescribed by others (11).

China covers approximately 20% of the world's population. As a developing country, China is confronted with the most challengeable medical funding issues. In fact, China has knitted the global biggest network of universal basic medical insurance and established a healthcare service system that encompasses both urban and rural areas. Social medical insurance in China contains three types which are the basic medical insurance for urban employees, basic medical insurance for urban residents, and the new rural cooperative medical system. By the end of 2016, China's social medical insurance has reached over 1.3 billion people across the country, accounting for more than 95% of the total population. Nonetheless, updating the policy level of medical insurance is still required.

Policy reforms in the Chinese medical care insurance system should maximize individual advantages. However, before it changes, access to a better understanding of the current state of financial toxicity as well as its negative impact on the QoL of patients must be opened, which could improve the interventions aimed at reducing financial distress, thus improving quality care and policy optimization. Our study intends to examine the economic costs of cancer care in the advanced lung cancer population using a validated financial toxicity tool (COST questionnaire). We also investigated the link between financial toxicity and HRQoL. This work might aid in improving resource allocation for early intervention by inferring the risk variables of financial damage in patients with lung cancer (12).

COHORT AND METHODS

Cohort

Patients aged $\geq$ 18 years with stage III to IV(AJCC, 8th edition) lung cancer (non-small and small cell lung cancer) who require continued multimodality therapies throughout time were eligible. The following criteria were included: (1) stage III–IV lung cancer without the opportunity for surgery, (2) ongoing anti-tumor therapies of drugs and injections, and (3) agree to receive this interview. The excluding criteria contained: (1) stage I–II lung cancer with the opportunity for surgery, (2) malignancies of metastasis to the lung, (3) participating in other clinical trials, and (4) refuse to take the interview. We excluded the stage II group of patients with lung cancer who missed the opportunity to receive thoracic surgery due to few of them (3 cases) appeared in our study. Ethics approval was acquired from the Human Research Ethics Committee of Xijing Hospital (KY20202077-C-1).

Variables and Outcomes

Information of the performance, tumor stage, and histological diagnose of the patients were extracted from electronic medical records from the Xijing database. We obtained direct information from patients on their marital status, job, family income, and household savings. The baseline financial situation of the patients was determined using previously published financial toxicity (FT) questionnaires (**Supplementary Table 1**) and translated into Mandarin (13). FT was evaluated by the COST instrument (10), translated into Mandarin. Financial toxicity was rated as strong by a score larger than the cohort's median COST (14). The Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire was used to measure the HRQoL (15, 16). The FACT-L instrument contains two parts, which are a common module for all patients with cancer (a 27 item cancer therapy function evaluation general scale, FACT-G) and a lung cancer-specific module (a 9-item lung cancer additional concern part), ranging from 0 to 136. It has been determined that a higher FACT score indicates a higher QoL.

Statistical Analysis

We summarized the baseline and financial status by descriptive statistics. To compare the average COST scores in patients, we used multivariable linear regression analysis with log transformation. We identified significant covariates in multivariable regression analysis ($P \leq 0.10$ was considered clinical significance). The Pearson correlation was used to assess the correlations between COST and FACT scores. If the coefficient was 0.20 to 0.39, the correlation was regarded as mild, 0.4–0.59 moderate, 0.60–0.79 strong, and $\geq$ 0.80 very strong. $P < 0.05$ (two-tailed) was considered statistically significant. All statistical analyses were performed using SPSS 22.0 (IBM, New York, USA).

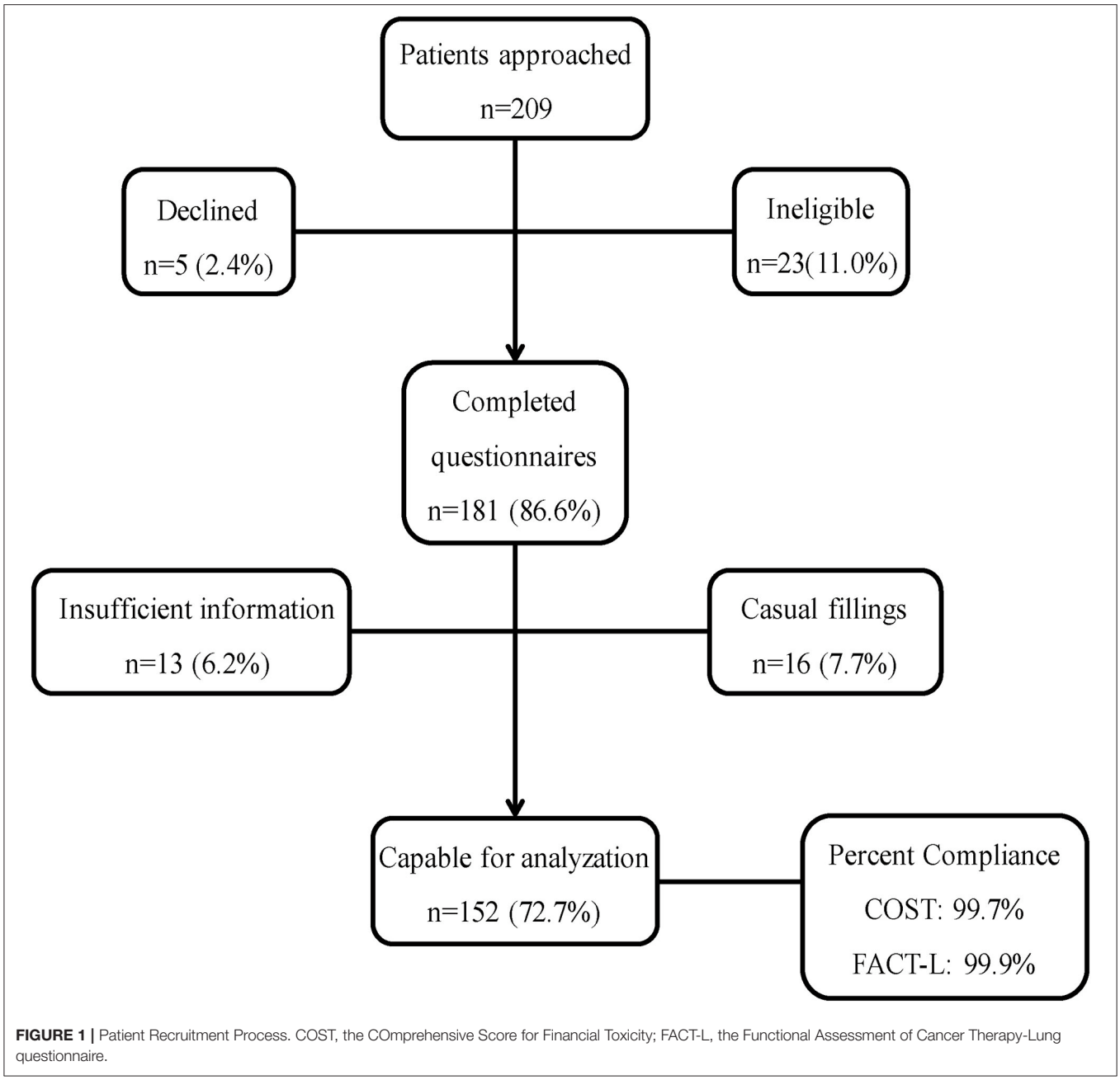

FIGURE 1 | Patient Recruitment Process. COST, the COmprehensive Score for Financial Toxicity; FACT-L, the Functional Assessment of Cancer Therapy-Lung questionnaire.

RESULTS

We accessed the cohort from September 2019 to January 2021. **Figure 1** showed the recruitment process. The baseline of the cohort included in the analysis is summarized in **Table 1**. We recruited 209 potential participants, of which 152 were eligible. The median age was 62.1 years (range 32–84 years). A total of 65.1% ($n = 99$) had metastasis and 44.9% ($n = 53$) had localized disease. The majority of patients had non-small cell carcinoma histology (63.2%, $n = 96/152$) followed by small cell carcinoma histology (27.0%, $n = 41/152$) and other lung cancer histology (9.8%, $n = 15/152$). The median value of the COST scores was 25.5 (range 4–42, mean ± SD 9.7 ± 0.8).

Financial State

Of the financial perspectives, most of the patients (90.8%, $n = 138/152$) had an household income <¥50,000 ($7,775) per year. The insurance condition of the cohort was that the majority of the cohort had social insurance (64.5%, $n = 98/152$), 20.4% of them had commercial insurance ($n = 31/152$), 22.0% of them had both ($n = 22/152$). Only one patient *(0.1%)* had no insurance. Housing mortgage holds the overwhelming majority of the loans of Chinese families in modern China, in all probability determining the disposable income of a family. Thus, we brought residence condition to reflect the financial state of the patient as its close relation to individual financial pressure. Due to elderly residences, most of the patients were the owner of the house

TABLE 1 | Patient demographics.

Characteristics	Values (*n*[%])
Age (y)	
Median	62.1
Range	32–84
Sex	
Male	81 (53.3)
Female	71 (46.7)
Marital state	
Married	144 (94.7)
Unmarried	8 (5.3)
Current smoker	
Yes	59 (38.8)
No	93 (61.2)
Insurance type	
Social insurance	98 (64.5)
Commercial insurance	31 (20.4)
Social & Commercial insurance	22 (14.5)
No insurance	1 (0.1)
Primary place of residence	
Owner/occupier—no mortgage	95 (62.6)
Owner/occupier with mortgage	45 (29.6)
Renting (>3 years)	8 (5.2)
Living with family/friends (>10 years)	2 (1.3)
Other	2 (1.3)
Current employment status	
Working full time	15 (9.9)
Working part time	8 (5.2)
Retired	101 (66.4)
Unemployed	27 (17.8)
Other (student, homemaker)	1 (0.7)
Change in employment status	
Yes	132 (86.8)
No	20 (13.2)
Household income per year (CNY)	
<20,000	36 (23.7)
20,000–49,999	102 (67.1)
50,000–99,999	9 (5.9)
>100,000	5 (3.3)
Current household savings (CNY)	
<1 month (reference)	63 (41.4)
1–6 months	41 (27.0)
7–12 months	16 (10.5)
>year	32 (21.1)
Stage	
III	66 (43.4)
IV	61 (40.1)
Histology	
Small-cell carcinoma	41 (27.0)
Non-small cell carcinoma	96 (63.2)
Other	15 (9.8)

CNY, China Yuan.

without a mortgage (62.6%, $n = 95/152$). While the occupiers with a mortgage were 29.6% ($n = 45/152$). A total of 14.5% ($n = 22/152$) of the patients had retirement salaries to meet medical costs. Most of our cohort was retired (64.1%, $n = 84/152$). Of others, 59.6% ($n = 28/152$) changed in income when the cancer treatment started.

Variables Associated With FT

Univariate analysis of variables related to FT was described in **Table 2**. Patients at a younger age (50–59, $P < 0.001$), employed but on sick leave, and had a lower income had increased levels of FT ($P < 0.05$). In multivariable modeling, we adjusted for potentially confounding variables and discovered patients who had <1 months' worth of household savings turned to have higher financial toxicity ($P < 0.05$).

When compared with this value, patients who had >1–6, 7–12 months' and >1 years' worth of savings scored 3.9 points (95% CI: 2.1 to 4.9, $P = 0.06$), 10.4 points (95% CI: 5.0 to 16.1, $P < 0.05$), and 22.6 points (95% CI: 11.6 to 26.3, $P < 0.001$) higher COST scores, respectively. As to employment condition, patients on sick leave had increased financial toxicity compared with employed patients (8.3, 95% CI: 6.3 to 11.6, $P = 0.04$) or retired (7.2, 95% CI: 4.2 to 14.6, $P = 0.02$).

