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Health economics disparities, inequality and inequity in healthcare services: Today's reality and tomorrow's challenges

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Health economics disparities, inequality and inequity in healthcare services: Today's reality and tomorrow's challenges

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Health Shocks and Household Education Burden—A Study From the Perspective of Relative Poverty Alleviation in China

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Health shocks and household education burden influence levels of expenditure on healthcare and education, which are two major non-discretionary expenditures for households. From the perspective of relative poverty alleviation in China and based on the peer effects theory, this study uses the dataset from the rural areas in CFPS database and employs the spatial Durbin model and spatial DID model to investigate—when a household suffers health shocks—the influence of such impact on the education burden of closely related households and to test the effect of single rescue policy in this circumstance. Further, this study employs a spatial mediating effect model to analyze the spatial transmission mechanism. The results indicate that when a household has health shocks, it can aggravate the education burden of closely related households through inter-household social networks. The findings substantiate that the targets of different rescue policies have cross effects and that single rescue policy does not have significant effect on the targets of other policies. To avoid the situation where rescue policies operate in silos and to reduce the internal coordination cost between different policies within a system, a coordinating mechanism should be established between different rescue policies to better alleviate relative poverty.

Keywords: health shocks, household education burden, peer effects, relative poverty, alleviation

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INTRODUCTION

Poverty and anti-poverty are among the major challenges that are facing today's world. As of the end of 2020, China had achieved the goal of comprehensively eliminating absolute poverty. In the future, the focus of the battle against poverty will shift from "absolute poverty" to "relative poverty"[1]. Different from absolute poverty, which is measured by the monetary value of food consumption, relative poverty relates to "relative deprivation" and is reflected through inequity in income allocation and access to public services and through lower levels of education, healthcare, senior care, and social security (1, 2). In comparison with absolute poverty, relative poverty is ever-developing, multidimensional, structured, and related to special groups (3). Existing study has indicated that there are significant differences in the measures required to alleviate the two

[1]The Fourth Plenary Session of the 19th Central Committee of the Communist Party of China called for "winning the tough battle against poverty and establishing long-term mechanisms for eliminating relative poverty".

types of poverty. Relative poverty has broader implications and much larger coverage; identifying people living in relative poverty requires not only consideration of the income dimension, which is the focus of absolute poverty, but also consideration of the needs (or expenditure) dimension, which is unique to relative poverty (4). As a result, previous approaches to alleviating absolute poverty, which mainly used income level to assess poverty, did not necessarily have a one-to-one corresponding relationship with targets of relative poverty alleviation and may have seriously underestimated the extent of poverty (5) and undermined the sustainability of poverty alleviation policies (6). The impact of relative poverty on individual development tends to last for a long time (7). Poverty alleviation through the social security system plays a more important role than does development-oriented poverty alleviation (8). As such, the government should ensure that a needs-oriented social security system is in place, focusing more on expenditures on education, healthcare, and housing, which are of critical significance to people's rights to subsistence and development (9, 10), and developing equitable public policies that are favorable to people living in relative poverty (11).

Based on the above discussion, this study is of the view that relative poverty alleviation should focus more on the sustainability of providing support through public finance. To avoid the situation in which rescue policies operate in silos and are not connected with one another, there is a need to develop a mechanism that coordinates various rescue policies or different social security programmes so that a comprehensive synergistic effect can be achieved.

In developing a coordinating mechanism, first, the government should investigate and test whether the targets of different rescue policies influence one another, as well as the mechanism by which the influences occur; this will serve as a foundation for the various rescue policies to achieve a coordinated effect. Existing study does not provide a definite conclusion on this issue. Certain studies have examined changes in households' decisions on spending when they experience an external shock and investigated the effect of single rescue policy. Take studies of the impact of health shocks on households' spending decisions as an example. Most studies find that the increased healthcare expenditures as a result of household members experiencing health shocks inevitably affect various aspects of household life, including the time allocation between work and leisure (12), consumption-savings ratio (13), and preference for investment risks (14), forcing the household to adjust their behaviors in making economic-related decisions (15) and ultimately creating a significant crowding-out effect on other household expenditures, such as income, labor supply, and education (16). This effect is more evident in rural households and households with a medium-level income (17, 18). Further, when an individual household member suffers health shock, the shock will spread within the entire household (19) and indirectly affect the economic life of other household members, thereby increasing the probability that the entire household will fall into relative poverty (20). Studies have found that fiscal expenditures on rescue policies, especially increased fiscal expenditures on social programmes, such as subsidies for healthcare and education for low-income residents, are more effective in alleviating relative poverty in rural areas than are development-oriented fiscal expenditures (21); this is because the former has a more significant effect on raising the cost of labor supplied by the poverty-stricken population (22).

Existing study has mainly focused on changes in spending decisions within households that have experienced health shocks but fall short of examining the impact of spending decisions made by the household in question on other households via the social networks between households. As a result, in alleviating relative poverty in the future, there might exist a connection cost between individual rescue policies that each aim at a single target; in other words, because a rescue policy focuses on one public service area, the impact of the policy is limited. Further, there may be an interactive effect between different rescue policies, and the effect of multiple overlapping rescue policies is unknown; this may cause issues such as the inaccurate identification of people in relative poverty and the low sustainability of poverty alleviation policies.

In summary, this study proposes that it is necessary to reduce the scope within which the identification of people in poverty is conducted. By examining how household spending decisions affect one another in a social network as well as the mechanism by which the influences occur, we can reveal the patterns of behaviors of special groups and therefore overcome the challenge of identifying people in relative poverty. Furthermore, we should take into full consideration the complex consequences of a rescue policy and, by developing a coordinating mechanism between rescue policies, effectively alleviate relative poverty. In view of this, this study uses the dataset from the rural areas in the China Family Panel Studies (CFPS) database and two major non-discretionary household expenditures—healthcare and education—as examples to investigate the two major issues. First, this study employs the spatial Durbin model and spatial difference in differences (DID) model to investigate—when a household suffers health shocks—the influence of the event on the education burden of other households that are close to the household in question and to test the effect of an existing single rescue policy in this circumstance. Second, this study employs the spatial mediating effect model to analyze the transmission mechanism between the health shocks and household education burden.

This study carries the following contributions. In terms of the perspectives, this study takes the peer effects as theoretical basis, and explores the feasibility of establishing a coordinating mechanism. The research findings are helpful to improve the accuracy of identifying relatively poverty objects, eliminate the inequality and inequity of rescue policy objects in policy acquisition. With regard to the contents, the analysis of the impact of education and other household expenditure after household suffering from health shocks is no longer limited to a single household. It extends to the spatial dimension. The empirical tests in this study can help develop a coordination mechanism between healthcare rescue policies and education rescue policies so that the rescue policies operating in silos can be eliminated and the connection costs between different policies within a system can be reduced. In terms of the

methods, the research models and analysis methods used in this study clearly cover three aspects of the research topic, namely, the correlation between target variables, the transmission mechanism and the effectiveness of current policies. It has laid a foundation for building a systematically integrated, effective, and multi-level social security system that will improve relative poverty alleviation.

RESEARCH DESIGN

Theoretical Basis and Research Hypothesis

China is a typical relationship-based society where people frequently interact with each other. As a result, an individual's behaviors are subject to the influence of the behaviors of surrounding groups that have similar characteristics (23); in other words, peer effects significantly affect people's behaviors (24). Peer effects are considered externalities that spill over from peers' characteristics and behaviors (25). Research has verified that peer effects exist in many aspects, such as children's behavior, household investment and consumption decision-making and so on (26, 27). Neighbors and relatives may directly affect the skills, information, and social opportunities of other members of the society who are, to a certain extent, close to these households (28, 29). In this case, when a household suffers health shocks, the event may not only widen the gap in wellbeing between the household experiencing health shocks and those in the same social space not experiencing such shocks, but also increase the probability that similar groups in the same social space will fall into relative poverty, resulting in the spatial transmission effect of poverty caused by health shocks. Despite the growing volume of research on the impact of peer effects on the behaviors of individuals and households, the issue above has not been empirically tested in previous research.

The logic of this spatial transmission process is presented in **Figure 1**, as follows. A serious disease first changes the spending structure of the patient's household *j*, and the urgent health expenditures crowd out other household spending. When the total health expenditure exceeds the household *j*'s total wealth, the household *j* may ask for help from relatives, friends, and neighbors, such as household *i*. This amounts to redistributing the economic risk caused by the health shocks to other households in the social network and reducing the consumption budget constraints of the households offering help, thereby increasing their economic burden. If the social network of the patient's household lacks the ability to bear such economic burdens, the health shock is highly likely to increase the risk that other households in the network will fall into relative poverty, resulting in the spatial transmission of relative poverty via the social network. Here, we focus on the spatial relativity of relative poverty.

Based on the analyses above, this study puts forward the following three hypotheses:

H1: Health shock not only affects the consumption decision-making of household in question, but also affects the consumption decision-making of households with similar characteristics to a certain extent.

H2: The possible transmission mechanism of this impact depends on the social network, which is completed in the form of transfer payments between closely related households.

H3: The effect of single rescue policies on the targets of other rescue policies is not clear.

Methods and Variable Selection

To test the above hypotheses, this study utilizes the spatial Durbin model, and constructs a spatial DID model and spatial mediating effect model, respectively, to empirically analyse—when a household suffers health shocks—the influence of such impacts on the education burden of closely related households and the effect of single rescue policy in this circumstance. It also analyses the influencing mechanism between the health shocks and household education burden that form through transfer payments between households.

The advantages of selecting the above models are as follows. First, the spatial econometric model has been widely adopted in analyzing social interactions between individual economic entities (30). Together, the spatial lag model, spatial error model, and spatial Durbin model constitute a spatial econometric model system. The spatial Durbin model not only can represent the impact of the core explanatory variables of the closely related households on the explained variables of the household in question, but also quantify the effects of other explanatory variables. Considering the distribution characteristics of the explained variables, this study adopts the spatial Tobit Durbin model to describe the impact on the household education burden after a closely related household suffers health shocks. Second, while the analysis of the effect of the integrated urban and rural medical insurance (IURMI) system performed using the spatial DID model can represent changes in household education burden in regions that first adopt the policy, it further reflects peer effects in household education burden in these regions. In addition, compared with the regular DID model, the spatial DID model can produce more consistent estimates; the greater is the spatial autocorrelation coefficients of the dependent variables, the more valid is the policy effect estimated by the spatial DID model (31). Third, with regard to the path through which the health shocks influence the household education burden of closely related household, based on the spatial Durbin model, the study draws from the mediating effect model of Wen et al. (32) to construct a spatial mediating effect model.

In summary, in the first part of the empirical analysis, the spatial Durbin model (model 1) and the spatial DID model (model 2) are constructed, as follows:

$$EDU_i = \rho wEDU_j + \beta_1 CHE_i + \delta_1 wCHE_j + \beta X + \delta wX + \mu \quad \text{(model 1)}$$

$$EDU_i = \rho wEDU_j + \gamma_1 T^* Treated_i + \gamma_2 wT^* Treated_j + \beta_1 CHE_i + \delta_1 wCHE_j + \beta X + \delta wX + \mu \quad \text{(model 2)}$$

In model (1), the explained variable EDU_i denotes the education burden of household *i*, which is measured by the household's