In **Table 2,** we identified risk factors for higher FT scores: (i) younger age (50–59), (ii) being employed but on sick leave, and (iii) with <1 month of savings. A total of 54.9% ($n = 52$) of our cohort had no risk factors. In total, 32.8% ($n = 61$) had one risk factor and 8.4% ($n = 24$) had two risk factors. Lastly, 3.8% ($n = 15$) had all three risk factors.

Association Between FT and QoL

The r-value of the COST score and FACT-L was 0.44 ($P < 0.0001$), which inferred a moderate correlation of the two variables (**Figure 2**), indicating that increased FT (lower COST) is moderately associated with decreased QoL (lower FACT-L).

DISCUSSION

Most of the patients with cancer received their treatment in China's public hospitals, while private ones contributed less in treating malignancies. Similar to previous studies (10, 17), this study recruited patients from a public hospital in West China who had all types of health insurance (social insurance, commercial insurance, and both). In contrast to Australia's and certain European nations' healthcare systems, China lacks comprehensive healthcare insurance coverage. Nonetheless, with 95% of its population covered, China's healthcare system may not be overly reliant on commercial insurance, in contrast to the United States, where around 33% of its population is uninsured (18, 19).

The cost of anti-tumor medications has decreased as a result of China's new policy on imported pharmaceuticals and the introduction of domestically made ones. However, ancillary expenditures for cancer therapy, such as transportation and lodging, vary by city. As a result, assessing the absolute quantities of the medical expenses of the patient directly may not be enough to assess the financial strain on the family

TABLE 2 | Patient characteristics and COST outcomes.

Characteristics	Univariate analysis		Multivariable analysis	
	Coefficient (95% CI)	*P*-value	Coefficient (95% CI)	*P*-value
Age (y)				
<50 (reference)				
50–59	10.1 (5.7 to 19.7)	<0.001	−5.6 (−9.8 to 8.6)	0.82
60–69	5.6 (4.2 to 8.9)	0.02	0.2 (−7.0 to 7.3)	0.56
70–79	1.3 (−2.2 to 5.1)	0.09	2.7 (−5.8 to 7.9)	0.33
>80	2.8 (−4.5 to 6.2)	0.16	1.2 (−8.9 to 10.3)	0.29
Sex				
Female (reference)				
Male	0.54 (−2.6 to 3.1)	0.49	2.7 (−0.9 to 4.3)	0.22
Marital state				
Married (reference)				
Unmarried	−5.7 (−6.4 to 2.8)	0.06	−3.3 (−4.1 to 2.2)	0.34
ECOG performance status				
0 (reference)				
1	1.0 (−5.3 to 6.6)	0.66	0.23 (−3.2 to 4.1)	0.82
≥2	−1.7 (−5.5 to 4.2)	0.46	−0.4 (−4.5 to 4.7)	0.76
Insurance type				
Social Insurance (reference)				
Commercial insurance	2.1 (−3.3 to 5.9)	0.52	−2.3 (−7.6 to 5.7)	0.43
Social and Commercial insurance	−8.6 (−13.8 to 4.5)	0.003	−4.6 (−6.3 to 0.2)	0.02
Current employment status				
Working full time/part time (reference)				
Employed, on sick leave	3.5 (−3.2 to 6.9)	0.05	5.6 (−6.8 to 9.9)	0.59
Retired	−6.2 (0.7 to 18.4)	0.04	1.6 (−6.8 to 9.9)	0.63
Unemployed	8.1 (−0.8 to 9.3)	0.08	1.2 (−7.8 to 10.2)	0.86
Household income per year (CNY)				
<20,000 (reference)				
20,000–49,999	2.8 (−6.2 to 8.9)	0.33	−2.8 (−4.6 to 7.0)	0.78
50,000–99,999	6.2 (−1.3 to 7.9)	0.55	−1.3 (−2.2 to 3.4)	0.59
>100,000	9.7 (3.8 to 13.4)	0.01	3.4 (−3.2 to 6.1)	0.42
Household savings				
<1 month (reference)				
1–6 months	1.9 (−1.0 to 2.8)	0.18	6.2 (0.3 to 8.6)	0.06
7–12 months	8.5 (2.8 to 14.1)	<0.001	4.5 (−1.2 to 6.2)	0.34
>1 year	11.3 (13 to 22.1)	<0.001	8.1 (6.4 to 15.4)	<0.001

ECOG, eastern cooperative oncology group; CNY, China Yuan.

of the patient in China. We examined FT in a sample of Chinese patients with lung cancer using COST established by De Souza et al. Our analysis discovered that patient demographic characteristics related to greater FT included younger age, being employed but on sick leave, and having smaller funds. These findings may aid in identifying potential patients who are at a higher risk of experiencing negative health outcomes.

Previous research has shown that anti-tumor medications cost higher for patients with advanced cancer (20), and they displayed a more severe financial toxicity than physical, familial, and emotional distress (21–23). Furthermore, our findings corroborated the idea that FT had a modest connection with HRQoL but did not precisely assess it, suggesting that FT may have a detrimental influence on patient well-being (24). Our findings indicated that the 50- to 59-year-old population was the most vulnerable to financial toxicity, which might be attributed to their general economic situation in modern China. Chinese residents aged 50–59 may face the greatest financial strain in society. It is commonly understood in Chinese culture that one of the goals of wealth is to provide care for the old. Chinese residents aged 50–59 typically bear this obligation since their parents aged 80–90 are incapacitated for life. They should share their time and wealth with their parents. Meanwhile, because their children aged 20–30 whose salary could not cover their mortgage payment, residents aged

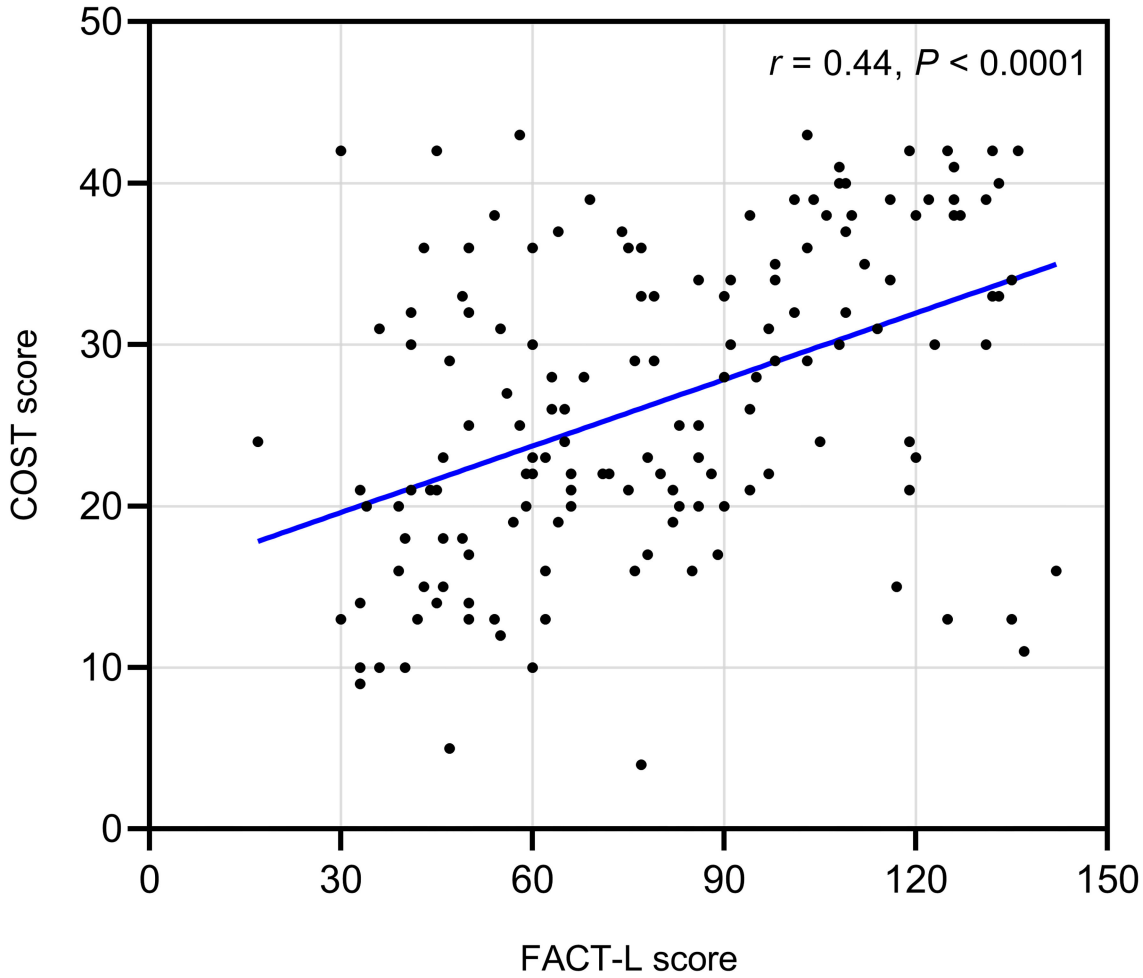

FIGURE 2 | Correlation between financial toxicity and health-related quality of life. Increased financial toxicity (lower COST) is moderately associated with decreased quality of life (lower FACT-L). Pearson correlation coefficient:*0.44*, $P < 0.0001$.

50–59 must assist their children on this issue. In such cases, if they were diagnosed with lung cancer and subsequently saddled with the related medical bills, their life may be made more difficult.

As mentioned, the Chinese healthcare system is mostly based on social insurance, which shows the Chinese government's constant efforts. However, even with commercial health insurance, China's healthcare system only covers hospital-related medical costs (drugs and inpatient stays), not transportation or lodging for specialist consultations. Meanwhile, according to the health care policy, residents in China must pay for medical bills in advance and then wait for reimbursement from the health insurance agency, which may make household savings critical for Chinese families. Remote inhabitants, on the other hand, may have a greater financial burden as a result of increased commuting costs and lengthier sick absences. Regrettably, our study was unable to substantiate the higher FT among patients residing in distant places.

In western countries, patients with cancer are able to get access to cancer care teams, including an oncologist, nurse practitioner, and case manager/ financial counselor. When they have any problems in receiving cancer therapies, they can contact one or some in the team to get professional assistance. While in China, such a team merely contains oncologists and nurse practitioners, which may cause bewilderment in facing financial issues associated with medical care, the oncologist and nurse practitioner are unqualified in answering the financial questions of patients. Oncologists in China feel the costs of medical care are important, yet they are poorly prepared to discuss costs with patients in the clinic. The customer representatives of large pharmaceutical companies such as Roche, Pfizer, and Merck may play this role, yet inevitably mixed with the company's interests when answering financial questions. Hence, there is an urgent need for the emergence of roles such as "financial counselor/case manager" in the cancer care team of China, who should be multi-professional such as medicine and economics, qualified to offer

professional help in giving or assessing financial issues during cancer therapies.

The medical data in China is hospital-independent. Unfortunately, there is no integrated platform for researches, making nationwide research on the financial burden upon patients with cancer very difficult. One weakness of our study was that it remained single-centered. A multi-centered cohort may reach a more realistic conclusion. Furthermore, as previously stated, our study did not include measuring FT in patients residing in distant locations, which may result in worse cancer outcomes.

This study aimed to raise awareness of the financial burden on lung cancer patients among policymakers and doctors, as well as to better identify individuals at the highest risks for cancer-related financial toxicity. It is undeniable that the entire society should work together to relieve such a burden. In order to address the lack of a countrywide platform holding medical data and to enhance policy optimization, future research should encompass additional locations of China as well as more forms of cancer.