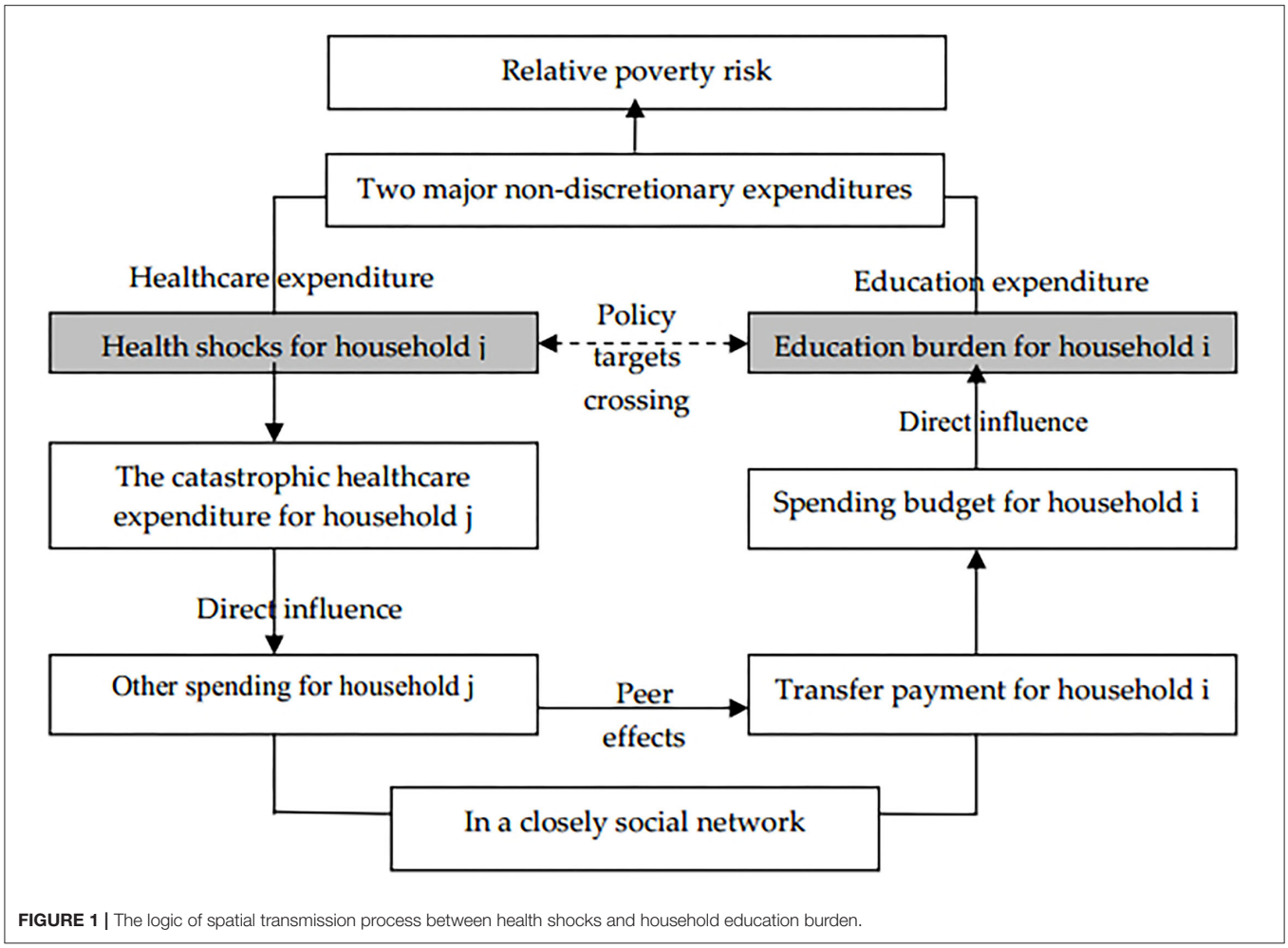

FIGURE 1 | The logic of spatial transmission process between health shocks and household education burden.

total education expenditure as a proportion of its total disposable income within the year, and its value is between 0 and 1. The core explanatory variable CHE_j is the catastrophic healthcare expenditure of closely related household j. The definition of catastrophic healthcare expenditure is based on the criteria of the World Health Organization (WHO); if, during the past 12 months, the ratio between the household's healthcare expenditure and the household's total expenditure, minus expenditures on food, is higher than 40%, then the household is deemed to have incurred a catastrophic healthcare expenditure and suffered health shocks, and the variable is assigned a value of 1; otherwise, it is assigned a value of 0. w denotes the spatial geographic weight matrix factor, namely, the distance between households in the sample. Rural villages in China are usually distributed based on family lines; households in the same village tend to belong to the same family tree and residents have the same family name. The shorter is the distance between households, the closer is the blood-based relations between the households, and the greater is the possibility that households will provide economic support to each other. Considering the statements above, this study uses "whether the households belong to the same village" to construct the spatial weight matrix. ρ denotes the spatial correlation between household education burden; when $\rho < 0$, it is deemed there is a spatial substitute effect between the education burdens of closely related households; when $\rho > 0$, there is a spatial spillover effect between the education burdens of closely related households; and when $\rho = 0$, there is no spatial effect between the education burdens of closely related households. Control variable X represents the household income level, preferred object for borrowing, whether the household receives government subsidies, the degree of the household's participation in social medical insurance, and whether the household has a mortgage. μ denotes the error.

To further investigate the effect of an existing single rescue policy interacting with the goals of other policies, model (2) introduces a spatial DID model to test the impact of two social security policies—the IURMI policy—on household education burden. The main content of the IURMI policy is the integration of the New Rural Cooperative Medical Scheme with the Urban Resident Basic Medical Insurance Scheme; the goal of this policy is to ensure that rural residents in regions where the policy is implemented have access to basic medical insurance that is comparable to that provided to urban residents, thereby increasing the medical insurance level of rural residents. In

TABLE 1 | Descriptive statistics.

Variable	Mean	Standard deviation	Min	Max
Household education burden	0.2193	0.2141	0	1
Catastrophic healthcare expenditure (occurrence is 1, non-occurrence is 0)	0.0763	0.2657	0	1
Net transfer payment (occurrence is 1, non-occurrence is 0)	0.3344	0.4720	0	1
Household income level (take logarithm)	10.3460	1.2967	2.5649	12.8212
Preferred object for borrowing (from 0 to 6, the objects are from banks and financial institutions to parents, relatives and friends. The larger the value, the closer the economic relationship is)	3.1979	2.0809	0	6
Household receipt of a fiscal subsidy (occurrence is 1, non-occurrence is 0)	0.5729	0.4949	0	1
Degree of participation in social medical insurance (expressed by the ratio of household insured persons to household size)	0.8252	0.3799	0	1
Mortgage (occurrence is 1, non-occurrence is 0)	0.1180	0.3228	0	1

practice, as the time when the IURMI policy was implemented differs among China's provinces, in referencing the approach described by Ma et al. (33), this study selects Chongqing (began implementation in 2008), Tianjin (began implementation in 2010), and Guangdong (began implementation in 2012), which were the first jurisdictions to implement the policy, as the treatment group; the other provinces (gradually began implementation after 2016) constitute the control group. Considering the lag of policy effect, the CFPS datasets for 2014 and 2018 are used as the pre-test and post-test data, respectively, to analyze the policy effect. Building on this, this study further incorporates into the model whether a household receives a general fiscal subsidy from the government, so as to examine the combined effect of the IURMI policy and general fiscal government subsidies. The general fiscal subsidy refers to the government's transfer payments made to low-income groups and people experiencing difficulties in everyday living to ensure that these groups can afford normal subsistence expenses. In model (2), *Treated* denotes whether a household in a province has implemented the IURMI policy. T denotes the point in time at which the IURMI policy began to demonstrate effects. The policy effects are measured based on whether γ_1, the coefficient of $T^*Treated_i$, is significant. If γ_1 is negative and significant, the IURMI system or general fiscal subsidies are effective in reducing household education burden; if γ_2 is negative and significant, the policies' influences on household education burden have peer effects. The definitions of the other variables in model (2) are the same as those in model (1).

In the second part of the empirical analysis, the following spatial mediating effect model is constructed to test the spatial transmission mechanism. At stage 1, we perform a regression analysis for the catastrophic healthcare expenditure of a closely related household CHE_j and the education burden EDU_i of household i using the spatial Durbin model. At stage 2, we perform a regression analysis of the catastrophic healthcare expenditure of a closely related household CHE_j and the net transfer payment M_i by the household i using the spatial Durbin model. At stage 3, we perform a regression analysis of the catastrophic healthcare expenditure of a closely related household CHE_j, the net transfer payment M_i by the household i, and the education burden EDU_i of household i using the spatial Durbin model.

$$
\begin{aligned}
EDU_i &= \rho wEDU_j + \beta_1 CHE_i + \delta_1 wCHE_j + \beta X \\
&\quad + \delta wX + \mu \qquad \text{(Stage 1)} \\
M_i &= \rho wM_j + \beta_1 CHE_i + \delta_1 wCHE_j + \beta X \\
&\quad + \delta wX + \mu \qquad \text{(Stage 2)} \\
\mathrm{EDU_i} &= \rho \mathrm{wEDU_j} + \beta_1 \mathrm{M_i} + \delta_1 \mathrm{wM_j} + \beta_2 CHE_i + \delta_2 wCHE_j \\
&\quad + \beta \mathrm{X} + \delta \mathrm{wX} + \mu \qquad \text{(Stage 3)}
\end{aligned}
$$

In the model, the explained variable *EDU* is the household education burden. The core explanatory variable *CHE* is the household's catastrophic healthcare expenditure. M is a mediating variable that is measured by whether the household has a net transfer payment over the past 12 months, namely, the difference between the total transfer payment the household made to other households at no cost and the total transfer payment the household received from other households at no cost. A positive value for M indicates a net transfer payment, and the variable is assigned a value of 1; otherwise, a value of 0 is assigned to the variable. During the three stages of the regression analysis, if the regression coefficients of the core explanatory variable at stage 1 and stage 2 and the mediating variable at stage 3 are all significant, then there is a mediating effect. ρ denotes the spatial correlation of the household education burden and the mediating variable; $\rho < 0$ indicates that there is a spatial substitute effect; $\rho > 0$ denotes that there is a spatial spillover effect, and $\rho = 0$ denotes that there is no spatial effect. The definitions of other variables are the same as those in model (1).

Dataset

The CFPS datasets for 2014 and 2018 collected by the Institute of Social Science Survey of Peking University are used for this study for two main reasons. First, the datasets contain abundant information on households' expenditures on healthcare and education, transfer payments, and public service utilization. Further, the full implementation of the IURMI programme

TABLE 2 | Regression results.

Variable \ Model	Spatial Dobbin model (model 1)	Spatial DID model (model 2)	Spatial DID model (model 2)
*w** catastrophic healthcare expenditure	0.0017*	0.0031**	0.0038***
	(0.0010)	(0.0012)	(0.0014)
*w** household income level	0.0008***	0.0013***	0.0016***
	(0.0002)	(0.0001)	(0.0001)
*w** preferred object for borrowing	0.0003*	0.0002*	0.0003*
	(0.0002)	(0.0001)	(0.0001)
*w** household receipt of a fiscal subsidy	−0.0001	−0.0001	
	(0.0007)	(0.0001)	
*w** degree of participation in social medical insurance	−0.0007		
	(0.0008)		
*w** mortgage	−0.0010	0.0002	0.00007
	(0.0011)	(0.0011)	(0.0012)
T* Treated		−0.0012	0.0008
		(0.0024)	(0.0008)
*w** T		−0.0015**	−0.0015**
		(0.0006)	(0.0007)
*w** Treated		−0.0007	−0.0036*
		(0.0016)	(0.0019)
*w** T* Treated		−0.0010	0.0007
		(0.0026)	(0.0007)
ρ	−0.0014*	−0.0034***	−0.0038***
	(0.0007)	(0.0007)	(0.0008)
LM test	[0.0000]	[0.0000]	[0.0000]
Wald test	[0.0000]	[0.0000]	[0.0000]
Adjusted R^2	0.5412	0.5304	0.5296

(1) The brackets are heteroscedasticity robust standard errors.
*(2) *, **, and *** are statistically significant at the significance levels of 10, 5, and 1%, respectively.*
(3) The result of LM test and Wald test are marked with p-value.

across China began in 2016; however, Chongqing, Tianjin, and Guangdong implemented the policy prior to that date. Therefore, the datasets for 2014 and 2018 provide appropriate information to analyze the influences of health shocks and the education burden and to analyze the spatial transmission mechanism of the influences, against the backdrop of the IURMI policy. Second, the data selected reflect three different micro levels (i.e., individual, household, and community) and provide a vivid picture of the changes in China's education, healthcare, and social welfare.

As the 2018 dataset does not contain a village code, in constructing the weight matrix, villages are matched with their codes in 2014. Further, records with missing information or inappropriate records within raw data were eliminated; therefore, a sample of 1,665 valid records was obtained.

RESULTS

Descriptive Statistics

Table 1 presents the descriptive statistics of the 2018 dataset. Households' average level of education burden is 21.93%. As a non-discretionary expenditure, education spending accounts for a relatively high proportion of households' daily consumption, indicating that using household education burden to examine the spatial influence of households' spending decisions is reasonable. The probability of occurrence of catastrophic healthcare expenditure is 7.63%. 33.44% of households receive a net transfer payment. The average household income is 19,632.17 yuan (about 3,100 US dollars), and 57.29% of the households in the sample receive general fiscal subsidies. The high proportion of households receiving general fiscal subsidies indicates that when both the household education burden and catastrophic healthcare expenditure are considered together, the overall risk of relative poverty increases. Among the households in the sample, 82.52% participate in social medical insurance. Further, the standard deviation of each indicator is relatively large, an indication that currently, there are significant differences in the living conditions among rural households in China.