CONCLUSION

The financial burden of cancer and cancer treatment has become more visible, as does the way to analyze it. Verified studies guarantee that accurate conclusions are provided in such fields. This study revealed that FACT COST is a relevant and reliable tool for lung cancer patients in China. Poorer psychological status and specific demographics are associated with increased financial toxicity (lower COST). Financial toxicity is modestly connected to HRQoL and may have a discernible relationship with HRQoL assessments.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Human Research Ethics Committee of Xijing Hospital, Approve Number: KY20202077-C-1. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JZ contributed to the conception of the study and performed constructive discussions. TX, YiZ, and YoZ performed the data collection and analysis. TX and LX wrote the manuscript. WY, HX, YC, and YaZ contributed to data analysis and manuscript preparation. SQ, FC, NC, MW, QJ, XY, and XC contributed to the revised manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.754199/full#supplementary-material

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Mapping of Female Breast Cancer Incidence and Mortality Rates to Socioeconomic Factors Cohort: Path Diagram Analysis

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Objectives: Breast cancer is the leading cause of death in women around the world. Its occurrence and development have been linked to genetic factors, living habits, health conditions, and socioeconomic factors. Comparisons of incidence and mortality rates of female breast cancer are useful approaches to define cancer-related socioeconomic disparities.

Methods: This was a retrospective observational cohort study on breast cancer of women in several developed countries over 30 years. Effects of socioeconomic factors were analyzed using a path diagram method.

Results: We found a positive, significant association of public wealth on incidence and mortality of breast cancer, and the path coefficients in the structural equations are −0.51 and −0.39, respectively. The unemployment rate (UR) is critical and the path coefficients are all 0.2. The path coefficients of individual economic wealth to the rates of breast cancer are 0.18 and 0.27, respectively.

Conclusion: The influence of social pressure on the incidence and mortality of breast cancer was not typical monotonous. The survival rate of breast cancer determined by the ratio of mortality rate to incidence rate showed a similar pattern with socioeconomic factors.

Keywords: mortality, breast cancer, incidence, socioeconomic factors, regression analysis, path diagram analysis

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INTRODUCTION

Through history, health was always one of the most fundamental issues of human development. In most of the historical stages, the culture, economy, trade, and war experienced in each country were part of objective existence, and closely associated with individual health problems (1). Health problems faced by human beings were influenced by the following aspects (2). First, the time (3) and space (4) on which human beings depend for survival constitutes the objective basis for the development of human society (5). The second reason was the basic living necessities. Third, human health issues are strongly tied to special spatial conditions (6, 7), such as longitude, latitude, altitude, and temperature (8). These environmental factors will cause or induce people to form a life and behavior habit or culture (9) that matches the geographical conditions (10, 11). Fourth, human

health problems tightly relate to social development (12–14). At different stages of development, human beings face different threats of diseases (3, 15). The types and severity of diseases were different in different regions and ethnic groups at the same historical stage (16). Hunger (17), disease (18), and death are the three basic threats for the objective existence of species (19), and the same is true of the advanced animals, i.e., human beings (20).

Today, cancers have brought a huge threat to human health. Human beings have made considerable progress in dealing with breast cancer, such as disease prevention (21), cancer screening (22), etiological analysis (23), targeted drugs (24, 25), and clinical surgery (26). Despite important advances in the understanding of oncogenesis and development in the past decades, breast cancer remains one of the most common cancers diagnosed among women and the leading cause of female cancer death (27). The risk of breast cancer was significantly increased in developing counties (28). The occurrence and development of breast cancer are complex and multi-stage processes, which prompt humankind to tackle at least two short- or long-term goals. On the one hand, it is urgent to develop new-targeted drugs or explore minimally invasive surgical techniques. On the other hand, it is important to consider the factors of breast cancer occurrence and development from the perspective of social/environment factors (29, 30) and their interactions (31) (e.g., support (32) and education, networks (33), and emotion (34)) on breast cancer occurrence and development. Numbers of individual and environmental factors may contribute to the risk of breast cancer and the prognosis in patients. Recently, the correlations between socioeconomic status and breast cancer incidence and mortality rates are increasingly recognized.

Studies have demonstrated that nature environmental, host genetic, and socioeconomic factors influence the breast cancer prevalence landscape with a far-reaching influence on racial disparity to subtypes of breast cancer (35). The socioeconomic effects on the incidence and death of the breast cancer need to pay enough attentions, the socio-economic disparities in breast cancer survival prevail in this relatively homogenous society (36). Note that the function of public wealth and individual wealth are different during the intervene process. Thus, the lower screening attendance for women with lower socioeconomic status, and higher socioeconomic status is linked to higher incidence but lower case fatality (37). Importantly, there is limited understanding of the contribution of social factors to control patterns (30). Further, the influence and interaction of many socioeconomic factors (e.g., disposable wealth and pressures of life) on breast cancer of women are complex, and it is difficult to expose the dominate factors by cutting off the cross effects of affecting factors. This study is critical for the influences of the socioeconomic factors on the development of breast cancer, with a purpose of providing socioeconomic information for the high-risk screening and diagnosis, prevention, and managing long-term surveillance care of female breast cancer. Besides, this study is useful for the instructive intervention of social welfare and public health policy, with consideration of the prevention and treatment on breast cancer of women in developed countries and regions.

METHODS

In this study, a retrospective observational cohort study on breast cancer of women in Denmark, Norway, Italy, New Zealand, Israel, France, Germany, and Japan between 1980 and 2012 was carried out. The regression analysis and multivariate analysis (path diagram analysis) for five factors, i.e., years, population, gross domestic product (GDP), gross domestic product per capita (GDPPC), and unemployment rate (UR), were adopted using Excel database function, and the effects of socioeconomic factors on breast cancer incidence and mortality rates were analyzed. The breast cancer incidence and mortality data from 1980 to 2012 were obtained from Global Cancer Observatory (GCO) (http://gco.iarc.fr/#cancer-overtime). The socioeconomic data (such as GDP, GDPPC, UR, and population) of several representative developed countries were obtained from National Accounts Main Aggregates Database. (https://unstats.un.org/unsd/snaama/Basic). An illustration of the incidence and mortality of breast cancer is provided in **Supplementary Figure S1**. For multi-factors problems, the multivariate multiple linear regression formula usually can be expressed as the sum function of intercept and the product of the variable and the partial regression coefficient. Using the regression equation of samples, the least square method was used to find coefficients to minimize the sum of squares (SS) of residual errors. The structure of path diagram analysis was represented by a series of regression parameters. Hypotheses involved the correlational and regression-like relations between the incidence/mortality rate and the socioeconomic factors. That is, some factors were observed variables and the others were latent variables. There might be a relationship between the observed variables and latent variables, and some variables maybe functions of other variables.

Path diagram analysis is a form of structural equation model (SEM) and is generally tested by regression analysis (38). The structural model is fitted by mathematical statistics methods and principles (39). After the series test and analysis, the most suitable model was available to represent multiple complex relationships between independent variables and variables. In this study, we focused on certain socioeconomic factors, such as time-dependent public wealth, living environment, including social population and unemployment ratio (40) (reads social pressure), and individual economic wealth. As well-known, these factors have complex interactions with each other. Therefore, path diagram analysis, based on multiple linear regression models, was used to explore the factors which influence female breast cancer using the multi-dimensional causality and related strength analysis (**Supplementary Figure S2**).

In this study, the sample includes information for numerical variables from several representative countries (e.g., Denmark, Norway, New Zealand, Canada, Israel, France, Germany, and Japan), such as information on economics and breast cancer during 1980–2012. The value of Ri ($i = 1$–5) is the stepwise route of the regression analysis. We assumed that the five factors (x_1, x_2, x_3, x_4, and x_5) of years, population, GDP, GDPPC, and UR affect the dependent variable, i.e., the incidence and

mortality rates (y_1, y_2) of breast cancer. Further, we supposed that time was the most basic variable, and GPD was a low-order variable. GDP as a function of social wealth was impacted by years, a measure of time, GDPPC, population, and UR, which were all high-order variables and affected by other variables (as shown in **Supplementary Table S1**). The survival rate of breast cancer was measured using the mortality-to-incidence ratio (MIR) (41) and to illustrate the effects of socioeconomic factors (42). All variables were normalized before regression analysis. In mathematical form, the regression equation of path diagram analysis was formed by linking these variables with some coefficients. During each process of regression, X_i is an independent variable, which consists of years, population, GDP, and GDPPC, and UR. Y_j ($j = 1$–5) is the dependent variable, in this case, the incidence rate and mortality rate of breast cancer. During the process of stepwise regression analysis, note that the identity of X_i (except for the lowest-order independent variable X_1) would transform into a dependent variable Y_j.

TABLE 1 | The ANOVA results of regression models for incidence rate.

Step	Variation sources	*df*	*SS*	*MS*	*F*	Significance F
I	Regression	5	4.0823	0.8164	47.8654	9.48E-36
	Residual	282	4.8101	0.0171		
	Total	287	8.8924			
II	Regression	4	17.1575	4.2894	102.9645	5.35E-54
	Residual	283	11.7895	0.0417		
	Total	287	28.9470			
III	Regression	3	3.5235	1.1745	44.5455	1.27E-23
	Residual	284	7.4880	0.0264		
	Total	287	11.0115			
IV	Regression	2	5.0085	2.5043	230.1414	3.23E-60
	Residual	285	3.1012	0.0109		
	Total	287	8.1097			
V	Regression	1	0.2594	0.2594	5.7892	0.0167
	Residual	286	12.8143	0.0448		
	Total	287	13.0737			

Significance F (F significant statistic) has the p that is less than the significance level of 0.05, so the regression equation has a statistical significance.

RESULTS

There is a significant relationship between breast cancer incidence and time and socioeconomic factors (i.e., population, GDP, GDPPC, and UR) ($R > 0.8$), except for factors identified by the stepwise regression model. The fifth regression analysis (for the model of population vs. time, $R < 0.2$), there are significant multi-factor correlations. This finding verifies that the model is reasonable. The main function of ANOVA table is used to judge the regression effect of regression model by joint hypotheses test (F-test). The ANOVA data of each step regression analysis is listed in **Table 1**. In the process of decreasing regression, the degree of freedom (df) of potential variables is reduced by one for each regression. The significant level, or F statistics for each step of the regression analysis has different p, which is less than the stated significance level of 0.05. Therefore, the regression equation for each step has the statistical significance of regression process. Further, the obtained interception and partial regression coefficient are used to express each regression equation. The revalued coefficients for the selected models of the multivariable analyses are presented in **Table 2**.

Note that the p of items of "intercept," "year," and "population" in the first regression are larger than the significance level of 0.05. The item of "GDPPC" in the second regression has no statistical significance ($^{**}p > 0.05$). These shows that, the hypothesis that female breast cancer mortality is a function of time and population is not statistically significant in the structural equations model. In addition, the hypothesis that population is a function of GDPPC has no statistically significance. Therefore, some path coefficients in this structural equation models need eliminated for the reasonable hypothesis and correction SEM model. According to the path coefficients, we can understand and identify the cause–effect relationship between the latent variables. Further, the path diagram based on the structural equation models are obtained and as shown in **Figure 1**. In the path diagram model, the magnitude of the path coefficient indicates the relationship between the influence degree of variables and dependent variables, while the positive and negative values indicate the positive and negative effects of the influence trend.

Year was the most basic time variable which was always related to the incidence of breast cancer, regardless of which implied value, the path coefficient is the largest, as shown in **Figure 1**. The weight of mapping relationship was the largest, which ultimately led to the highest degree of impact on breast cancer incidence. In addition, social public wealth (GDP) has a greater impact on the incidence of breast cancer. Its negative value (−0.51) reflected that the incidence of breast cancer declines with the increase of GDP, which was benefited from the improvement of public health conditions, the development of medical technology, disease prevention and control propaganda, and other interventions. The influence of social pressure (UR), personal economic wealth (GDPPC), and population on the incidence of breast cancer is very close (the path coefficients are about 0.2). In different structured variance models, the positive and negative of path coefficients remain unchanged, but the values of path coefficients were different. These deep-seated socioeconomic relations were not discussed here.

However, the mortality and socioeconomic factors of patients with breast cancer are different from the incidence of breast cancer as shown in **Figures 2A,B**. The direct impact of year and population were not significant, and thus, we eliminated the two factors. The increase of public wealth helped to reduce the mortality rate of patients with breast cancer, but the increase of personal wealth (GDPPC) and social pressure (UR) induced the increase of mortality rate of patients with breast cancer. Therefore, reasonable control of personal economic wealth and release of social pressure are helpful to prolong the survival rate of patients with breast cancer. The path coefficients obtained by low-order regression are consistent with the incidence variables.

TABLE 2 | A structural equations model based on the regression analysis of the incidence and mortality rates of female breast cancer.

Step		Coefficients	Standard errors	T stat	*P*-value	Lower 95%	Upper 95%
I (Incidence)	Intercept	−20.208	2.0584	−9.8175	9.24E-20	−24.2597	−16.1563
	Year	20.7499	2.0960	9.8999	5.02E-20	16.6242	24.8756
	GDP	−0.5088	0.0550	−9.2508	5.74E-18	−0.6171	−0.4006
	GDPPC	0.1795	0.0616	2.9114	0.0039	0.0581	0.3008
	UR	0.1864	0.0371	5.0271	8.87E-07	0.1134	0.2594
	Population	0.1956	0.0282	6.9352	2.77E-11	0.1401	0.2511
I (Mortality)	Intercept	3.1114	2.7758	1.1209	0.2633	−2.3526	8.5755
	Year	−2.6725	2.8265	−0.9455	0.3452	−8.2364	2.8913
	GDP	−0.3906	0.0742	−5.2658	2.77E-7	−0.5366	−0.2446
	GDPPC	0.2654	0.0831	3.1927	0.0016	0.1018	0.4290
	UR	0.1967	0.0500	3.9332	0.0001	0.0983	0.2952
	Population	0.0170	0.0380	0.4475	0.6548	−0.0578	0.0919
II	Intercept	12.0378	4.2787	2.8134	0.0052	3.6157	20.4598
	Year	−12.1658	4.3577	−2.7918	0.0056	−20.7434	−3.5881
	GDP	1.3156	0.0856	15.3741	3.42E-39	1.1472	1.4841
	GDPPC	0.1652	0.1295	1.2755	0.2032	−0.0898	0.4202
	UR	0.3932	0.0746	5.2720	2.68E-07	0.2464	0.5400
III	Intercept	−23.3425	3.1094	−7.5072	7.84E-13	−29.4629	−17.2222
	Year	24.28957	3.1530	7.7036	2.22E-13	18.0833	30.4958
	GDP	−0.64	0.0565	−11.3269	8.63E-25	−0.7512	−0.5288
	GDPPC	−0.77568	0.0922	−8.4125	1.99E-15	−0.9572	−0.5942
IV	Intercept	−25.0936	1.3344	−18.8053	7.37E-52	−27.7201	−22.4671
	Year	25.5634	1.3453	19.0016	1.41E-52	22.9154	28.2114
	GDP	−0.3654	0.0291	−12.5382	5.13E-29	−0.42272	−0.3080
V	Intercept	−6.3643	2.6814	−2.3735	0.0183	−11.6422	−1.0864
	Year	6.5029	2.7027	2.4061	0.0168	1.1832	11.8227

In this structural equations model, the dependent variables (i.e., incidence rate and mortality rate) have the highest ranking. We assume that the other variables are their independent variables no matter whether implied values or not. That is, the breast cancer incidence and mortality rates are no longer used as variables to explore structural equation models after first-order regression. The underlined values of p in the table indicate the mathematical relationships that are not of statistical significance.

DISCUSSION

Effects of Wealth Factors

The effect of country-independent GDP values on the incidence and mortality of breast cancer in women based on years were shown. As an important macroeconomic indicator, GDP best measured the economic strength and wealth of a country. The national GDP has an economic impact on the living standards and health of citizens. As seen, the influence of GDP on the incidence of diseases showed a significant separation phenomenon, and the effect of GDP on the mortality of diseases showed a significant separation phenomenon. At lower national GDP (i.e., the national economic status is in poverty), the incidence and mortality of female breast cancer were both higher. In addition, the incidence and mortality are highly concentrated in the range of 50–200 (per 100,000 persons) and 20–60 (per 100,000 persons). Under higher national GDP, where the national economic status was in rich and defining threshold was 10,000 billion, a good quasi-linear relationship between the incidence and mortality of female breast cancer and GDP was shown. When the GDP was between 10,000 and 30,000 billion, the incidence and mortality of female breast cancer increased slowly with the increase of GDP. This phenomenon might be related to the source of national wealth and industrial level. These factors might produce benefits to working women and work pressure, working environment, and labor intensity. When the GDP was >30,000 billion, the influence of GDP on the incidence and mortality of breast cancer shows a significant bifurcated separation phenomenon, such as "o" and "h/p" in **Figures 2A,B**.

There were possible reasons for this pattern. First, some samples reflected that the country were wealthy, where the living standard of people significantly improved. In these countries, the increasing incidence and mortality of breast cancer were related to over nutrition, obesity, and other problems associated with rapid economic development. In addition, in these countries, the working intensity of the people was surplus/deficiency, which led to the deviation of individual physique from the healthy range (43). Second, in other emerging economies, with the increase of GDP, the national investment in research and development of preventive medicine and medical technology was enhanced. The national awareness of disease prevention and health has significantly grown, resulting in a gradual decline in the incidence and mortality of breast cancer. Therefore, the low-income countries need to allocate sufficient resources to increase

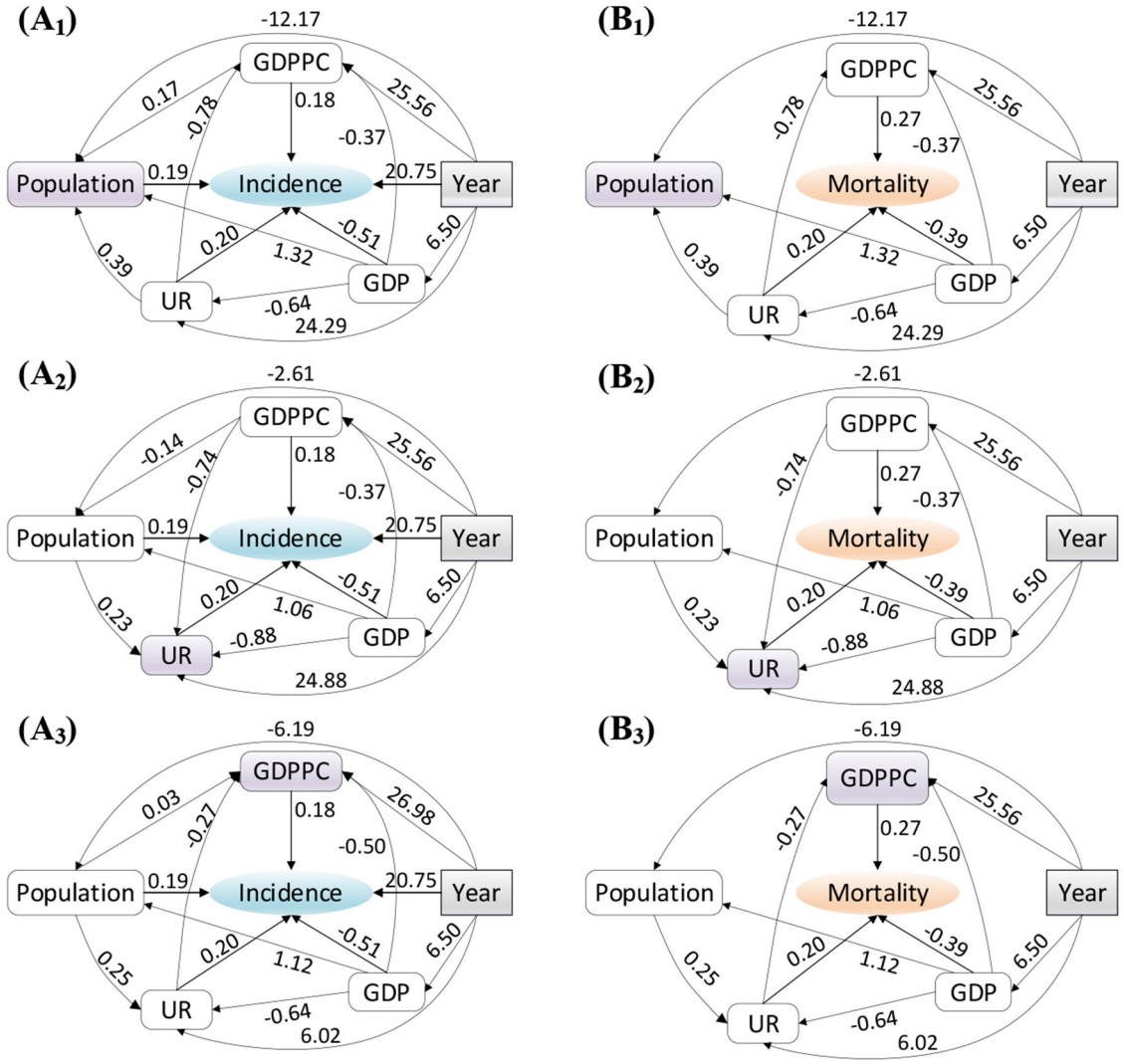

FIGURE 1 | Structural equations model used to illustrate the relation between the **(A)** incidence and **(B)** mortality rates and socioeconomic factors. Among many variables, subscripts are used to represent high-order variables, of which subscript 1, 2, and 3 correspond to high-order variables population, UR and GDPPC respectively.

screening participation (44). Thereafter, it is available for the high quality of occurrence data and the adoption of accurate methods to estimate incidence and mortality.

As an important reference indicator for improving the per capita income level and living standard of residents, the GDPPC indirectly reflects the average purchasing power level of social individuals and the degree of independence of life. GDPPC was additionally used as an important economic index for individuals and families, and is related to the objective conditions of life and the judgment of the facts and values of the state (e.g., happiness index (45)). High GDPPC might enhance the individual happiness through the individual's independent, free, and pleasurable experience in life. The economic index reduces cancer incidence and mortality (46). In **Figures 2C,D**, the influence of per capita GDP on the incidence of female breast cancer and the trend of mortality have a power function change trend, but there is clear difference in the two key parameters of coefficient and power index. For example, the coefficient of the power function of incidence rate is two times the power function of mortality rate.