Impacts of Health Shocks on Household Education Burden

In order to verify the rationality of spatial Durbin model selected in this study, we first conducted Moran's I test and LM test. Moran's I test is widely used to verify the spatial correlation of variables and LM test provides suggestions for spatial model selections (34). Moran's I test results of household education burden and net transfer payment are −0.3215 (significant at 1% level) and −0.2852 (significant at 1% level), respectively. The result shows that two variables have spatial correlation. In

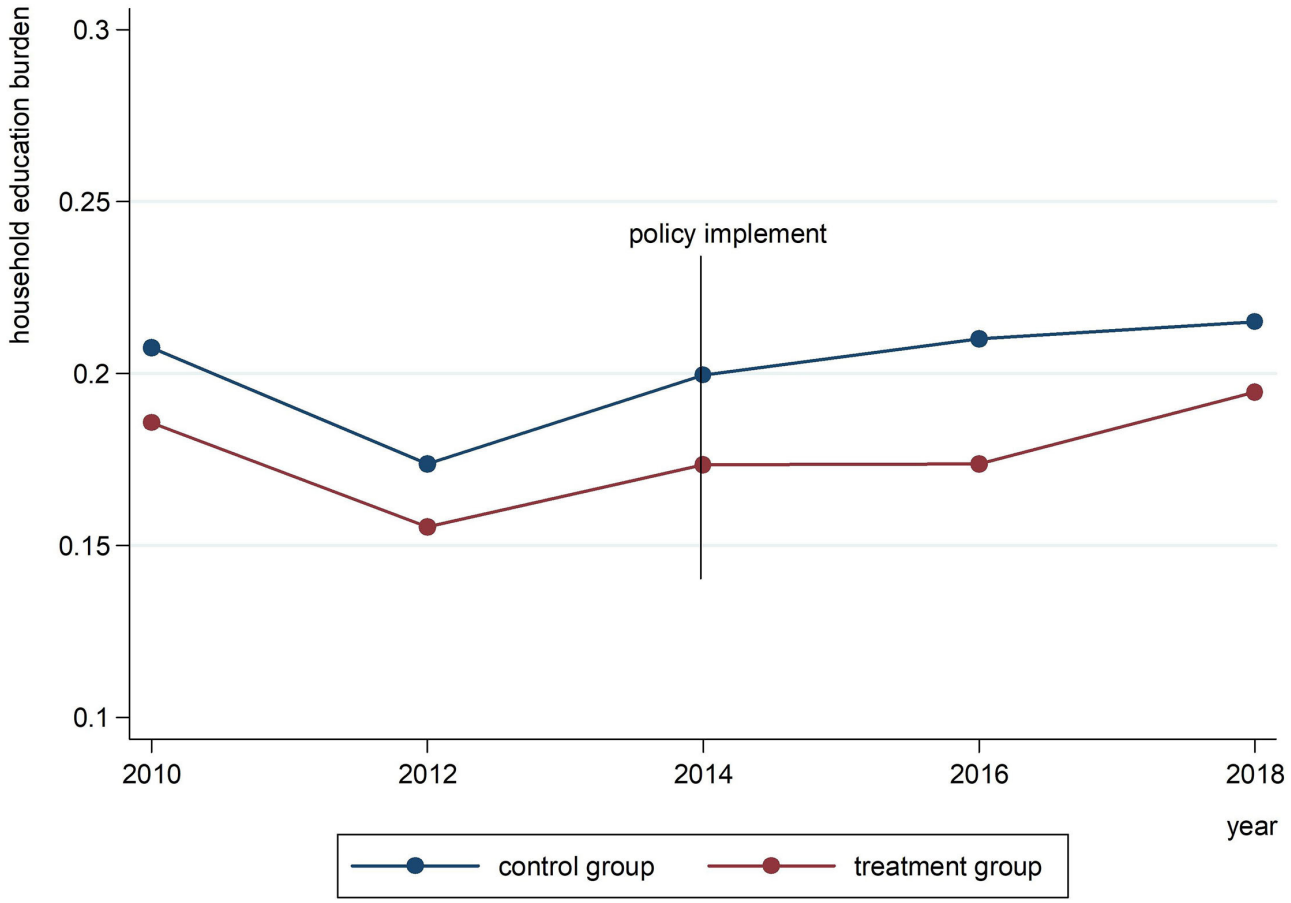

FIGURE 2 | The parallel trend test.

Table 2, based on the LM test, the null hypothesis that there is neither spatial nor error dependence is rejected at the 1% level under all three models. In this case, the spatial Durbin model is superior to other spatial models (35). Next, we conducted Wald test. The results show that the Wald tests all reject the null hypothesis. It is reasonable to use the spatial Durbin model in terms of data.

In addition, we used the CFPS datasets over the years to carry out the parallel trend test. The dots in **Figure 2** below represent the average level of household education burden in each year. Before the implementation of the IURMI policy, the trend of the treatment group is parallel to that of the control group between 2010 and 2014, and the average household education burden of the control group is higher than that of the treatment group, which may be related to the high level of economic development of Tianjin, Chongqing and Guangdong.

In **Table 2**, column 2 presents the results for the spatial Durbin model; column 3 presents the result for the spatial DID model in which adoption of the IURMI policy is the explanatory variable, and column 4 presents the result for the spatial DID model in which the interaction between two variables (i.e., adoption of the IURMI policy and the receipt of a fiscal subsidy) is the explanatory variable. The regression coefficient of *w**catastrophic healthcare expenditure, which warrants special attention in all three models, is positive and significant at the 1, 5, and 10% levels; this finding indicates that when a household suffers health shocks, the catastrophic healthcare expenditure incurred by this household will significantly increase the education burden of closely related households, suggesting that currently, the two non-discretionary household expenditures—healthcare and education—influence each other. Further analysis indicates that neither variables *w**household receipt of a fiscal subsidy and *w**degree of participation in social medical insurance in model 1 nor the coefficients of T*Treated and *w**T*Treated in model 2 and 3 are significant at the 10% level. This finding suggests that both the IURMI policy and the government's general fiscal subsidy do not significantly reduce household education burden. The above results indicate that the targets of different social security policies may have interactive influences on each other through specific spatial transmission mechanisms. Although single rescue policy (e.g., the medical insurance policy) may be effective with a single policy goal (e.g., a household's catastrophic healthcare expenditure), after considering the social network relations between households and the interactive influences

TABLE 3 | Regression results.

Model / Variable	Stage 1	Stage 2	Stage 3
w^*catastrophic healthcare expenditure	0.0017*	0.0006*	0.0036*
	(0.0010)	(0.0003)	(0.0019)
net transfer payment			0.0027*
			(0.0017)
w*household income level	0.0008***	0.0004***	0.0012***
	(0.0002)	(0.0000)	(0.0004)
w*preferred object for borrowing	0.0003*	0.0001***	0.0006***
	(0.0002)	(0.0000)	(0.0003)
w* household receipt of a fiscal subsidy	−0.0001	−0.0005**	0.0006
	(0.0007)	(0.0002)	(0.0015)
w^*degree of participation in social medical insurance	–0.0007	−0.0011***	−0.0014
	(0.0008)	(0.0003)	(0.0016)
w* mortgage	−0.0010	−0.0004	−0.0020
	(0.0011)	(0.0003)	(0.0021)
ρ	−0.0014*	−0.0005**	−0.0028*
	(0.0007)	(0.0002)	(0.0015)
LM Test	[0.0000]	[0.0000]	[0.0000]
Wald test	[0.0000]	[0.0000]	[0.0000]
Adjusted R^2	0.5412	0.4981	0.5473

(1) The brackets are heteroscedasticity robust standard errors.
*(2) *, **, and *** are statistically significant at the significance levels of 10, 5, and 1%, respectively.*
(3) The result of LM test and Wald test are marked with p-value.

between different policy targets, the original rescue policy does not have a spillover effect on other policy goals (e.g., household education burden). This conclusion further validates the importance of establishing the mechanism proposed by this study to coordinate different rescue policies.

The other variables have the same signs in the regression results under the three models; although certain variables are not significant, such results are consistent with the expected results. The coefficient of w*household income level is significant at the 1% level. This finding implies that the income level of closely related households is positively correlated with the household education burden and that the households are likely to bear the risk together; if the social network of the household has a fragile economic capacity, the health shocks will increase the risk that households in the social network as a whole may fall into relative poverty. w*preferred object for borrowing is significant at the 10% level, indicating the assumption that rural households decrease risk by borrowing from households in the same village is to a certain extent reasonable; the higher the tendency that the household borrows from parents, relatives, and good friends, the more likely it is that the household education burden will be aggravated. ρ is negative and significant, indicating that there is a substitution effect between household education burden and that close households in the same village may help each other with paying for education.

Impact Mechanism Between Health Shocks and Household Education Burden

The above conclusions confirm that there are interactive spatial influences between health shocks and household education burden, but do not clarify the influencing mechanism. **Table 3** employs the spatial mediating effect to analyze the mechanism at three stages.

For all three stages, the LM test and Wald test result rejects the null hypothesis at the 1% level, indicating that the spatial Durbin model is reasonable to use. The estimate of the impact of catastrophic healthcare expenditure on household education burden derived under the spatial Durbin model at stage 1 of the analysis is exactly the same as the result derived from model 1 in **Table 2**. At stage 2, the results of the spatial Durbin model that analyses catastrophic healthcare expenditures and households' net transfer payment indicate that w^*catastrophic healthcare expenditure is positive and significant at the 10% level, indicating that if a household incurs a catastrophic healthcare expenditure, the probability that the household of closely related households will occur a net transfer payment will increase; that is, closely related households in the same village may borrow from each other. At stage 3, the results of the spatial Durbin model that analyses households' catastrophic healthcare expenditures, net transfer payments, and education burden indicate that w^*catastrophic healthcare expenditure is still positive and significant at the 10% level, once again substantiating that the targets of the two rescue policies investigated by the study—healthcare and education—may affect each other. Further, net transfer payment is also positive and significant at the 10% level. The results of the three-stage regression analysis using the comprehensive mediating effect model confirm that when a household suffers health shocks and incurs a catastrophic healthcare expenditure, the economic impacts may increase the probability that the closely related households in the same village will occur a net transfer payment, and further change the consumption budget constraints and

increase the education burden of closely related households. This transmission of economic impacts occurs via the inter-household social network when households provide economic support to each other.

The regression results for other variables in **Table 3** essentially have the same signs as those in **Table 2**. ρ is negative at all three stages of the regression analysis, indicating that both household education burden and transfer payments have a spatial substitute effect. This finding indirectly substantiates that transfer payments are a mediating path through which households help each other pay for healthcare.

CONCLUSIONS AND IMPLICATIONS

Conclusions

This study uses a dataset from rural areas in the CFPS database and two major non-discretionary household expenditures (i.e., healthcare and education) as examples to investigate the two major issues from the perspective of relative poverty alleviation. First, this study employs a spatial Durbin model and spatial DID model to investigate, when a household suffers health shocks, the influence of the impacts on the education burden of closely related households and to test the effect of an existing single rescue policy in this circumstance. Second, this study employs a spatial mediating effect model to analyze the transmission mechanism for the health shocks and household education burden. The results from this study indicate that in rural China, when a household suffers health shocks, the economic impacts may increase the probability that the closely related households in the same village will occur a net transfer payment and further change the consumption budget constraints and increase the education burden of closely related households via the inter-household social network when households provide economic support to each other. This conclusion indicates that the targets of the two rescue policies—healthcare and education—may influence each other. The results from this study further confirm that single rescue policy does not have a spillover effect on other targets and offer evidence that supports establishing a mechanism to coordinate different rescue policies.

Implications and Policy-Making

In the future, to develop a systematically integrated, efficient, and multilevel social security system and achieve relative poverty alleviation, system designs should focus more on three aspects of governance coordination.

The first aspect is coordination between households with similar characteristics. The development of rescue policies should not be limited only to households that directly experience health shocks. The research conclusions of this study indicate that due to the existence of inter-household social networks, rescue policies should also consider households that have similar characteristics to those of the target households. A record system can be developed for similar households or communities to incorporate groups with similar characteristics into the scope of risk management, so as to overcome the challenges in identifying people in relative poverty and reduce the likelihood of region-wide relative poverty.

The second aspect is coordination between policy targets. The research conclusions of this study also indicate that the development of rescue policies should take into consideration the interactive influences between policy targets. For example, the targets of the education poverty alleviation policy should not only pertain to the population who are in educational poverty but should also incorporate the population in spending-based poverty. This approach will help to ensure that all policy goals are addressed in policies and to improve the effect of single rescue policies and the effect of relative poverty alleviation.

The third aspect is coordination between short-term and long-term rescue policies. When a household suffers from temporary external shocks, although single rescue policy may be effective in achieving a single policy goal of social security, after considering the inter-household social network and the interactive influence between policy goals, original rescue policies no longer generate significant effects regarding achieving other policy goals. Therefore, there is a need to establish a long-term sustainable rescue policy to eliminate other complications resulting from the interactions of policy goals.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: [http://www.isss.pku.edu.cn/cfps/sjzx/gksj/index.htm].

AUTHOR CONTRIBUTIONS

ZL: conceptualization, methodology, formal analysis, and writing-original draft preparation. XW: formal analysis, writing-review, editing, and supervision. YC: resources, data curation, validation, and supervision. All authors have read and agreed to the published version of the manuscript.

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Sociodemographic Determinants of Willingness and Extent to Pay for COVID-19 Vaccine in India

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Background: Responding to the fast transmission rates and increasing fatality rates, countries across the world expedited the development and deployment of the vaccine for coronavirus disease 2019 (COVID-19). Evaluation of individuals' willingness to pay (WTP) would provide pertinent information regarding future demand and financing preferences, which shall help to devise the effective payment strategy for COVID-19 vaccination.

Methods: A nationwide, cross-sectional, and self-administered online survey using a structured questionnaire was conducted to identify the sociodemographic determinants of willingness and extent to pay for COVID-19 vaccine in India. A non-probability convenience sampling followed by snowball sampling was employed to recruit participants (n = 3,341). The likelihood of sociodemographic determinants to predict willingness and extent to pay was modeled using the multivariate binary logistic regression analysis.