There were several reasons for this finding. First, women have a high degree of initiative and enthusiasm in the pursuit of personal value and economic wealth before the onset of breast cancer. At the same time, the increase in personal income, work stress, and work intensity was increased significantly, which results in an increase in the incidence of breast cancer. This result is different from the previous study. However, the effect on mortality is different. Overall mortality was greater among the patients with breast cancer of the lowest income group than in the highest one (47). When income is low, expensive medical

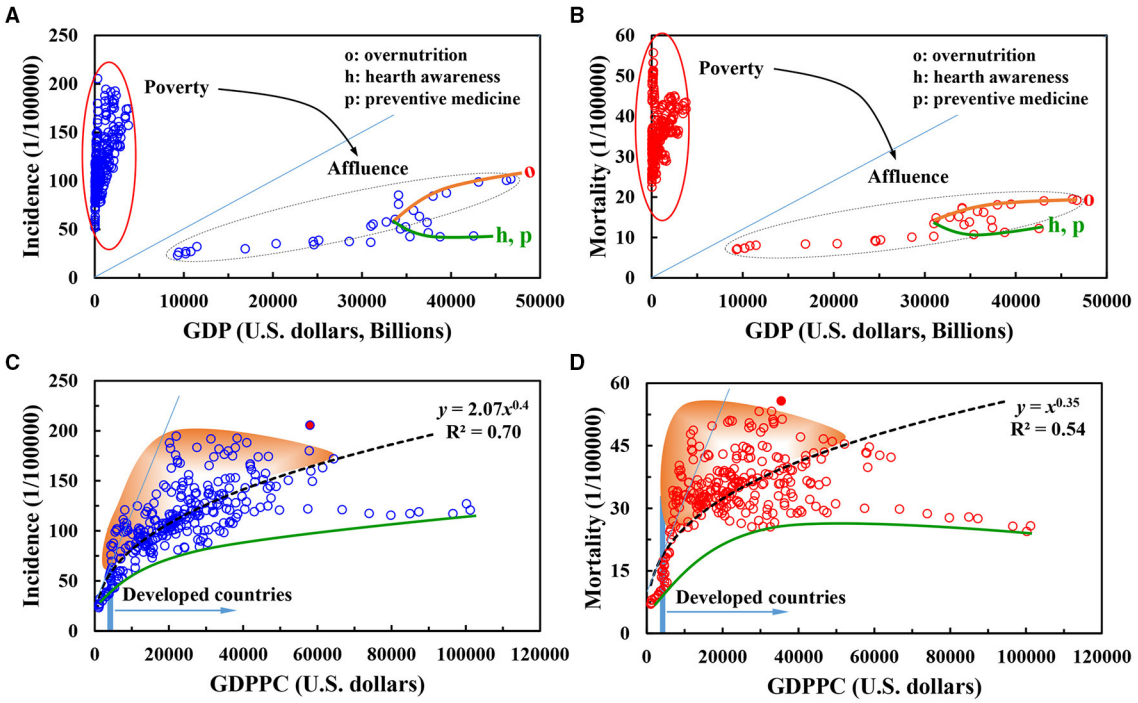

FIGURE 2 | (A–D) Differentiated effects of social public wealth and per capita income level on incidence and mortality rates of female breast cancer.

expenses are major stressor for patients with breast cancer. The economic resources have a great impact on families. All aspects of stress will promote the negative beliefs in patients with breast cancer, further resulting in accelerated illness and death. This was represented in the upper part of the fitted curve. In wealthy families, the presence of patients with breast cancer will not put significant economic pressure on families or related members. After the pain and suffering caused by the disease, patients with breast cancer are willing to pay for better therapy and nursing. Furthermore, an open-minded attitude of life has reduced the mortality rate to some extent.

Effects of Society Pressure

Sociological pressure is accompanied by every process of growth. Specifically, health deterioration from unemployment is likely to be large, and unemployment is a public health problem that needs more focus (48). Usually, an increase in the UR is a signal of economic weakness and a reflection of social pressure. For individual, the unemployment or insecure employment closely relates to the degree of happiness and social pressure, specifically psychological complaints, and life satisfaction. The impact of UR on individuals is reflected in psychological stress, which in turn affects breast cancer incidence and mortality of an individual. A 1% increase in unemployment is associated with a significant increase in colorectal cancer mortality in both men and women (49). As an important chronic disease, breast cancer was associated with the national UR on the affected individuals.

Figure 3 shows the association of the country-independent UR on the incidence and mortality rates of female breast cancer. The UR has a reverse corresponding relationship with the economic growth rate, this trend is consistent to the structure equation analysis result. When the UR is too high, it impacts the income of unemployed group, and psychologically increases the insecurity of the unemployed. Some unemployed individuals may cause a series of problems in the case of poor psychological quality (50). This involuntary diffusion effect will increase the insecurity of workers in the industry, thereby increasing the overall insecurity of the society and having an important impact on the physical and mental health of individuals (51).

With the gradual increase of the UR, the incidence of breast cancer showed a growth trend of power function $y = 42.27x^{0.48}$ ($R^2 = 0.30$) **Figure 3A**; breast cancer mortality showed a power function $y = 12.93x^{0.48}$ ($R^2 = 0.28$) **Figure 3B**. Incidence and mortality have the same power exponent for the power function of independent variables, which can reflect the consistency of social pressure factors on individuals in the population (52). This consistency accounts for the dependence of human beings on social production relations and/or basic survival needs (53). These needs, which are of great importance to the quality of life and health factors of individuals (e.g., safety, food, and shelter), relate to the cognitive level of individuals themselves.

In addition, there is an approximate three-fold relationship between the coefficient of the incidence power function and the coefficient of the mortality power function, which relates to the individual's desire for life, health, and happiness (54). This result reads the 5-year survival rate (more than 60%), which is hoped to be a useful information for the patients of breast cancer. In this sense, external social pressure (such as, unemployment)

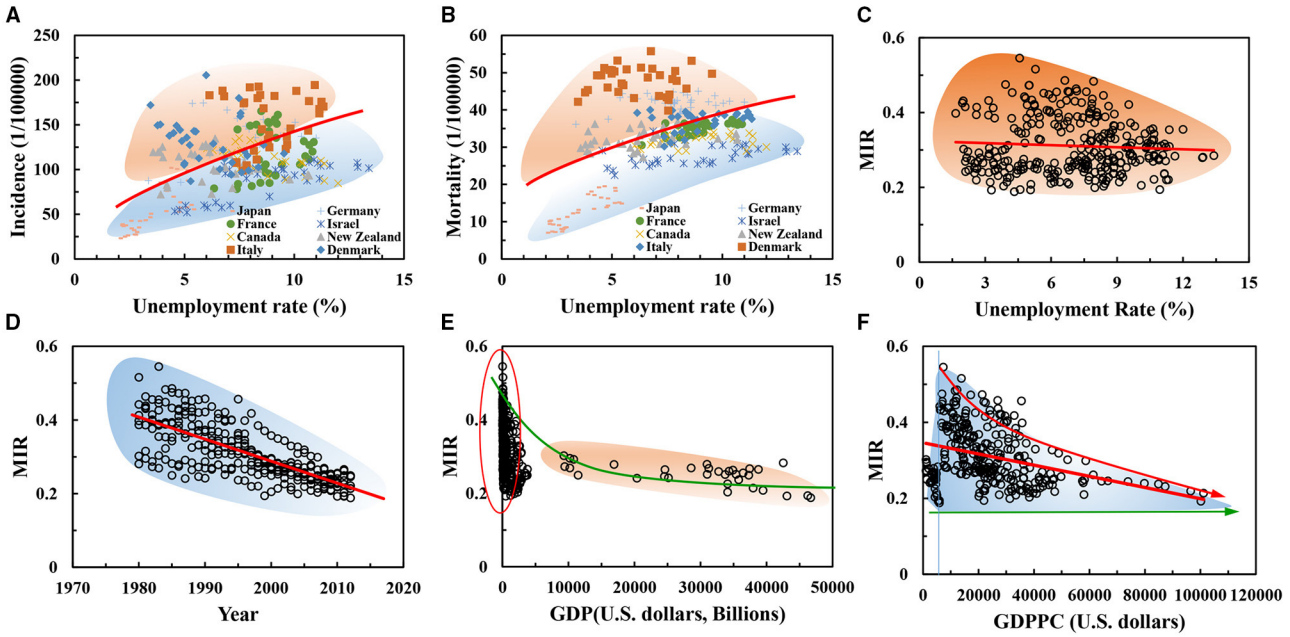

FIGURE 3 | (A–F) Effects of socioeconomic factors on the mortality-to-incidence ratio (MIR) of female breast cancer.

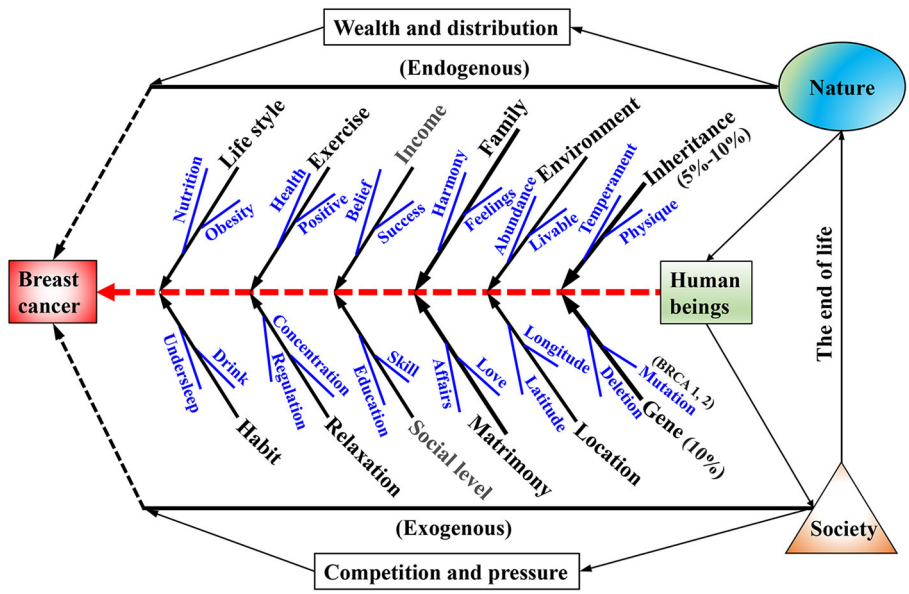

FIGURE 4 | Fishbone diagram of the affecting factors both from nature and society on the female breast cancer.

might be fitted discretely in the curve of UR-incidence and mortality of breast cancer. However, the effects of unemployment are clear. Our results are broadly consistent with literature (55), unemployment significantly increases the risk of being dead at the end of follow-up by nearly 50%. The fact may ask for the deep think on the unemployment insurance system for the potential protective effects on the patients of breast cancer (50).

On MIR

The 5-year survival rate of breast cancer usually is proxied by MIR of breast cancer for women health (42), Adams et al. investigated the accessibility and importance of mammography services (56). We further investigated the influences of four socioeconomic factors (such as, years, GDP, GDPPC, and UR) on MIR of female breast cancer, as shown in **Figures 3C–F**.

In **Figure 3**, a sharp increase in the MIR of female patients with breast cancer was revealed with the increase of GDP and GDPPC from 1980 to 2012, see **Figures 3E,F**. MIR obeyed a power function from the trend of the power function of incidence and mortality aforementioned, but the correlation coefficient of regression analysis is small and the dispersion degree of data is high. However, the impact of the increased UR on MIR was almost constant, see **Figure 3C**. Therefore, the scatter plot shows that the differentiation was serious, which was mainly related to the physical quality, personal will, and survival belief of individual (57).

As shown in **Figure 4**, the influence factors both from nature and society are various and are not available using a single way. The pathogenesis of breast cancer is not only related to the living environment, individual differences, the nature of work, and social roles, but also related to the socioeconomic factors of its comprehensive results. At present, there are still many unknowns in these studies, such as the structural coefficient between the factors and the influence weight. With the development of information network and the improvement of the accessibility of public statistics data sharing, there may be more connections between the factors that originally belong to the network, which need researchers to further carry out the research work of logical carding and model construction. Due to limited space, we cannot investigate the various factors from nature to society for breast cancer. To investigate the influence maps between the socioeconomic issues and breast cancer, we focused on two groups socioeconomic data in this study, one is endogenous wealth and distribution related to economic development (GDP and GDPPC), and the other is exogenous completion and pressure related to individual survive (UR and population). These factors were readily available and involved in cancer control, such as population-level incidence rates, death rates, and survival rates. Further, the socioeconomic factors based on development were investigated by using stepwise regression analysis and path diagram analysis.

CONCLUSION

Social public wealth has a threshold limit on the regulation of breast cancer occurrence and development. The public wealth produces significant intervention ability until the value reaches at a certain level. The impact of social pressure (UR) on the incidence and mortality of female breast cancer was not typical monotonous but showed a power function trend in a specific range. Individual economic wealth has a strong intervention effect on the incidence and mortality of breast cancer. The survival index determined by the ratio of mortality to incidence showed a similar pattern with socioeconomic factors.

Bivariate analysis generally supported the results of univariate analysis. By using path coefficients and structured equations, the multivariable structured equation model analysis further accurately delineates the impact of socioeconomic factors on breast cancer incidence and mortality. The first-order structural equation model was subjected to socioeconomic factors, but the second-order structural equation model was related to the correlation between socioeconomic factors. Structural equation and path coefficient show that UR and personal wealth have important effects on the incidence rate and mortality of female breast cancer. On the one hand, doctors and hospitals can advise social forces to pay attention to and maintain a fair and warm social environment, on the other hand, they can appeal the government to consider the medical security mechanism for special groups and diseases (e.g., women breast cancer) in the allocation of public resources. In addition, the establishment and expression of mathematical models related to socioeconomic factors were of great value to the accurate analysis and quantitative prediction of the occurrence and development of breast cancer, and further provide an effective theoretical basis for the prevention and treatment of female breast cancer.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

QP: conceptualization, investigation, methodology, data curation, funding acquisition, and writing—original draft preparation. XR: software, validation, formal analysis, resources, visualization, and writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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SUPPLEMENTARY MATERIAL

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Comparison of Disability-Adjusted Life Years (DALYs) and Economic Burden on People With Drug-Susceptible Tuberculosis and Multidrug-Resistant Tuberculosis in Korea

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In the future, tuberculosis (TB) will place a heavy burden on the aging population in Korea. To prepare for this crisis, it is important to analyze the disease burden trend of drug-susceptible tuberculosis (DS-TB) and multidrug-resistant tuberculosis (MDR-TB). Measuring disability-adjusted life years (DALYs) and economic burden on MDR-TB patients can help reduce the incidence of TB. Accordingly, in this study, we measured the DALYs and economic burden on DS-TB and MDR-TB patients in 2014–2017 using a combination of National Health Insurance claims data, Annual Report on the Notified TB data, and Statistics Korea's mortality data. The incidence-based DALY approach implemented involved the summation of years of life lost and years lived with disability. For measuring economic burden, direct and indirect costs incurred by patients were totaled. From 2014 to 2017, DALYs per 100,000 people with DS-TB were 56, 49, 46, and 40, respectively, and DALYs per 100,000 people with MDR-TB were 3, 2, 2, and 2, respectively. The economic burden for the DS-TB population from 2014 to 2017 was $143.89 million, $136.36 million, $122.85 million, and $116.62 million, respectively, while that for MDR-TB was $413.44 million, $380.25 million, $376.46 million and $408.14 million, respectively. The results showed a decreasing trend in DALYs and economic burden for DS-TB, whereas MDR-TB was still found to be burdensome without a specific trend. With respect to age, the economic burden for both DS-TB and MDR-TB was higher among men than among women till ≤79 years. Conversely, the economic burden for women aged ≥80 years was higher as compared to their male counterparts. In conclusion, the incidence and spread of TB in all areas of society must be suppressed through intensive management of MDR-TB in the older population. We hope that the national TB management project will proceed efficiently when the infectious disease management system is biased to one side due to the COVID-19 pandemic.

Keywords: tuberculosis, drug-susceptible tuberculosis, multidrug-resistant tuberculosis, disability-adjusted life years, economic disease burden, South Korea

INTRODUCTION

Tuberculosis (TB) is a highly infectious disease (1, 2) that has led to the deaths of approximately one billion people worldwide over the past two centuries (3). However, TB is not expected to lead to a global public health crisis by the year 2035, as anticipated by the global strategy for the second half of TB. The situation is improving, although very slowly. The goal of the World Health Organization (WHO) was to reduce the incidence of TB by 4% per year between 2015 and 2020. However, according to a global TB report in 2020, the incidence of the disease decreased by about 2% per year during this period. Similarly, the mortality reduction target set at 7% per year was not achieved, with the achievement of a 3% decrease in mortality from 2015 to 2020 (4).

Meanwhile, drug-resistant TB (DR-TB) has emerged as an important target for TB control worldwide. Drug resistant TB can stem from improper management including poor compliance and wrong treatment as well as from direct transmission. Multidrug-resistant tuberculosis (MDR-TB) refers to tuberculosis that is resistant to at least both isoniazid and rifampicin and extensively drug-resistant tuberculosis (XDR-TB) is an extensively drug-resistant TB that is resistant to any fluoroquinolone and at least one of three injectable second-line drugs in addition to MDR-TB resistance, on drug-susceptibility testing (DST) microbiologically (5). Confronting the threat of COVID-19, we are unsure if the recently decreased drug-susceptible tuberculosis (DS-TB) and MDR-TB prevalence is due to lack of accurate information about real TB patients or improved quarantine policies of social distancing adopted for infectious TB (6).I n 2019, it was reported that about 465,000 TB patients developed resistance to rifampicin, the most effective drug for TB, of which 78% had MDR-TB (7). MDR-TB has been observed in most countries around the world. It is more prominent in 30 countries where the economic burden is the highest on people with MDR-TB (8).

South Korea has high TB incidence and mortality rates. The incidence of TB in South Korea is the highest among the Organization for Economic Cooperation and Development (OECD) countries (9). The plausible reasons for the high burden of TB in South Korea could be as follows. (1) high prevalence of latent TB infection in the elderly after the Korean War (1950–1953), (2) an increasing population with diabetes, (3) previous inadequate TB patient management, (4) immigrants from high-burden countries, and (5) characteristics of M. tuberculosis strain of Beijing lineage (10). Additionally, there is a high risk of recurrence and incidence of MDR-TB all over the world (11). In 2017, a total of 36,044 TB patients were reported in Korea, of which 681 were infected with MDR-TB; in addition, 1,816 TB deaths were reported (12). Furthermore, Korea is experiencing rapid aging. Moreover, TB mortality in the older population (individuals aged over 80) increased by ∼35% from 2001 to 2016 (13).

Based on these statistics, TB will put a heavy burden on Korea in the future. To prepare for this crisis, it is important to analyze the disease burden trends of DS-TB and MDR-TB based on the age and sex of the affected population (14–17). The need to strengthen the management of MDR-TB has emerged as an effective approach to the reduction of TB incidence. Since 2005, diagnosis and treatment of active TB had been fully supported by the extended national health insurance benefit coverage, classified as severe disease. TB case monitoring and financial support were reinforced since 2009. In addition, starting with TB close contacts since 2015, latent TB was also included to the extended national health insurance category. Moreover, for the MDR-TB patients, financial support for the living expenses and prior deliberation process for the new MDR-TB drugs have begun (18). Recently, efforts for improving medication adherence with digital health initiatives such as video observation treatment (VOT) are being tried (19), and prior deliberation process for the new MDR-TB drugs enhanced prescription of new TB drugs, funded by government. Still, further public attention is needed to help Korean doctors to be aware of government's recommendation regarding drug usage as well as treatment of TB.

There is a lack of research for the measurement of health outcomes of MDR-TB patients with the use of a standardized methodology as a result of limited data sources and difficulties in selecting subjects. In this study, National Health Insurance (NHI)-integrated data can be used as a source of information for the calculation and comparison of the DALYs of and economic burden on TB patients with different levels of drug resistance to generate reliable evidence. Therefore, this research aimed to identify the current disease burden and trends of DS-TB and MDR-TB in South Korea and calculate the economic burden on patients utilizing NHI-integrated data from 2014 to 2017.

MATERIALS AND METHODS

Data Source and Participants

This study was conducted using a combination of the Annual Report on the Notified TB data, NHI claims data, and Statistics Korea's mortality data. The Annual Report on the Notified TB data was prepared to analyze information pertaining to TB patients diagnosed or treated at public health centers and hospitals across the country and to plan, implement, and evaluate national TB management policies based on the results. The data were collected through the integrated disease and health management system, NHI claims data refers to a sample research data, customized research data, and health disease indicators based on evidence accumulated from the NHIS. Statistics Korea's mortality data is a compilation of death reports acquired from Eup, Myeon, Dong administrative welfare centers, and Si/Gu offices in the country (foreign missions for overseas Koreans) based on resident registration sites.

In this study, MDR-TB patients and DS-TB patients were selected as participants. The description of the codes and criteria for selecting participants are as follows. Participants diagnosed with TB-related ICD-10 codes were selected (A15-A19, U84.30, and U84.31). MDR-TB patients were diagnosed with U84.30 (MDR-TB), U84.31 (XDR-TB), and rifampin-only resistant TB, while other participants were diagnosed with DS-TB. The U84.30 code is assigned to patients with TB bacteria resistant to two or more anti-TB drugs, including isoniazid and rifampin. The U84.31 code is for TB patients resistant to isoniazid and rifampin,

one or more quinolone drugs, and one or more of the three injections, capreomycin, kanamycin, and amikacin.

Incidence-Based Disability-Adjusted Life Years Approach Methods

The disability-adjusted life years (DALY) approach was used as a methodology in this research, and the incidence-based DALY approach was measured by totaling the values corresponding to years lived with disability (YLD) and years of life lost (YLL). One DALY indicates that 1 year of full health was lost to disease, disability, and early death; as DALYs increase, the gap with the ideal health level widens, which suggests an increase in disease burden. The incidence-based DALY approach was measured by totaling the values corresponding to YLD and YLL, and detailed calculation methods are shown in Yoon and Yoon (20). To calculate YLD, the DISMOD II program should be used. The program helps determine the age of incidence and duration of TB. Upon inputting the values for incidence, fatality, and mortality rates into the program, the age and duration of TB incidence are automatically calculated. The DISMOD II program was developed by WHO and has been used since the Global Burden of Disease (GBD) 2000, and the DISMOD II program makes it easy to change the number of age groups for variables as needed. This is very useful when the epidemiological variables are listed in a different age group from the age group trying to represent the YLD results (21). The DISMOD II program is used to measure the incidence-based DALY approach, and detailed methods of calculation are described elsewhere (22). To measure YLL, mortality data for TB (A15–A19) and life expectancy by age, gender, and year should be used using Statistics Korea's statistical yearbook for the cause of death. This will help measure the burden of TB disease in Korea (23, 24).

The incidence rate was primarily measured using NHI claims data, which generated YLD values. Mortality and fatality rates were measured using Statistics Korea's statistical yearbook for the cause of death. To measure YLL, the mortality rate and expected life expectancy for TB patients by age, gender, and year were measured using the Korean life table and the statistical yearbook (25). Cause-specific disability weights (DW) were 0.318 and 0.434 for DS-TB and MDR-TB, respectively. To calculate YLD, YLL, and DALYs per 100,000 people, the mid-year population data by age, gender, and year from Statistics Korea were used (26).

Economic Burden

The economic burden was measured as the sum of direct and indirect costs for TB patients. For this calculation, NHI claims data and Korean health panel data were used. Direct costs were classified as medical and non-medical costs. In medical costs, insured medical costs include the total inpatient/outpatient medical and drug expenses, while uninsured medical costs include costs of service not covered by insurance. Furthermore, non-medical costs include transportation and caregiver costs (**Table 1**).

Indirect cost refers to productivity loss due to morbidity and premature mortality. Productivity loss due to morbidity includes the loss of time in outpatient visits and hospitalization, as well as loss of the average daily income. Subsequently, productivity loss due to premature mortality involves the number of deaths, life expectancy, and average annual income. Indirect cost also includes the loss of productivity due to use of hospital medical and loss of future income as a result of early death.

TABLE 1 | Economic disease burden variables.