Results: Out of 3,341 participants, 68% (n = 2,271) were willingness to pay for COVID-19 vaccine. Results showed significantly higher odds for willingness to pay among participants who were single [adjusted odds ratio (aOR) = 1.394, $p < 0.01$] and having a family size of 4 members (aOR = 1.346, $p < 0.01$). The adjusted odds ratio sizably increased from 1.396 for participants whose monthly income was between INR 10,000 and 20,000/month to 2.240 for participants whose monthly income was above INR 50,000/month. Further, out of 2,271 of those participants who were willingness to pay for COVID-19 vaccine, majority (n = 1,246, 54.9%) of participants were willingness to pay below 50% of COVID-19 vaccine cost. This study found that those who are single (aOR = 0.688, $p < 0.01$), having an income between INR 20,000 and 50,000/month (aOR = 0.686, $p < 0.05$), and those who belonged to

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socially disadvantaged category (aOR = 0.450, $p < 0.01$) were estimated to have significantly lower odds of willingness to pay more than 50% of COVID-19 vaccine cost.

Conclusion: This study observed that majority of those participants who willingness to pay for COVID-19 vaccine were willingness to pay only up to 50% of COVID-19 vaccine and income was observed as a precursor predictor of the willingness and extent to pay for COVID-19 vaccine. The understanding on the willingness and extent to pay for COVID-19 vaccine and its sociodemographic determinants will be helpful for making the strategic decisions related to the financing of COVID vaccine in India.

Keywords: COVID-19, vaccine, willingness to pay, sociodemographic factors, India

INTRODUCTION

The unprecedented coronavirus disease 2019 (COVID-19) crisis has posed a substantial threat to global public health. COVID-19 has reported over 374.7 million cases and has claimed 5.66 million lives globally as on 31 January 2022 (1). The pandemic has resulted in a significant change in the behavior of our society and impacted individuals' physical and mental health (2). Due to the lockdown imposed worldwide to curb the spread of coronavirus disease 2019, the economic activities also suffered a setback, causing a reduction in employment opportunities (3). Coronavirus disease 2019 has impacted people's lives considerably by affecting their health and economic wellbeing (4).

As no antiviral drug has been accepted for the effective treatment of the novel coronavirus disease 2019 so far, vaccination has been identified as a crucial intervention to control its spread and potency (5). Vaccines are the most cost-effective health technology to contain an infectious disease and play a significant role in averting deaths and hospitalization caused by coronavirus disease 2019 (6). Responding to the fast transmission rates and increasing fatality rates (7), countries across the world dedicated themselves to develop the vaccine for coronavirus disease 2019. The global partnership culminated in the fastest development of a vaccine in history. Now that, the vaccine is available in the market; pharmaceutical companies, research organizations, and governments worldwide are expediting the vaccine's preparation, manufacturing, and administration to vaccinate maximum individuals across the varied age groups (8).

However, many challenges are associated with large-scale production and equitable access and distribution of the vaccine. The manufacturers and the government are accelerating their efforts to achieve maximum vaccination coverage on the supply side. Still, the public's unexplored perception or valuation for COVID-19 vaccination on the demand side may hamper the successful establishment of vaccination campaigns (8). The vaccination cost, including the vaccine expenses, its dissemination, and administration, is sizably high (8). Currently, the government across the world, including India, is bearing the maximum cost of the vaccine and is making it available for free for the population (9). But, the cost of vaccine production and other indirect costs will lead to an immense fiscal burden on the government in the future (8). With the subsequent booster doses required to control the current pandemic and its future outbreaks, strategies are required to address issues of the financial affordability of the vaccine (10). The governments worldwide cannot regularly pay for booster shots for the population, as it adds to the fiscal deficit. The government may need to modify its course of action and require the public to pay a proportion of the vaccination cost, given its budget limitations on healthcare spending and the economic burden (3).

The cost of vaccination is a significant factor associated with the extent of willingness (11) to uptake the vaccine despite its known efficacy. Therefore, it becomes imperative to know if the people would be willing to purchase the vaccine. The willingness to pay (WTP) for vaccination is a monetary measure of people's inclination and perception for vaccination, indicating the trade-off between the benefits of the vaccination and the personal economic cost (12, 13). Evaluation of individuals' WTP would provide pertinent information regarding future demand and financing preferences, which shall help to devise the best payment strategy for COVID-19 vaccination (8, 14).

Studies have found that willingness to pay is significantly affected by various sociodemographic determinants (12, 14). The relationship of these determinants with WTP varies in different communities. The sociodemographic determinants that influence WTP for vaccination include age, gender, social category, education, occupation, income, family size, marital status, etc.

The willingness to pay may be higher in older people than the younger ones, as the elderly are more vulnerable and at a relatively higher risk of getting inflicted with COVID-19 (15). In the Indian context, "Scheduled Caste" (SC), "Scheduled Tribes" (STs), and "Other Backward Classes" (OBCs) are categorized as the socially disadvantaged groups (16), as they straggle behind the others due to their economic and social backwardness. Both the gender and being part of socially disadvantaged group affect the willingness to pay for the vaccine. A study reported that females and the Schedule Caste/Tribe social groups were willingness to pay lesser for COVID-19 vaccination (5). Education can positively influence WTP, as more knowledge increases awareness of the disease. Occupation can significantly predict willingness to pay, as individuals associated with healthcare or public dealing would be more willingness to pay, considering the higher risk of infection. However,

some studies have also reported that occupation is not a significant predictor for vaccination (17) and those with better educational status (having Bachelor's degree) was negatively associated with COVID-19 vaccination (18). Individuals with low intention for vaccine uptake also negatively influence willingness to pay for the vaccine cost. Income has a strong association with WTP, as individuals with higher income can afford the vaccine and would be willingness to pay more (5, 8). Family size may also significantly affect willingness to pay because an increase in family size would increase the financial burden, thereby lowering saving-income ratios (19). Similarly, an unmarried/single individual may be more willingness to pay due to less financial responsibilities than a married individual.

It is evident that the sociodemographic indicators influence WTP to a great extent. Hence, it becomes vital for the government and organizations to identify the determinants affecting WTP for COVID-19 vaccination and their association to formulate interventions for specific populations (14). Literature on WTP estimation and identification of the related determinants for COVID-19 vaccine in India is limited. In this context, this study was conducted to identify the sociodemographic determinants of willingness and extent to pay for COVID-19 vaccine in India. This study covers a wider geographic area, including all the regions of India, thus it would be helpful for the government and policymakers to devise population and region-specific strategies for COVID-19 vaccine financing.

METHODOLOGY

Study Design and Sample

This study following a cross-sectional study design was conducted through a nationwide self-administered online survey using a structured questionnaire between the period of October 2020 and December 2020 in India. The survey was conducted before the commencement of COVID-19 vaccination in India and included only the participants aged 18 years and above who are currently living in India. This study adapted convenience sampling method to recruit the participants. The invitation link of this study questionnaire was disseminated through the social media platforms such as WhatsApp, Facebook, Twitter, Telegram, and emails. This study considered only those participants who had access to internet-enabled devices such as desktop, laptop, smartphone, tablet, and alike. This study, therefore, included only those participants who have the ability to read though and they lack formal education. Followed by that, this study further employed snowball sampling method to recruit additional participants by requesting invited participants to share the invitation link (Google Forms) to their peers and contacts. The Google Forms contained the contact details of the investigator to facilitate the participants in this study, if they require. Subsequently, a number of study participants who required assistance in filling up the form directly contacted the investigators, which further facilitated the completion of the questionnaire. The minimum required sample size ranged between 433 and 577 based on expected proportion of 25–50% population willingness to pay for vaccine with 5% absolute precision, 1.5 as the assumed design effect, and 95% CI (20). Nevertheless, this study recruited a total of 3,341 participants to understand the factors associated with willingness to pay.

Study Questionnaire

The questionnaire for the survey was prepared in the English language and was translated to local language for the dissemination of the questionnaire nationwide using the Google Forms. This self-administered questionnaire primarily consisted of multiple sections, such as sections assessing sociodemographic characteristics, knowledge and perception toward COVID-19, information sources of vaccine, and participant's willingness to accept and to pay for the proposed COVID-19 vaccine (full complete doses in the vaccine schedule). Out of these varied domains of this broad questionnaire, this study focused on the sociodemographic factors associated with the willingness and extent to pay for COVID-19 vaccination in India.

Statistical Analysis

The primary outcome of this study is to determine the proportion of population spread across the varied socioeconomic and demographic groups who are willingness to pay for COVID-19 vaccine across in India and to further identify the particular sociodemographic variables that play a significant factor to determine the willingness and extent to pay for COVID-19 vaccine. The respondents were asked that what percentage of the vaccine cost they are planning to pay comfortably. Those who marked "0%" were classified as the "not willingness to pay" group and those who marked any of the other response (25% and below, 26–50%, 51–75%, and more than 75%) were classified to the "willingness to pay" group. Descriptive statistics were performed followed by bivariate analyses to assess the presence of any association between sociodemographic variables and willingness/extent to pay for COVID-19 vaccine in India. This study employed the multivariate binary logistic regression analysis to identify the sociodemographic determinants of the willingness and extent to pay in two steps. In the first step, the multivariate binary logistic regression analysis was performed on the entire sample size of 3,341 participants. In the second step, the regression was employed on 2,271 participants who were reported to be willingness to pay for COVID-19 vaccine. The extent of willingness to pay ranged between the four categories (25% and below, 26–50%, 51–75%, and more than 75%) and since the frequency count of different categories of independent variables (sociodemographic factors) were quite low, therefore, the four categories of dependent variable (extent to willingness to pay) were merged into two categories (below 50% and above 50%) and the multivariate binary logistic regression analysis was subsequently performed (21). The adjusted odds ratios with 95% CI and p-values ($p < 0.05$) were reported. The data were analyzed using the IBM SPSS Statistics version 25.

Ethical Consideration

This study was approved by the Institutional Research Ethics Committee, Post Graduate Institute of Medical Education and Research (PGIMER), <city>Chandigarh</city>, India (INT/IEC/2020/SPL-795). The informed consent was obtained at the beginning of the survey and only those participants provided consent taken to the webpage of the questionnaire.

RESULTS

Willingness to Pay and Sociodemographic Factors

Table 1 presents the details of sociodemographic characteristics of the participants and proportion of willingness to pay for COVID-19 vaccine. Out of 3,341 participants, 51.4% ($n = 1,718$) were females. Majority of the participants ($n = 1,835$, 54.6%) are aged between 26 and 45 years and were reported to be married ($n = 2,022$, 60.5%). A large proportion ($n = 1,272$, 38.1%) of participants were educated up to primary school level, while 29.3% ($n = 978$) of participants were lacked formal education. Around 32.7% ($n = 1,091$) of participants were educated more than primary school level. Participants who were working (government or private employees and selfemployed) recorded the highest proportion of about 58.2% ($n = 1,944$) as compared to 22.2% ($n = 742$) of participants who were not working and 19.6% ($n = 655$) who were students. A considerable number of the participants ($n = 1,413$, 42.3%) reported having monthly income "above INR 50,000," while 16.5% ($n = 552$) of the participants was having a monthly income below INR 10,000. Looking at the family size, 41.1% ($n = 1,372$) of the participants reported a family size of "more than 4 members." Majority of the participants (62%, $n = 2,073$) belonged to general category, whereas socially disadvantaged categories, namely, Other Backward Class (OBC), Scheduled Caste (SC), and Scheduled Tribes (STs) recorded a proportion of 20.2 ($n = 675$), 11.6 ($n = 387$), and 6.2% ($n = 206$), respectively. Of the total participants, North region of the country recorded the highest proportion of 34.8% ($n = 1,162$), whereas the South region of the country recorded the least proportion of 14.6% ($n = 487$).

The bivariate analysis between sociodemographic characteristics and willingness to pay for COVID-19 vaccine is given in **Table 2**. Notably, across all the sociodemographic groups, number of participants who are willingness to pay for COVID-19 vaccine is higher than that of those who are not willingness to pay for COVID-19 vaccine (**Table 2**). The bivariate analysis showed that sociodemographic variables such as age, marital status, education, occupation, income, family size, and social category are significantly and independently associated to willingness to pay for COVID-19 vaccine (p-value < 0.05). Majority of the females ($n = 1,166$) and males ($n = 1,105$) were willingness to pay for COVID-19 vaccine and females (51.3%) recorded higher percentage than males (48.7%). Those who were willingness to pay among the "26 to 45 years" age group (53.7%) were sizably greater than the other age groups. Further, willingness to pay for COVID-19 vaccine is higher for those who were married (57.7%), those who completed their primary school level education (39.3%), those who are employed (56.7%), those having income "above INR 50,000/month" (45.7%), those with family size of four members (39.5%), and those who belong to the general category (64.5%).

The multivariate binary logistic regression analysis between sociodemographic variables and willingness to pay for COVID-19 vaccine is given in **Table 3**. The Nagelkerke R^2 showed that the model is explaining 5.8% of the variation in willingness to pay for COVID-19 vaccine. The Omnibus Tests of Model Coefficients gives a chi-square of 141.227 significant beyond 0.001 indicates that the model (with explanatory variables) has a good fit. The analysis estimated the overall accuracy of 69.7% in correctly predicting the probabilities. Sociodemographic variables such as marital status, education, occupation, income, family size, and category observed to be significantly associated with willingness to pay for COVID-19 vaccine after adjusting for other variables. The analysis showed significantly higher odds for willingness to pay among participants who were single than the married

TABLE 1 | Description of socio-demographic factors for willingness to pay.

Variables	*N* (%)
Gender	
Female	1,718 (51.4)
Male	1,623 (48.6)
Age	
25 and below	1,024 (30.6)
26–45 years	1,835 (54.9)
46 and above	482 (14.4)
Marital status	
Married	2,022 (60.5)
Single (Not married/divorced/widowed/-separated)	1,319 (39.5)
Education	
No formal education	978 (29.3)
Primary school level	1,272 (38.1)
More than primary school	1,091 (32.7)
Occupation	
Not working	742 (22.2)
Student	655 (19.6)
Employed (Government or private employees and self-employed)	1,944 (58.2)
Income	
Below INR 10,000/month	552 (16.5)
INR 10,000 to INR 20,000/month	531 (15.9)
INR 20,000 to INR 50,000/month	845 (25.3)
Above INR 50,000/month	1,413 (42.3)
Family size	
More than 4 members	1,372 (41.1)
4 members	1,241 (37.1)
Less than 4 members	728 (21.8)
Social category	
General	2,073 (62.0)
OBC	675 (20.2)
SC	387 (11.6)
ST	206 (6.2)
Region	
East & north east	990 (29.6)
West & central	702 (21.0)
North	1,162 (34.8)
South	487 (14.6)

TABLE 2 | Bivariate analysis between sociodemographic characteristics and willingness to pay.

Variables	Willingness to pay		Chi-square value	*p*-value
	Not willing to pay (n = 1,070, 32%)	Willing to pay (n = 2,271, 68%)		
Gender			0.018	0.894
Female	552 (51.6%)	1,166 (51.3%)		
Male	518 (48.4%)	1,105 (48.7%)		
Age			11.673	0.003
25 and below	286 (26.7%)	738 (32.5%)		
26–45 years	616 (57.6%)	1,219 (53.7%)		
46 and above	168 (15.7%)	314 (13.8%)		
Marital status			23.150	<0.001
Married	711 (66.4%)	1,311 (57.7%)		
Single (Not married/divorced/widowed/separated)	359 (33.6%)	960 (42.3%)		
Education			29.368	<0.001
No formal education	274 (25.6%)	704 (31.0%)		
Primary school level	379 (35.4%)	893 (39.3%)		
More than primary school	417 (39.0%)	674 (29.7%)		
Occupation			7.917	0.019
Not working	229 (21.4%)	513 (22.6%)		
Student	184 (17.2%)	471 (20.7%)		
Employed (Government or private employees and self-employed)	657 (61.4%)	1,287 (56.7%)		
Income			45.095	<0.001
Below INR 10,000/month	228 (21.3%)	324 (14.3%)		
INR 10,000–20,000/month	192 (17.9%)	339 (14.9%)		
INR 20,000–50,000/month	274 (25.6%)	571 (25.1%)		
Above INR 50,000/month	376 (35.1%)	1,037 (45.7%)		
Family size			16.306	<0.001
More than four members	477 (44.6%)	895 (39.4%)		
Four members	345 (32.2%)	896 (39.5%)		
Less than four members	248 (23.2%)	480 (21.1%)		
Social category			22.754	<0.001
General	609 (56.9%)	1,464 (64.5%)		
OBC	242 (22.6%)	433 (19.1%)		
SC	155 (14.5%)	232 (10.2%)		
ST	64 (6.0%)	142 (6.3%)		
Region			2.267	0.519
East & north east	308 (28.8%)	682 (30.0%)		
West & central	214 (20.0%)	488 (21.5%)		
North	385 (36.0%)	777 (34.2%)		
South	163 (15.2%)	324 (14.3%)		

ones [adjusted odds ratio (aOR) = 1.394, 95% CI: 1.146–1.695, p-value < 0.01]. All the income categories (vs. monthly income <10,000 INR) were found to be significant (p-value < 0.05). The adjusted odds ratio sizably increased from 1.396 for participants whose monthly income was between INR 10,000 and 20,000/month to 2.240 for participants with monthly income above INR 50,000/month. This is indicative of the fact that higher the income, more the chances for willingness to pay for COVID-19 vaccine. The participants who were having a family size of four members (vs. more than four members) (aOR = 1.346, 95% CI: 1.134–1.597, $p < 0.01$) had significant higher odds for willingness to pay. The participants who belonged to the disadvantaged categories, namely, "Other Backward Class" (aOR = 0.797, 95% CI: 0.657–0.968, $p = 0.022$) and "Scheduled Caste" (aOR = 0.682, 95% CI: 0.541–0.860, p-value < 0.01), were observed to be less probable for willingness to pay. Similarly, participants who were educated more than primary school level (vs. participants who lacked formal education) (aOR = 0.666, 95% CI: 0.540–0.821, $p < 0.001$) and participants who were employed (vs. not working) (aOR = 0.599, 95% CI: 0.483–0.743, $p < 0.01$), as well those who

were students (aOR = 0.690, 95% CI: 0.530–0.898, $p = 0.006$) registered significantly decreased odds for willingness to pay.

Extent of Willingness to Pay and Sociodemographic Factors

Table 4 presents the bivariate analysis between sociodemographic characteristics and extent of willingness to pay for COVID-19 vaccine. Out of 2,271 participants, who were willingness to pay, around 54.9% ($n = 1,246$) were ready to pay up to 50% of COVID-19 vaccine cost and the remaining 45.1% ($n = 1,025$) were willingness to pay more than 50% of COVID-19 vaccine cost. Sociodemographic variables, namely, gender, age, marital status, education, occupation, income, family size, and social category, were found to be significantly associated with extent of willingness to pay (p-value < 0.05) as per the bivariate analysis. Majority of those who were willingness to pay more than 50% of COVID-19 vaccine cost are males compared to females (51.3 vs. 48.3%, $p = 0.008$). In contrast, more than half of the participants who were willing to pay up to 50% were females (53.9%) against their male counterparts (46.1%). Participants who are willingness to pay more than 50% majorly belonged to the "26 to 45 years" age group (56.2%). Similarly, married participants dominated both the group of those who "willingness to pay up to 50%" (52.2 vs. 47.8%, $p < 0.01$) and those who are "willingness to pay more than 50%" (64.4 vs. 35.6%, $p < 0.01$) of COVID-19 vaccine cost as compared to single (not married/divorced/separated/widowed) participants. Strikingly, least percentage of those participants who were willingness to pay more than 50% were educated more than primary school level as compared to participants who lacked formal education (25.1 vs. 35.7%, $p < 0.001$). A great majority of those participants who were willingness to pay more than 50% are employed as compared to non-working participants (69.4 vs. 14.3%, $p < 0.001$). The higher income groups observed to be having the higher percentage of those participants who were willingness to pay more than 50%. The participants who are in the income group of "more than INR 50,000/month" recorded to be significantly higher in number as compared to those participants who are earning INR below 1,000/month (59.8 vs. 10.3%, $p < 0.001$). Difference in the percentage distribution between the groups of those participants who are having family size less than four members (37.5%) and four members (38.4%) was minimal. Only 24.1% of those participants who willingness to pay more than 50% were having a family size more than 4 members. Around 68.4% of those participants who were willingness to pay more than 50 and 61.2% of those participants who were willingness to pay up to 50% belonged to general category.

The results of the multivariate binary logistic regression analysis between sociodemographic variables and extent of willingness to pay for COVID-19 vaccine are given in **Table 5**. The analysis estimated adjusted odds ratios (aOR) for those participants who were willingness to pay more than 50% of COVID-19 vaccine cost. The Omnibus Tests of Model Coefficients recorded a chi-square of 262.487 significant beyond 0.001 that indicates that the model (with explanatory variables) has a good fit. The Nagelkerke R^2 shows that the model is explaining 14.6% of the results. The analysis estimated the overall accuracy of 64.8% in correctly predicting the probability. Sociodemographic variables such as marital status, occupation, income, family size, and social category were observed to be significantly associated with extent of willingness to pay for COVID-19 vaccine after adjusting for other variables (**Table 5**).

This study found that those participants who are employed (vs. not working) (aOR = 1.930, 95% CI: 1.469–2.536, $p < 0.001$), having income above INR 50,000/month (vs. income below INR 10,000/month) (aOR = 1.851, 95% CI: 1.361–2.516, $p < 0.001$), and those participants having family size less than four members (vs. family more than four members) (aOR = 1.461, 95% CI: 1.148–1.859, $p = 0.002$) have significantly higher odds of willingness to pay more than 50% of COVID-19 vaccine cost. In contrast, the variable groups such as those participants who are single (not married/divorced/separated/widowed) (vs. married) (aOR = 0.688, 95% CI: 0.552–0.858, $p = 0.001$), having an income between INR 20,000 and 50,000/month (vs. income below INR 10,000/month) (aOR = 0.686, 95% CI: 0.501–0.939, $p = 0.019$), and those who belonged to the SC category (vs. general social category) (aOR = 0.450, 95% CI: 0.327–0.619, $p < 0.001$) were estimated to have significantly lower odds of willingness to pay more than 50% of COVID-19 vaccine cost.

DISCUSSION

Studies conducted in low- and middle-income countries (LMICs) such as Malaysia (22), Indonesia (14), and Ecuador (23) reported that majority of the participants were willingness to pay for COVID-19 vaccine. Similarly, this study also recorded that around 68% of the participants were willingness to pay for COVID-19 vaccine, thereby indicating relatively high demand for COVID-19 vaccine. This can be attributed to the high impact of COVID-19 on health and economic life of the people (24). Literature on willingness to pay for vaccine in India is limited. One such study conducted in Bhopal district of India observed that despite high acceptance of COVID-19 vaccine among people, willingness to pay for COVID-19 vaccine is minimal (5), which is in contrast with this study. The difference may be due to the study design and methods adopted. Moreover, this particular study was conducted only in a particular geographical location in India. This study, in fact, is unique in itself, as it is one of the initial attempts made to assess the willingness and extent to pay for the proposed vaccine and to further examine its association with sociodemographic factors through a large online survey spanning across major geographical regions of India.

Results of the multivariate binary logistic regression analysis observed that marital status, education, occupation, income, family size, and social category are significant predictors of willingness to pay for COVID-19 vaccine. Specifically, being single, belonging to the higher-income group, and having a less family size have significantly higher odds for willingness to pay for COVID-19 vaccine. In the previous study conducted in India, those who were single recorded higher percentage in intention

TABLE 3 | Association between the sociodemographic variables and willingness to pay ($n = 3,341$) using the multivariate binary logistic regression analysis.

Variable	Coefficient	Adjusted OR (95% CI)[a]	*p*-value
Gender			
Female		Ref	
Male	0.044	1.044 (0.896–1.218)	0.579
Age			
25 and below		Ref	
26–45 years	−0.055	0.947 (0.765–1.171)	0.613
46 and above	0.023	1.023 (0.766–1.366)	0.877
Marital status			
Married		Ref	
Single (Not married/divorced/widowed/separated)	0.332	1.394 (1.146–1.695)	0.001
Education			
No formal education		Ref	
Primary school level	−0.092	0.912 (0.751–1.107)	0.353
More than primary school	−0.406	0.666 (0.540–0.821)	<0.001
Occupation			
Not working		Ref	
Student	−0.371	0.690 (0.530–0.898)	0.006
Employed (Government or private employees and self-employed)	−0.513	0.599 (0.483–0.743)	<0.001
Income			
Below INR 10,000/month		Ref	
INR 10,000–20,000/month	0.334	1.396 (1.078–1.809)	0.011
INR 20,000–50,000/month	0.425	1.530 (1.210–1.934)	<0.001
Above INR 50,000/month	0.807	2.240 (1.767–2.840)	<0.001
Family size			
More than four members		Ref	
Four members	0.297	1.346 (1.134–1.597)	0.001
Less than four members	0.016	1.016 (0.835–1.237)	0.871
Social category			
General		Ref	
OBC	−0.226	0.797 (0.657–0.968)	0.022
SC	−0.383	0.682 (0.541–0.860)	0.001
ST	−0.061	0.941 (0.680–1.301)	0.712
Region			
East & north east		Ref	
West & central	0.050	1.051 (0.845–1.308)	0.652
North	−0.096	0.908 (0.750–1.100)	0.324
South	−0.001	0.999 (0.778–1.283)	0.994

[a]*Adjusted OR (95% CI) = adjusted odds ratio and the corresponding 95% confidence interval.*

The analysis predicted probabilities for those who were willing to pay.

The Nagalkerke R-Square value (0.058) showed that the model explains 5.8% of the variation in willingness to pay for COVID vaccine as determined by set of socio-demographic predictors.