Variables			Detailed Variables
Direct cost	Medical cost	Insured medical cost	Inpatient, outpatient, drug cost
		Uninsured medical cost	Proportion of non-covered services expenditure
	Non-medical cost	Transportation cost	Number of outpatient visits Average transportation cost by disease category
		Caregiver cost	Hospitalization Average day caregiver cost
Indirect cost	Productivity loss due to morbidity		Number of outpatient visits Hospitalization Average daily income
	Productivity loss due to premature mortality		Number of deaths Average annual income

Indirect cost loss appears to be a social loss, but the Health Insurance Review & Assessment Service (HIRA) does not generally implement policies that take into account indirect costs, and therefore the impact of TB is underestimated. With similar policies, in the case of rare diseases, medical institutions that can be diagnosed as well as treated continuously are concentrated in the metropolitan area, thus, patients living in rural areas were burdened with travel costs. The government is helping people with rare diseases to manage them by consulting, diagnosing and supporting patients with such diseases in the community. It is creating an education and request system through the establishment of a network of local medical services (27).

Ethics Statement

This study was approved by the Institutional Review Board of National Evidence-based Healthcare Collaborating Agency (IRB No. NECAIRB19-008, NECAIRB20-003, NECAIRB21-013). Informed consent was not required because public data from the NHIS database of de-identity were used.

RESULTS

Years Lived With Disability, Years of Life Lost, and Disability-Adjusted Life Years Due to DS-TB and MDR-TB

According to the data on DS-TB patients in the year 2017, 59.5% of this patient population was male, while 40.1% was female, and the average age was 59.6 years. In terms of income quintile, medical aid was 9.9%, and regional/workplace subscribers accounted for the majority 90.1%. In the MDR-TB group, 65.1% were men and 34.9% were women, with an average age of 53.5 years. In the income quintile, medical aid was 12.1%, and regional/workplace subscribers accounted for 87.9% (**Table 2**).

TABLE 2 | Characteristics of drug-susceptible tuberculosis and multidrug-resistant tuberculosis patient, 2017.

Variables		Drug-susceptible tuberculosis		Multidrug-resistant tuberculosis		*p*-value
		N	%	*N*	%	
Gender	Male	16,607	59.9	323	65.1	0.0197
	Female	11,096	40.1	173	34.9	
Age		59.59 ± 19.60		53.51 ± 17.66		<0.0001
Income quintile	Medical AID	2,735	9.9	60	12.1	0.0005
	1	4,760	17.2	103	20.8	
	2	5,147	18.6	106	21.4	
	3	5,891	21.3	110	22.2	
	4	7,113	25.7	95	19.2	
	5	2,057	7.4	22	4.4	
Health insurance type	Medical AID	2,735	9.9	60	12.1	0.1004
	Region/Workplace	24,968	90.1	436	87.9	
	Total	27,703	100.0	496	100.0	

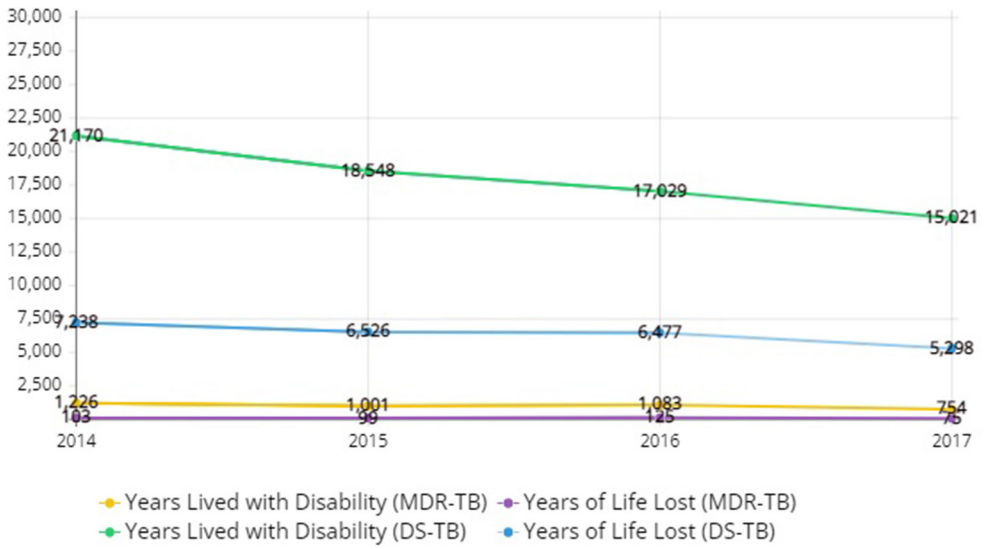

FIGURE 1 | Disability-adjusted life years, years of life lost, years lived with disability due to drug-susceptible tuberculosis and multidrug-resistant tuberculosis in Korea, 2014–2017.

Figure 1 shows the YLL, YLD, and DALY of DS-TB and MDR-TB from 2014 to 2017. DALY is the sum of YLL and YLD. With regard to DALY of DS-TB, there is a decrease from 28,408 DALYs in 2014 to 20,319 DALYs in 2017. MDR-TB also decreased from 1,329 DALYs in 2014 to 829 DALYs in 2017. A consistent decreasing trend for YLL and YLD can be noticed in the figure.

In DALYs per 100,000 people with DS-TB, the values were higher, as the data of an older population was considered. In terms of total DALYs for men and women, it was found to have decreased by 29% from 56 in 2014 to 40 in 2017. Overall, men with DS-TB had higher DALYs than their female counterparts. For most men with MDR-TB in all age groups, DALYs corresponded to 1 in 2017, a slight decrease from 2014. Contrary to the case of men, in women, DALYs appeared to be inconsistent across all age groups. The overall DALYs for men and women were found to have decreased by 33% from 3 in 2014 to 2 in 2017. Overall, no significant gender difference was found in DALYs for MDR-TB patients (**Table 3**).

Economic Burden Due to DS-TB and MDR-TB

Figure 2 shows the direct cost, indirect cost, and total cost of DS-TB and MDR-TB from 2014 to 2017. The total cost of DS-TB decreased from $143.89 million in 2014 to $116.62 million in 2017. The total cost of MDR-TB decreased slightly from $413.44 million in 2014 to $408.14 million in 2017. Nevertheless, it was still burdensome.

The total cost of DS-TB in 2017 was the highest among men in their 40s and 50s. This parameter was relatively similar among women for all age groups. The total cost for both men and women

TABLE 3 | Disability-adjusted life years (DALYs) due to drug-susceptible tuberculosis (DS-TB) and multidrug-resistant tuberculosis (MDR-TB) by gender and age, DALYs per 100,000 people, 2014–2017.

Variables		DS-TB DALYs				MDR-TB DALYs				DS-TB DALYs per 100,000				MDR-TB DALYs per 100,000			
		2014	2015	2016	2017	2014	2015	2016	2017	2014	2015	2016	2017	2014	2015	2016	2017
Male	0–9	152	109	57	52	4	–	–	–	6	5	2	2	0	–	–	–
	10–19	1,624	1,491	1,081	882	47	47	35	23	51	49	37	32	1	2	1	1
	20–29	2,348	1,938	1,598	1,381	68	78	81	40	68	55	45	39	2	2	2	1
	30–39	1,858	1,716	1,467	1,225	78	42	75	39	46	44	38	32	2	1	2	1
	40–49	2,909	2,314	2,300	1,967	71	33	44	47	65	52	52	45	2	1	1	1
	50–59	3,244	3,184	2,855	2,601	54	65	66	54	81	78	69	62	1	2	2	1
	60–69	1,851	1,809	1,830	1,600	30	58	37	17	84	77	73	60	1	2	1	1
	70–79	2,006	1,702	1,722	1,533	30	12	16	10	154	127	126	107	2	1	1	1
	≥80	848	846	1,052	911	4	3	2	6	236	212	239	189	1	1	0	1
Female	0–9	42	20	22	22	–	–	–	–	2	1	1	1	–	–	–	–
	10–19	881	735	586	479	49	16	41	16	30	26	22	19	2	1	2	1
	20–29	1,888	1,572	1,528	1,150	211	219	244	97	60	50	48	36	7	7	8	3
	30–39	1,626	1,409	1,149	1,001	332	287	276	177	42	37	31	28	9	8	7	5
	40–49	1,432	1,122	1,076	930	236	104	123	151	33	26	25	22	5	2	3	4
	50–59	1,288	1,129	950	912	54	58	96	74	32	28	23	22	1	1	2	2
	60–69	981	771	800	752	29	37	34	42	42	31	30	27	1	1	1	2
	70–79	2,129	1,855	1,859	1,501	26	35	26	21	120	103	103	81	1	2	1	1
	≥80	1,302	1,354	1,573	1,420	8	5	13	14	154	148	160	135	1	1	1	1
Male Total		16,839	15,108	13,963	12,152	385	338	356	237	66	59	55	48	2	1	1	1
Female Total		11,569	9,965	9,542	8,167	944	762	853	593	46	39	37	32	4	3	3	2
Total		28,408	25,074	23,505	20,319	1,329	1,099	1,208	829	56	49	46	40	3	2	2	2

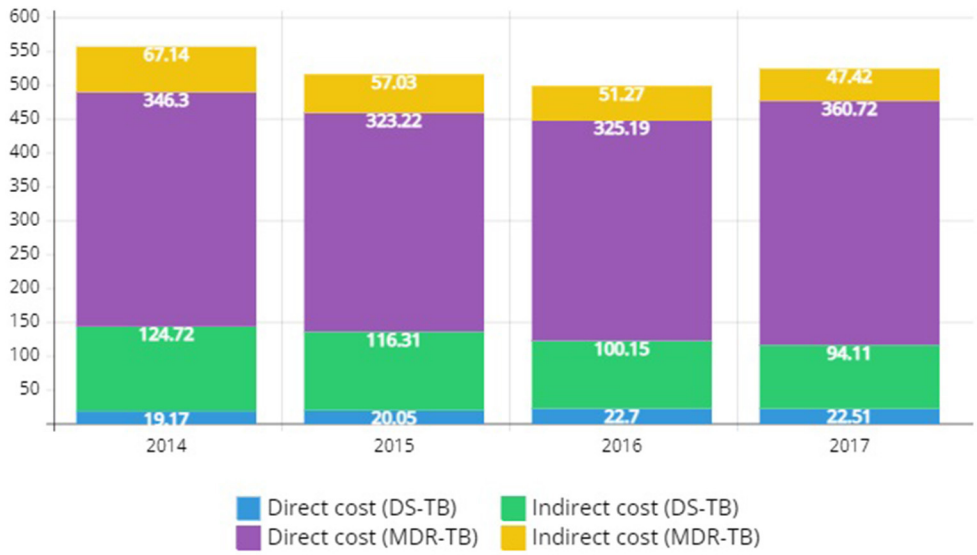

FIGURE 2 | Economic disease burden of drug-susceptible tuberculosis and multidrug-resistant tuberculosis in Korea, 2014–2017 (Discount rate: 3%, Unit: $1 million).

experienced a 19% decrease from $143.89 million in 2014 to $116.62 million in 2017. MDR-TB was high for men in their 40s and older for women in their 70s and older. The total cost for men and women showed a slight decrease from $413.44 million in 2014 to $408.14 million in 2017. The decrease in death cost as part of indirect costs is believed to be the reason for this decline (**Table 4**).

In total cost by category, the direct cost of DS-TB in 2017 was $22.51 million, and the indirect cost was $94.11 million. This gave a total cost of $116.62 million. Medical costs account for a high percentage of direct costs, and productivity loss due to premature mortality account for 96% of indirect costs. From 2014 to 2017, the total cost showed a decreasing trend, which was estimated to be due to a decrease in death cost. The direct cost of MDR-TB in 2017 was $360.72 million and the indirect cost was $47.42 million, which gives the total cost of $408.14 million. Hospitalization cost constituted 60% of the direct cost, outpatient cost 31%, and care cost 8%. Productivity loss due to morbidity accounted for 96% of the indirect costs, which contradicts the finding for DS-TB. Compared to 2014, the total cost decreased slightly in 2017, which is estimated to be a result of a decrease in disease costs as part of indirect costs (**Table 5**).