The Omnibus Tests of Model Coefficients gives a Chi-Square of 141.227 ($p < 0.001$) indicates the new model has a good fit.

The analysis estimated the overall accuracy of 69.7% in correctly predicting the probabilities.

to receive vaccine than those who were married (25), which indicates high demand for COVID-19 vaccine among this group. In this study, respondents having monthly income measured between INR 10,000 and 20,000, INR 20,000 and 50,000, and more than INR 50,000 recorded higher odds for willingness to pay. Most of the studies related to willingness to pay for COVID-19 vaccine, observed increasing income as a precursor predictor for willingness to pay (5, 8, 14, 22, 24). Hence, these study findings on income are in line with the existing literature. The participants of those who are having a family size of 4 members and less than four members recorded higher odds of 1.346 and 1.016, respectively, for willingness to pay. It indicates that the increased family size acts as an affordability barrier for the members to pay for COVID-19 vaccine cost. Literary evidence has also revealed that absence of affordability barrier is positively associated to the willingness to pay for COVID-19 vaccine (22). Similarly, the

TABLE 4 | Bivariate analysis between sociodemographic characteristics and extent of willingness to pay (n = 2,271).

Variables	Extent of willingness to pay (n = 2,271)		Chi-square value	p-value
	Willing to pay up to 50% (n = 1,246, 54.9%)	Willing to pay more than 50% (n=1,025, 45.1%)		
Gender			6.958	0.008
Female	671 (53.9%)	495 (48.3%)		
Male	575 (46.1%)	530 (51.7%)		
Age			18.112	<0.001
25 and below	450 (36.1%)	288 (28.1%)		
26–45 years	643 (51.6%)	576 (56.2%)		
46 and above	153 (12.3%)	161 (15.7%)		
Marital status			37.764	<0.001
Married	651 (52.2%)	660 (64.4%)		
Single (Not married/divorced/widowed/separated)	595 (47.8%)	365 (35.6%)		
Education			26.713	<0.001
No formal education	338 (27.1%)	366 (35.7%)		
Primary school level	491 (39.4%)	402 (39.2%)		
More than primary school	417 (33.5%)	257 (25.1%)		
Occupation			127.200	<0.001
Not working	366 (29.4%)	147 (14.3%)		
Student	304 (24.4%)	167 (16.3%)		
Employed (Government or private employees and self-employed)	576 (46.2%)	711 (69.4%)		
Income			159.864	<0.001
Below INR 10,000/month	218 (17.5%)	106 (10.3%)		
INR 10,000–20,000/month	203 (16.3%)	136 (13.3%)		
INR 20,000–50,000/month	401 (32.2%)	170 (16.6%)		
Above INR 50,000/month	424 (34.0%)	613 (59.8%)		
Family size			10.036	0.007
More than four members	511 (41.0%)	384 (37.5%)		
Four members	502 (40.3%)	394 (38.4%)		
Less than four members	233 (18.7%)	247 (24.1%)		
Social category			29.506	<0.001
General	763 (61.2%)	701 (68.4%)		
OBC	242 (19.4%)	191 (18.6%)		
SC	165 (13.2%)	67 (6.5%)		
ST	76 (6.1%)	66 (6.4%)		
Regions			2.195	0.533
East & north east	387 (31.1%)	295 (28.8%)		
West & central	266 (21.3%)	222 (21.7%)		
North	425 (34.1%)	352 (34.3%)		
South	168 (13.5%)	156 (15.2%)		

disadvantaged social categories such as OBC and SC registered lower odds than general category for willingness to pay.

Strikingly, this study found that those who were educated more than primary school level, which includes even those who completed graduation and postgraduation level recorded less odds for willingness to pay than those who lacked formal education, which is inconsistent with the existing literature in India (5). Similarly, this study found lower odds willingness to pay among participants who are employed than those who are not working. A study conducted in Malaysia, a LMIC, observed that education and employment level are not a significant predictor of willingness to pay for COVID-19 vaccine (11). In contrast, another study conducted in Ecuador observed that employment status is a significant positive predictor, whereas education level is insignificant predictor of willingness to pay (23). Many other studies in LMICs did not report education and occupation level, a significant predictor of willingness to pay for COVID-19 vaccine, though they found related variables

TABLE 5 | Association between the sociodemographic variables and extent of willingness to pay (n = 2,271) using the multivariate binary logistic regression analysis.

Variable	Coefficient	Adjusted OR (95% CI)[a]	*p*-value
Gender			
Female		Ref	
Male	0.048	1.049 (0.878–1.258)	0.609
Age			
25 and below		Ref	
26–45 years	−0.199	0.819 (0.647–1.037)	0.098
46 and above	−0.169	0.844 (0.602–1.185)	0.328
Marital Status			
Married		Ref	
Single	−0.374	0.688 (0.552–0.858)	0.001
Education			
No formal education		Ref	
Primary school level	−0.069	0.933 (0.751–1.160)	0.535
More than primary school	−0.214	0.807 (0.626–1.040)	0.097
Occupation			
Not working		Ref	
Student	0.026	1.026 (0.745–1.414)	0.875
Employed (Government or private employees and self-employed)	0.658	1.930 (1.469–2.536)	<0.001
Income			
Below INR 10,000/month		Ref	
INR 10,000–20,000/month	0.044	1.045 (0.743–1.470)	0.800
INR 20,000–50,000/month	−0.377	0.686 (0.501–0.939)	0.019
Above INR 50,000/month	0.616	1.851 (1.361–2.516)	<0.001
Family size			
More than four members		Ref	
Four members	0.143	1.154 (0.944–1.412)	0.163
Less than four members	0.379	1.461 (1.148–1.859)	0.002
Social category			
General		Ref	
OBC	−0.144	0.866 (0.685–1.094)	0.227
SC	−0.798	0.450 (0.327–0.619)	<0.001
ST	−0.023	0.978 (0.673–1.419)	0.905
Regions			
East & north east		Ref	
West & central	−0.027	0.973 (0.755–1.254)	0.834
North	0.019	1.020 (0.813–1.279)	0.867
South	−0.137	0.872 (0.647–1.175)	0.367

[a]Adjusted OR (95% CI) = adjusted odds ratio and the corresponding 95% confidence interval.

The analysis predicted probabilities for those who were willing to pay more than 50%.

The Omnibus Tests of Model Coefficients gives a Chi-Square of 141.227 ($p < 0.001$) indicates the new model has a good fit.

The Nagalkerke R^2 value (0.146) showed that the model explains 14.6% of the variation in extent of willingness to pay for COVID vaccine as determined by set of socio-demographic predictors.

The analysis estimated the overall accuracy of 64.8% in correctly predicting the probabilities.

such as being healthcare worker, knowledge toward disease and vaccination, employee size in workplace, and others significantly associated with willingness to pay (8, 14, 22). A study in Chile described that a great majority opined that government should finance the vaccine for all (24). Similarly, in another study, 63.92% discoursed that the government should provide COVID-19 vaccine for free (23). A study conducted in China reported that large proportion of the respondents believe that government and health insurance should pay finance some or all of COVID-19 vaccine cost (8). This could be the prime reason behind the educated and those who are employed were not willingness to pay for COVID-19 vaccine, as they may believe that it is the government or employers' responsibility to provide COVID-19 vaccines for its citizen and employees, respectively.

This study further explored the sociodemographic determinants of extent of willingness to pay. It recorded 54.9% of those participants who were willingness to pay for COVID-19 vaccine that were ready to pay up to 50% of COVID-19 vaccine cost. Previous study conducted in India reported an average willingness to pay around INR 141 (USD 1.9) for COVID-19 vaccine with full efficacy (5). In Malaysia, around 28.9% of the respondents willingness to pay an amount of USD 23 (22), whereas in Indonesia, a majority of 78.3% were willingness to pay USD 57.2 for COVID-19 vaccine (14)In this study, the multivariate binary logistic regression analysis results for extent of willingness to pay indicated that those who are employed, having higher income, and family size of less than four members have significantly higher odds of willingness to pay more than 50% of COVID-19 vaccine cost. Further, this study found those who are single, having an income between INR 20,000 and 50,000/month, which represents the middle-income class in India (26), and those who belonged to

SC category registered significantly lower odds for willingness to pay more than 50% of COVID-19 vaccine cost. Notably, specific sociodemographic determinants such as having above INR 50,000 per month and having family size less than four members found to be positively predicting both the willingness and extent to pay for COVID-19 vaccine, while factor namely belonging to a disadvantaged category negatively predicts the willingness and extent to pay for vaccine.

This study faces some limitations. First, as the study followed non-probability-based convenient and snowball sampling method to collect the required information, there may be a possible selection bias as the sample was not chosen at random. Further, this study cautions possible information bias, since the respondents may have a tendency to give socially-desirable responses. Therefore, the generalization of the findings of this study needs to be made with caution. Second, since this study followed cross-sectional design, the sociodemographic predictors of willingness and extent to pay for COVID-19 vaccine point toward associational relationships and not necessary a causal one. Longitudinal studies need to be conducted especially during different phases of the pandemic to confirm the causal temporal relationships with willingness and extent to pay for COVID-19 vaccine. Third, though the study attempted to cover the respondents from all the geographical locations of India, however, the southern Indian region elicited relatively less respondents and, therefore, was less represented as compared to other regions. Fourth, a sizable portion of the sample (around 32%) was not willingness to pay for the vaccine; the reasons for this need to be further explored possibly through mixed method approaches such as in-depth interviews, focus group discussions, and alike.

Despite the limitations, it is worth mentioning that the concept of willingness and extent to pay for COVID-19 vaccine and its sociodemographic determinants are not much discussed topics in India. The sample covered by this study through a nationwide online survey is relatively large (3,341 participants) comparing to previous nationwide studies on the similar theme (11, 22). Further, this study has provided a crucial information on the proportion of people who were willingness to pay COVID-19 vaccine cost up to certain magnitude, which can be used as a starting point for conducting similar temporal studies on the same theme to gather more evidence to identify a plausible range within which majority of Indians are willingness to pay out for COVID-19 vaccination out of their own pocket. In addition, this study attempted to explore and identify the specific sociodemographic factors that significantly predict both the willingness and extent to pay for COVID-19 vaccine, which shall help government and policymakers to design appropriate financing strategies to fund the cost of COVID-19 vaccine.

CONCLUSION

The devastating impact of COVID-19 on physical, mental, social, and economic life of the people has increased the demand for COVID-19 vaccine. This study is helpful for making the strategic decisions related to the financing of COVID-19 vaccine in India. This study observed that majority of those participants who willingness to pay for vaccine were willingness to pay only up to 50% of COVID-19 vaccine and income was observed as a precursor predictor of the willingness and extent to pay for vaccine. The honorable Prime Minister of India in his monthly radio broadcast announced booster dose for health and frontline workers (27), possibly extending to the public as well. India is a country with mixed health system where the involvement of private players in the vaccination is imperative to meet the increased demand for COVID-19 vaccine. Hence, the understanding on the willingness and extent to pay for COVID-19 vaccine and its sociodemographic determinants will help in effective and optimal financing and deployment strategies for COVID-19 vaccine.

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 Institutional Research Ethics Committee (INT/IEC/2020/SPL-795), Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TK and BPad conceptualized the study and designed the tools. TK, BPad, KJ, DS, LJ, JV, PS, VC, BPat, SK, RS, SP, SB, NR, VR, KG, BM, LS, MG, and AA conducted the study at national level and collected the data. All authors reviewed drafts, provided edits, and approved the final submission of the manuscript.

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Impacts of the Internet on Health Inequality and Healthcare Access: A Cross-Country Study

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Access to information and resources through the Internet has become an increasingly critical aspect of contemporary life. Based on the WHO Health Equity Assessment Toolkit (HEAT) and cross-country panel data, this paper investigates the effect of Internet access on health inequality across different income groups. The results indicate that access to the Internet significantly improves the average health condition and alleviates health inequality. In addition, employing cross-country data from the Global Burden of Disease (GBD) database, this paper further examines the social and economic determinants of access to healthcare. Specifically, it is found that Internet access significantly facilitates healthcare access and mitigates the negative impact of income inequality on healthcare access. Considered together, these findings shed light on the importance of the Internet in reducing health inequality and improving healthcare access.

Keywords: internet, health inequality, healthcare access, income inequality, cross-country

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INTRODUCTION

Reducing health inequality and improving healthcare access are of vital importance in the field of public health, both academically and practically speaking. On the one hand, health inequality, which generically refers to systematic differences in the health status or in the distribution of health resources between different population groups, has substantial social and economic impacts on individuals and societies (1, 2). On the other hand, addressing health literacy, enhancing the physician-patient relationship, and identifying cost-effective resources are essential means of promoting access to healthcare, which can translate into significant public health gains. One of the most prominent characteristics of current public health services is that healthcare has been undergoing a major digital transformation due to the extensive use of information and communication technologies (ICTs). In particular, the widespread diffusion of the Internet has enabled better access to health information and resources, generating both distributional and aggregate effects on health outcomes (3–6). For instance, web-based medical service (WBMS), which is defined broadly as a cooperative relationship between Internet technology and medical service, has been considered one of the most innovative health services in the digital age (7, 8). The use of WBMS, such as telehealth, eHealth, and mHealth, has greatly facilitated the distribution of health-related information and resources via the Internet across different social groups. Therefore, the increasing prevalence of the Internet has empowered people worldwide, in general and especially those in need, to access healthcare at the point of care or remotely. Healthcare providers have been using the Internet to enhance their skills and knowledge and, more importantly, to provide patients with assistance and guidance if necessary (9, 10). Despite the important role that Internet access plays in public health, relatively few studies have systematically examined the distributional and aggregate effects of the Internet on health outcomes.