DISCUSSION

This study measured the change in the status of TB burden for DS-TB and MDR-TB in Korea from 2014 to 2017 and evaluated the disease burden for each age group and gender. DS-TB-related DALYs per 100,000 people were found to have decreased over the study period (59, 49, 46, and 40, respectively). Subsequently, DALYs per 100,000 people for MDR-TB slightly decreased and then sustained during the observed period (3, 2, 2, and 2, respectively). The economic burden of DS-TB consistently reduced from 2014 to 2017, while that of MDR-TB fluctuated each year with no specific trend.

DALYs per 100,000 people showed a decreasing trend for DS-TB and MDR-TB. In 2017, the DALYs per 100,000 people were 40 for DS-TB and 2 for MDR-TB. By gender, DALYs per 100,000 people was higher in men than those in women with DS-TB (men 48, women 32), but for MDR-TB, they were no significant difference between men and women (men 1, women 2). Previous study also showed a trend of decreasing DALYs per 100,000 people of general TB from 2014 to 2017, with 63 DALYs per 100,000 people for men and 36 DALYs per 100,000 people for women in 2017 (25). By age, DALYs per 100,000 people increased for DS-TB with an increase in age. For MDR-TB, it was found to be higher in middle-aged patients. In a 2015 study on the disease burden on Korean patients, TB DALYs per 100,000 people was 121 for men and 76 for women, and DALYs per 100,000 people for male patients aged 80 or older was approximately 92% higher than that for female patients (28). In a 2017 TB study, DALYs per 100,000 people aged 80 or older was 279 males and 166 females, about 68% higher in males than females (25). In this study, men over 80 years of age showed 40% higher than women in DS-TB DALYs per 100,000 people (men 189, women 135). However, in MDR-TB DALYs per 100,000 people, there was no difference between men and women over 80 years of age (men 1, women 1).

In a 2015 study of economic burden, the total cost of TB was found to be $616.80 million, with a direct cost of $199.40 million and an indirect cost of $417.40 million (28). In this study, the total cost of DS-TB had a decreasing trend, whereas the total cost of MDR-TB was different for each year, with no specific trend. The difference between the total costs for DS-TB and MDR-TB tended to increase every year. In 2014, the total cost of MDR-TB was 2.9 times higher than that of DS-TB, whereas, in 2017, it was 3.5 times higher. This is because the total cost of MDR-TB was higher for patients aged more than 80.

TABLE 4 | Total cost of drug-susceptible tuberculosis (DS-TB) and multidrug-resistant tuberculosis (MDR-TB) by gender and age, 2014–2017 (Discount rate: 3%, Unit: $1 million).

Variables		DS-TB total cost				MDR-TB total cost			
		2014	2015	2016	2017	2014	2015	2016	2017
Male	0–9	0.01	–	0.07	–	0.19	0.09	0.03	0.05
	10–19	0.27	0.10	0.08	0.25	2.33	2.09	1.59	1.59
	20–29	4.28	2.61	1.59	3.73	10.66	8.61	8.94	8.34
	30–39	9.69	10.19	6.27	5.23	18.81	14.49	13.76	12.92
	40–49	42.70	33.24	32.01	35.84	47.16	35.37	32.12	35.67
	50–59	50.43	53.10	44.27	41.60	75.50	71.44	65.07	61.70
	60–69	15.77	16.02	17.19	13.97	47.87	47.13	46.62	54.86
	70–79	1.35	1.32	1.10	1.83	45.29	40.48	42.36	50.12
	≥80	0.47	0.29	0.54	0.88	26.69	28.59	33.16	40.56
Female	0–9	–	–	–	–	0.16	0.03	0.03	0.08
	10–19	0.07	0.02	0.06	0.03	1.61	1.47	0.98	1.15
	20–29	2.01	2.46	4.10	0.88	9.06	6.73	6.26	7.06
	30–39	4.27	3.92	1.52	1.18	10.79	8.63	7.75	7.52
	40–49	3.81	4.16	4.21	2.58	11.22	10.23	9.82	8.51
	50–59	4.38	5.34	4.55	3.60	14.75	13.34	12.52	12.13
	60–69	2.81	1.78	2.56	2.23	15.29	16.03	14.53	17.13
	70–79	1.01	0.98	1.42	1.41	36.52	34.54	33.98	34.41
	≥80	0.56	0.83	1.30	1.39	39.54	40.96	46.94	54.33
Male Total		124.97	116.87	103.12	103.32	274.51	248.29	243.65	265.82
Female Total		18.91	19.49	19.73	13.29	138.94	131.96	132.81	142.32
Total		143.89	136.36	122.85	116.62	413.44	380.25	376.46	408.14

TABLE 5 | Total cost of drug-susceptible tuberculosis (DS-TB) and multidrug-resistant tuberculosis (MDR-TB) by category, 2014–2017 (Discount rate: 3%, Unit: $1 million).

Variables			DS-TB total cost				MDR-TB total cost			
			2014	2015	2016	2017	2014	2015	2016	2017
Direct cost	Total		19.17	20.05	22.70	22.51	346.30	323.22	325.19	360.72
	Medical cost	Insured medical cost	10.50	10.96	12.31	11.30	200.36	186.92	186.91	214.99
		Uninsured medical cost	6.70	7.14	8.05	9.58	114.96	103.83	105.16	113.23
	Non-medical cost	Transportation cost	0.14	0.14	0.15	0.12	1.92	1.94	1.96	1.96
		Caregiver cost	1.83	1.82	2.20	1.51	29.06	30.53	31.16	30.55
Indirect cost	Total		124.72	116.31	100.15	94.11	67.14	57.03	51.27	47.42
	Productivity loss due to morbidity		6.99	6.02	6.18	4.21	63.76	53.54	46.38	45.62
	Productivity loss due to premature mortality		117.72	110.30	93.97	89.90	3.39	3.49	4.89	1.80
Total cost			143.89	136.36	122.85	116.62	413.44	380.25	376.46	408.14

According to the GBD study, the total DALYs for infectious diseases in 2017 was 6.5% of that of TB for all age groups, which is higher for patients aged 65 or above at 17% (29). Statistics Korea predicts that the older population, aged 65 years or older, in the country will increase by 46% in the next 50 years (24). With the rapid growth of the aging population, a high burden of TB on the older is expected in the future. Thus, it is necessary to prioritize TB management among this older population in Korea.

MDR-TB is a central issue in TB management due to its low treatment success rate, high mortality rate, and high disease burden. To increase the treatment success rate of MDR-TB, early diagnosis, appropriate treatment, and effective patient management must be accomplished by the national TB management system; there must be an efficient workforce capable of integrating and managing these aspects with the larger system (30). MDR-TB is declining in Korea. To increase the treatment success rate of MDR-TB, treatment support from the NHIS was initiated in 2014 by including TB as a rare and intractable disease to ensure that patients are eligible to receive reimbursement for treatment expenditure (31), and health insurance benefits. As a result, patients have been exempted from economic burden since July 2016.

Meanwhile, the influx of foreign TB, especially MDR-TB patients, is increasing due to an increase in the inflow of people in Korea from high-risk countries for TB on the account of employment, education, and migration (32). Furthermore, the settlement of North Korean defectors has also increased (33). They need appropriate management interventions since they might become an undiscovered source of infection as a result of frequent movement within groups and limited access to medical due to their illegal stay in the country (34, 35).

One study limitation was that fewer MDR-TB deaths were selected due to limitations in data sources. This is because MDR-TB deaths in the current year were analyzed in the study. Consequently, the YLL of MDR-TB was lower than that of DS-TB. However, these limited data alone confirmed that the DALYs of MDR-TB was low. In future studies, it will be necessary to select the data source to include a wide range of MDR-TB patients as subjects.

Despite these limitations, the significance of this study is that it can be used as the basis for understanding the disease burden of TB by comparing DALYs and economic burden according to the presence or absence of drug resistance with the use of integrated data. Due to limitations in data sources and difficulties in selecting MDR-TB subjects, the current research on health outcomes using standardized methodologies is insufficient. However, this paper can be used as a reference study.

Through this study, DALYs and economic burden on patients were compared for the study period of 2014–2017 according to TB resistance (DS-TB and MDR-TB). It was found that the total cost for DS-TB decreased and MDR-TB caused a huge social burden. Although the number of MDR-TB patients was fewer than that of DS-TB, the cost burden was extremely high for MDR-TB. In society, the aging population is rapidly increasing. Therefore, the incidence and spread of TB in all areas of society can be suppressed through intensive management of MDR-TB in the older population.

To reduce the threat of early community transmission and resistance development for TB, public-private mixed collaboration for TB management was launched in 2009 (10). The main elements of this collaboration are strict monitoring of patients, investigation of close contacts, and financial support for patients. In the same context, The Korea Centers for Disease Control & Prevention has implemented a review process for the approval of new TB drugs used to treat patients with multidrug-resistant tuberculosis (MDR-TB) since September 2016 to prompt initiation of MDR TB treatment to reduce early community transmission (36). In addition, Korean government authorities are performing the active TB screening of elderly people even though concerns related to cost-effectiveness and medical issues like morbidity remain (37).

In particular, national-level MDR-TB patient management and support are required to reduce the number of TB deaths. While implementing a comprehensive TB management plan in Korea, the allocated budget should be increased based on the priorities. We hope that the national TB management plan will soon be efficiently implemented given the fact that the country's infectious disease management system is currently prioritizing the management of the COVID-19 over other diseases.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://nhiss.nhis.or.kr/bd/ay/bdaya001iv.do. This study used the National Health Information Database (NHIS-2019-1-662) of the National Health Insurance Service (NHIS).

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by National Evidence-Based Healthcare Collaborating Agency. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SL, MJK, and I-HO: conceptualization, data curation, and writing—original draft. SL and I-HO: writing—review and editing. SHL, H-YK, H-SK, and I-HO: supervison. All authors contributed and approved the article.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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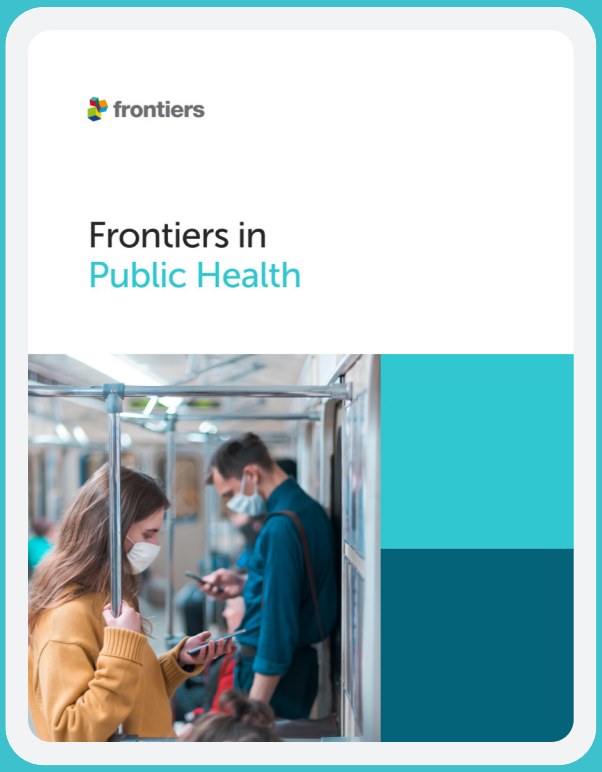

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