To address this critical gap in the literature, this paper conducts a cross-country study to investigate the impacts of the Internet on health inequality and healthcare access. First, this paper quantifies the effect of Internet access on health inequality across different income groups. It is found that increased access to the Internet significantly reduces health inequality and improves the overall health condition. The gap in health status between the poor and the rich would be reduced if the Internet became more accessible. The pattern persists when we control for a wide range of variables that potentially influence health inequality in the estimation. Second, this paper explores the social and economic determinants of healthcare access. Specifically, among all of the factors included in the estimation, we focus on the impacts of Internet access, income inequality, and their interaction. It is shown that an improvement of Internet access facilitates healthcare access, while an increase in income inequality impedes access to healthcare. Moreover, Internet access significantly mitigates the negative impact of income inequality on healthcare access.

The main contributions of this paper are threefold. First, this paper sheds light on the relationship between the Internet and major health outcomes. We show that Internet access plays an important role in influencing health inequality and healthcare access. Our findings suggest that increasing Internet penetration and reducing barriers to accessing health information could be promising public health interventions. Second, this paper makes a novel contribution by investigating how Internet affects the relationship between income inequality and healthcare access. Our findings suggest that Internet access mitigates the negative impact of income inequality on healthcare access, which reinforces the important role of the Internet in shaping health outcomes. Third, this paper contributes to a better understanding of the factors associated with health inequality and healthcare access based on representative data. This paper conducts an empirical study using cross-country panel data covering a large number of developed and developing countries over a period of more than two decades. The rich and comprehensive data allow us to fully exploit the variations across countries and over time in the estimations. It provides a useful tool for future research investigating longstanding health disparities and the means to leverage new technology to narrow the gaps in public health.

The rest of the paper is organized as follows. Section 2 provides the literature review. Section 3 describes the methodology, including the data and sample, measurements of variables, and estimation methods. Section 4 presents the results, including descriptive statistics, baseline results, and robustness checks. Section 5 discusses the implications of and future directions for research. Finally, Section 6 concludes.

LITERATURE REVIEW

This paper builds upon two strands of literature. The first strand of literature examines the impacts of Internet access on economic development and health outcomes. The second strand of literature focuses on health inequality, healthcare access, and their determinants and measurements.

The Internet is the global system of interconnected computer networks that has revolutionized communications and commercial modes by allowing information to be distributed and accessed effortlessly from anywhere (11). The Internet, which carries a wide variety of resources and services, also provides a powerful and general ability to support access to digital information by numerous applications (12). Over past decades, technological progress has yielded substantial performance improvements in networking and resulted in significantly declining unit costs of information processing (13). These performance improvements and the associated cost reductions have greatly accelerated the diffusion of Internet access since the 1990s, although considerable regional disparities remain (14, 15). Economic activities in the Internet age are increasingly interrelated due to complementarities among dense networks, online services and diverse applications (16). While national economies and large enterprises have reaped large benefits from the technological revolution, individual consumers and small businesses have been some of the major beneficiaries of the Internet's empowering influence (17, 18). In addition to economic development, the Internet is playing a vital role in influencing health outcomes (3, 4, 19, 20). The diffusion of the Internet has dramatically reduced informational frictions and given people unprecedented sources of health information (5, 21, 22). Access to health information via the Internet is redefining the roles of patients and medical practitioners since the flow of health information to patients is no longer controlled by physicians (23). It has been well documented that a remarkably large proportion of Internet users look online for information about health (24). Internet access is found to be positively correlated with the use of healthcare and thus health outcomes, providing evidence underlining the growing importance of the Internet as a valuable source of health related information (6, 25–27). Internet-based telehealth encompasses a wide range of physician-patient communication through online portals so that people are able to access medical services remotely and take better control of their healthcare (9, 10, 28). Moreover, eHealth and health informatics, with a broad definition covering healthcare practices supported by digital processes and Internet communications, improve the health, well-being, and economic functioning of society by promoting the efficient and effective use and analysis of information in the Internet era (29–32). Despite a number of health benefits provided by the Internet, it has also been documented in the literature that accessing health information on the Internet and the rapidly evolving digital environment could lead to the problems of healthcare misinformation, health-related fake news, and infodemic (33–35). These problems become more pronounced during the pandemic and could cause adverse health effects (36–38). In consideration of the fact that the Internet offers widespread access to health information and become an important resource to learn about health for users worldwide, the health benefits associated with Internet access still outweigh the potential drawbacks (39).

There is ample evidence in the literature that various social and economic factors, including age, education, gender, ethnicity, family status, employment status and income level,

have important impacts on people's health (40–42). Health inequities are systematic differences in the health status of different population groups, which can be observed in many health outcomes such as life expectancy, self-assessed mental health, and mortality (2). These inequities can impose significant social and economic costs on both individuals and societies (1, 43). Public health practitioners, researchers, and policy-makers have long endeavored not only to improve overall health status but also to reduce health inequality through the right mix of public health policies (44). Increasing the use of health information technology, enhancing health literacy, and implementing health programs targeting socially disadvantaged groups are possible means of promoting health equity (45, 46). Several methods have been employed in the literature to measure the degree of health inequality. The concentration index approach, which quantifies the extent of socioeconomic-related inequality in a health indicator, has enjoyed increasing popularity in related studies (47). A major component of achieving universal health coverage is ensuring that people of different socioeconomic groups have access to quality healthcare (48). Social, economic, demographic, cultural, and geographic factors affect people's ability to access healthcare (49). Limited availability of health services is a barrier that reduces access to healthcare. For instance, physician shortages could lead to longer wait times and delayed care (50). The effective implementation of information technology in healthcare is part of the solution to this problem (51). Healthcare access and quality can be approximated by measuring mortality rates from causes that should not be fatal in the presence of effective and high-quality medical treatments (i.e., amenable mortality). Improving healthcare access is an important step toward reducing health inequality (52).

METHODOLOGY

Data and Sample

This paper conducts a two-tier empirical analysis using cross-country panel data. First, to examine the impact of Internet access on health inequality, we employ the WHO Health Equity Assessment Toolkit (HEAT), which enables users to calculate summary measures of health inequality using an existing database of disaggregated data (53, 54). HEAT contains disaggregated data from the WHO Health Equity Monitor database (2021 update). The data are based on reanalysis of Demographic and Health Surveys (DHS), Multiple Indicator Cluster Surveys (MICS) and Reproductive Health Surveys (RHS) conducted in various countries. The same methods of calculation for data analysis were applied across all surveys in to generate comparable estimates across countries and over time. Specifically, HEAT allows for the assessment of health inequality based on a wide range of health indicators (e.g., reproductive, maternal, and newborn health) along different dimensions (e.g., economic status, education, place of residence, subnational region, age, and sex). Note that the sample period ranges from 1993 to 2019. Given that the survey data were not available annually for all countries, the overall sample is an unbalanced panel dataset comprising 83 countries and 272 country-year observations.[1]

Second, to further scrutinize the social and economic determinants of access to healthcare, we utilize the Global Burden of Disease (GBD) database, which provides a comprehensive and systematic worldwide assessment of mortality and morbidity from major diseases, injuries, and risk factors (55, 56). The GBD provides an important tool for quantifying health loss from numerous diseases, injuries, and risk factors so that health systems can be improved, and disparities can be reduced. Measuring mortality rates due to causes that are considered amenable to healthcare is one way to characterize average levels of personal healthcare access and quality (57–59). Based on cause of death data and risk exposure data and estimates from the GBD 2016, the Healthcare Access and Quality (HAQ) Index is constructed for 194 countries from 1990 to 2016. The sample, which is an unbalanced panel dataset due to data availability, consists of 1156 country-year observations.[2]

Measurements of Variables

Dependent Variable

To measure the degree of health inequality (*HealthInequality*), we employ the absolute concentration index (ACI), which is calculated based on the infant mortality rate (*IMR*) in HEAT. The IMR is defined as the number of deaths per 1,000 live births of children under 1 year of age and is considered to be an important measure of health condition (60–62). It is widely used as an indicator to quantify the level of health disparity (63–65). Specifically, we focus on health inequality associated with economic status, which is determined using a wealth index. Regarding economic status, within each country, the wealth index was divided into 10 equal subgroups, namely, wealth deciles, in which each group accounts for 10% of the population. Subgroups are ranked from the most-disadvantaged (i.e., poorest) to the most-advantaged subgroup (i.e., richest).

The ACI is calculated as:

$$ACI = \sum_j p_j \left(2x_j - 1\right) y_j \tag{1}$$

Where, p_j denotes the population share of subgroup j, x_j represents the relative rank of subgroup j, and y_j indicates the estimate for subgroup j. Note that, if there is no inequality, the ACI is equal to zero. Negative values indicate a concentration of the IMR among the poor subgroups, while positive values indicate a concentration of the IMR among the rich subgroups. The ACI characterizes the health inequality across population subgroups with different economic statuses.

To measure and evaluate healthcare accessibility (*HealthcareAccess*) across countries and over time, the HAQ Index is constructed on the basis of principal component analysis, providing an overall score of healthcare access and quality on a scale of 0–100 across locations from 1990 to 2016. The HAQ Index is sourced from the GBD 2016 results

[1]The list of countries and territories is presented in the **Supplementary Table S1**.
[2]The list of countries and territories is presented in the **Supplementary Table S2**.

(66–68). Patterns of performance on the overall HAQ Index vary considerably across countries, with most countries in the highest decile located in Europe and almost all of the countries in the lowest decile clustered in sub-Saharan Africa. These substantial variations in the HAQ Index, both across countries and over time, allow us to examine the social and economic determinants of access to healthcare.

Key Independent Variable

The key independent variable of interest is the Internet access (*Internet*), that is, the individuals using the Internet as a proportion of the population. Internet access data are sourced from the World Development Indicators (WDI) developed by the World Bank. According to the definition of the indicator, Internet users are individuals who have used the Internet (from any location) through a computer, mobile phone, personal digital assistant, digital TV, etc. Access to the Internet can be provided via a fixed or mobile network.

Income inequality (*IncomeInequality*) is characterized by the Gini coefficient, which is a synthetic measure of statistical dispersion intended to represent the inequality within a nation. The Gini coefficient ranges from 0 (in the case of perfect equality) to 1 (a situation in which one person has all of the income and everyone else has none in an economy). A higher Gini coefficient indicates greater income inequality, with high-income individuals receiving much larger shares of the total income of the population. Previous studies have emphasized the relationship between income inequality and health outcomes (69–72). Following previous studies (73), income inequality data are collected from the Standardized World Inequality Database (SWIID).

Control Variables

The set of control variables includes gross domestic product (GDP), GDP per capita, trade liberalization, and government effectiveness, which are described in detail below.

(1) *GDP* is the monetary measure of all the final goods and services produced in a specific time period by a country. We use the logarithm of GDP to measure a nation's overall economic development. GDP data are in current U.S. dollars and are taken from the WDI.

(2) GDP per capita (*GDPPC*) is determined by dividing GDP by the population. We use the logarithm of GDP per capita to proxy the standard of living in a country. GDP per capita data are sourced from the WDI and measured in current U.S. dollars.

(3) Trade liberalization (*TL*) is the sum of exports and imports of goods and services measured as a share of GDP. We employ the measure of trade liberalization to characterize the degree to which countries are open to international trade. It has been documented in the literature that trade liberalization plays an important role in shaping health inequality and healthcare access (74–76). Trade liberalization data are collected from the WDI.

(4) Government effectiveness (*GE*) captures the perception of the quality of public service, the quality of civil service and the extent of its independence from political pressure, the quality of policy formulation and implementation, and the credibility of the government's commitment to these policies. The measure of government effectiveness is reported in the standard normal unit, with a mean of zero and a standard deviation of one and ranging from ∼-2.5 to 2.5, with higher values corresponding to better governance. It has been shown in the literature that government effectiveness and institutional performance have important impacts on health outcomes (77–79). Government effectiveness data are sourced from the Worldwide Governance Indicators (WGI) (80).

Table 1 summarizes all of the variables used in this study, including variable names, measures, codes, and sources.

Estimation Methods

In the first step, to explore how Internet access affects health inequality, we estimate the following equation:

$$HealthInequality_{it} = \alpha + \beta \times Internet_{it} + \mathbf{X_{it}}'\Gamma + D_t + \varepsilon_{it} \quad (2)$$

In Equation (2), $HealthInequality_{it}$ represents the degree of health inequality of country i in year t, and $Internet_{it}$ denotes the level of Internet access of country i in year t. The key coefficient of interest, β, captures the impact of Internet access on health inequality. Note that $\mathbf{X_{it}}$ is a vector of various control variables, and D_t indicates the time fixed effect. Following convention, α is the intercept and ε_{it} is the idiosyncratic disturbance term.

In the second step, to further examine the social and economic determinants of healthcare access, we adopt the following estimation:

$$\begin{aligned} HealthcareAccess_{it} &= \alpha + \beta_1 \times Internet_{it} + \beta_2 \\ &\times IncomeInequality_{it} + \beta_3 \times Internet_{it} \\ &\times IncomeInequality_{it} + \mathbf{X_{it}}'\Gamma \\ &+ D_i + D_t + \varepsilon_{it} \end{aligned} \quad (3)$$

In Equation (3), $HealthcareAccess_{it}$ indicates the healthcare accessibility of country i in year t, $Internet_{it}$ denotes the level of Internet access of country i in year t, and $IncomeInequality_{it}$ represents the degree of income inequality of country i in year t. The main coefficients of interest, β_1, β_2, and β_3, characterize the effects of Internet access, income inequality, and the interaction between Internet access and income inequality on access to healthcare, respectively. $\mathbf{X_{it}}$ is a vector of various control variables as in Equation (2). D_i denotes the country fixed effect and D_t indicates the time fixed effect. Last, α is the constant term and ε_{it} is the error term.

RESULTS

Descriptive Statistics

Table 2 displays the descriptive statistics of all of the variables in the empirical estimations. As indicated in **Table 2**, there are large variations in health inequality, healthcare access and Internet access both across countries and over time, enabling us to systematically explore their relationships using estimation methods.

TABLE 1 | Summary of variables.

Variable	Measure	Code	Source
Panel A: The impact of Internet access on health inequality (1993–2019)			
Health inequality	The absolute concentration index calculated based on the infant mortality rate across different economic status groups in a country	HealthInequality	WHO
Health indicator	The average infant mortality rate in a country	IMR	WHO
Panel B: The social and economic determinants of access to healthcare (1990–2016)			
Healthcare accessibility	The overall score of healthcare access and quality in a country	HealthcareAccess	GBD
Income inequality	GINI index, a synthetic measure of statistical dispersion to represent the inequality in a country	IncomeInequality	SWIID
Panel C: Independent and control variables in both analyses			
Internet access	The individuals using the Internet as a proportion of the population	Internet	WDI
Gross domestic product	The logarithm of GDP in current U.S. dollars	GDP	WDI
Gross domestic product per capita	The logarithm of GDP per capita in current U.S. dollars	GDPPC	WDI
Trade liberalization	The ratio of the sum of exports and imports of goods and services to GDP	TL	WDI
Government effectiveness	Government effectiveness index from the Worldwide Governance Indicators	GE	WGI

Baseline Results

Table 3 displays the estimation results regarding the influence of the Internet on health inequality. As shown in Column (1) of **Table 1**, the coefficient of Internet access is positive and statistically significant at the 5% level. It is worth noting that the mean value of the ACI is −5.23, and the median value of the ACI is −4.68, implying a concentration of the IMR among the poor subgroups. A higher level of Internet access is associated with an increase in ACI and a decrease in health inequality. Therefore, in terms of health condition, the gap between the poor and the rich would be reduced if the Internet became more accessible. Column (2) of **Table 1** indicates that the effect stemming from the Internet remain positive and significant after controlling for a wide variety of variables that influence health inequality.

Table 4 reports the regression results regarding the impact of Internet access on the IMR. The identification essentially replaces the dependent variable in Equation (2) with the IMR of country i in year t (i.e., IMR_{it}), allowing us to further explore the influence of the Internet on the overall IMR, in addition to health inequality. Column (1) of **Table 2** shows that the coefficient of Internet access is negative and statistically significant at the 1% level. The magnitude of the coefficient implies that a 10% increase in the level of Internet access is related to a decrease of approximately 0.11 deaths per 1,000 live births. When including a full set of control variables in the estimation, Column (2) of **Table 2** demonstrates that, all else being equal, a higher level of Internet access is related to a decline in the overall IMR. In addition, as expected, variables such as GDP, GDP per capita, trade liberalization, and government effectiveness tend to decrease the average level of IMR.

Table 5 shows the estimation results of Equation (3), focusing on the social and economic determinants of healthcare access. Columns (1) and (2) of **Table 3** include only the factors of Internet access and income inequality, respectively. It is found that an improvement in Internet access significantly facilitates healthcare access, while an increase in income inequality significantly impedes access to healthcare. Column (3) of **Table 3** further incorporates various control variables and confirms the similar effects of Internet access and income inequality on healthcare access. Finally, Column (4) of **Table 3** includes the interaction term between Internet access and income inequality. The coefficient of the interaction term is positive and statistically significant, implying that Internet access mitigates the negative impact of income inequality on healthcare access.

Granger Causality Test

In our study, the relationships among the Internet, health inequality and healthcare access have been empirically identified. However, it is important to determine the causality among these variables to further establish the cause-effect links. Following previous studies (81–83), we conduct dynamic panel Granger causality tests to analyze the causal relationship among the key variables. The results of the Granger causality tests are presented in **Table 6**. As shown in Panel A of **Table 6**, only the F-statistic of *Internet* to *HealthInequality* is significant at 5%, indicating that the Internet is an important and robust cause of health inequality, but health inequality does not cause the diffusion of

TABLE 2 | Descriptive statistics.

Variable Code	Observation	Mean	Standard deviation	Minimum	Maximum
Panel A: The impact of Internet access on health inequality (1993–2019, 83 countries)					
HealthInequality	272	−5.230	3.792	−16.604	3.760
IMR	272	55.642	27.408	5.146	147.377
Internet	272	12.661	15.391	0	66.790
GDP	272	23.695	1.620	19.115	28.375
GDPPC	272	7.106	0.940	5.321	9.443
TL	272	65.944	31.336	1.378	194.351
GE	272	−0.631	0.460	−2.058	0.658
Panel B: The social and economic determinants of access to healthcare (1990–2016, 194 countries)					
HealthcareAccess	1,164	52.967	22.524	10.600	97.100
IncomeInequality	771	38.178	8.445	17.300	62.300
Internet	1,156	18.027	26.164	0	98.240
GDP	1,105	23.525	2.377	17.499	30.560
GDPPC	1,105	8.031	1.586	4.556	11.561
TL	1,055	83.962	51.348	0.021	583.314
GE	1,116	−0.054	0.987	−2.260	2.241

TABLE 3 | The impact of Internet access on health inequality (1993–2019).

Model	HealthInequality	
Variables	(1)	(2)
Internet	0.040**	0.036**
	(0.016)	(0.018)
GDP		−0.549***
		(0.193)
GDPPC		0.645*
		(0.360)
TL		0.012
		(0.011)
GE		−0.395
		(0.772)
constant	−5.735***	1.714
	(0.423)	(4.773)
Year fixed-effect	Yes	Yes
Observation	272	272
R^2	0.217	0.292
Adjusted R^2	0.199	0.265

Standard errors in parentheses.
*$p < 0.10$.
**$p < 0.05$.
***$p < 0.01$.

TABLE 4 | The impact of Internet access on the IMR (1993–2019).

Model	IMR	
Variables	(1)	(2)
Internet	−1.087***	−0.219*
	(0.102)	(0.125)
GDP		−1.490
		(1.512)
GDPPC		−12.150***
		(2.557)
TL		−0.110*
		(0.064)
GE		−9.695***
		(3.621)
constant	69.410***	181.213***
	(2.308)	(36.667)
Year fixed-effect	Yes	Yes
Observation	272	272
R^2	0.467	0.622
Adjusted R^2	0.408	0.573

Standard errors in parentheses.
*$p < 0.10$.
**$p < 0.05$.
***$p < 0.01$.

Internet in the reverse direction. As seen from Panel B of **Table 6**, the bidirectional causality between *Internet* and *HealthcareAccess* is significant at 1%. To this end, policies aimed at boosting Internet development will eventually improve healthcare access in the long run. Last, the F-statistic of *IncomeInequality* to *HealthcareAccess* is significant at 5%, implying that income inequality is an important and robust explanatory variable for healthcare access.

Robustness Checks

To validate the empirical findings in **Tables 3**–**5**, we further conduct a wide set of robustness checks using

TABLE 5 | The social and economic determinants of access to healthcare (1990–2016).

Model	HealthcareAccess			
Variables	**(1)**	**(2)**	**(3)**	**(4)**
Internet	0.028***		0.021***	−0.023
	(0.006)		(0.008)	(0.021)
IncomeInequality		−0.165***	−0.160***	−0.149***
		(0.055)	(0.053)	(0.053)
GDP			5.462***	5.078***
			(1.117)	(1.125)
GDPPC			−1.869	−1.577
			(1.146)	(1.148)
TL			0.013**	0.015***
			(0.005)	(0.005)
GE			1.671***	1.697***
			(0.474)	(0.472)
Internet × IncomeInequality				0.001**
				(0.001)
constant	52.519***	62.916***	−55.398***	−49.183**
	(0.142)	(2.104)	(19.154)	(19.265)
Country fixed-effect	Yes	Yes	Yes	Yes
Year fixed-effect	Yes	Yes	Yes	Yes
Observation	1,156	763	717	717
R^2	0.988	0.991	0.993	0.993
Adjusted R^2	0.985	0.988	0.991	0.991

Standard errors in parentheses.
*$p < 0.10$.
**$p < 0.05$.
***$p < 0.01$.

TABLE 6 | Panel causality tests.

	F-statistics	*p*-value	Null hypothesis for the tests
Panel A: The impact of Internet access on health inequality (1993–2019)			
Internet → HealthInequality	4.458	0.035	Internet does not Granger-cause HealthInequality.
HealthInequality → Internet	0.347	0.556	HealthInequality does not Granger-cause Internet.
Panel B: The social and economic determinants of access to healthcare (1990–2016)			
Internet → HealthcareAccess	522.965	0.000	Internet does not Granger-cause HealthcareAccess.
HealthcareAccess → Internet	126.973	0.000	HealthcareAccess does not Granger-cause Internet.
IncomeInequality → HealthcareAccess	6.053	0.014	IncomeInequality does not Granger-cause HealthcareAccess.
HealthcareAccess → IncomeInequality	0.361	0.548	HealthcareAccess does not Granger-cause IncomeInequality.

alternative estimations, different samples, alternative measures, and subsamples.

Regarding the impact of Internet access on health inequality, **Table 7** shows the results using pooled OLS estimations. The pooled OLS estimation results, in which the data on different units are pooled together with no assumptions about individual differences, are consistent with the fixed-effect estimates in **Table 3**. This pattern further affirms that access to the Internet significantly reduces health inequality.

With respect to the impact of Internet access on the IMR, **Table 8** displays the results using different samples with more observations. Note that the WDI includes more extensive data on the IMR, as compared to HEAT. The results based on larger samples are qualitatively similar to the results presented in **Table 4**. This outcome implies that increased Internet access is associated with a decrease of the overall IMR.

With regard to the social and economic determinants of healthcare access, **Tables 9**, **10** report the results using alternative measures of Internet access and subsamples based on the median value of Gini coefficient, respectively. Since the key explanatory variable of interest is Internet access, we utilize two alternative measures, namely the number of Internet servers per million people and the number of broadband Internet subscribers per hundred people, both of which are sourced from the WDI. Columns (1) and (2) of **Table 9** confirm that better access to the Internet significantly improves the healthcare access. The results are robust to the alternative measures of Internet access. In addition, to justify the moderating effect of Internet access, we categorize the total sample into two subsamples of equal size based on the degree of income inequality. Columns (1) and (2) of **Table 10** report the estimation results using subsamples that are greater and less than the median value of the Gini coefficient (i.e., 38.2), respectively. The positive and significant impact of the Internet on healthcare access exists in countries that are more unequal in terms of income distribution (i.e., higher Gini coefficient). The analogous positive and significant effect does not exist in countries with a lower degree of income inequality (i.e., lower Gini coefficient). Taken together, the subsample analysis suggests that access to the Internet tends to bridge the gap in healthcare access between the poor and the rich in highly unequal societies. This finding provides evidence of the moderating role of Internet access, consistent with the baseline results in **Table 5**.

DISCUSSION AND IMPLICATIONS

Policy Implications

This paper sheds empirical light on the relationship between access to the Internet and major health outcomes, which could provide several important implications for policy-makers. First, health inequality refers to the unjust and avoidable differences in health across the population and between different population groups. These widespread differences have detrimental effects on people's living conditions and overall health status (1, 2, 43). In particular, health inequality affects people from

TABLE 7 | Robustness checks using alternative estimations.

Model	(1)	(2)
Sample	WHO Sample	
Variables	HealthInequality	
Internet	0.089***	0.077***
	(0.014)	(0.018)
GDP		−0.450***
		(0.171)
GDPPC		0.774**
		(0.339)
TL		0.017**
		(0.008)
GE		−1.402***
		(0.477)
constant	−6.363***	−3.064
	(0.278)	(3.897)
Year fixed-effect	No	No
Observation	272	272
R^2	0.467	0.622
Adjusted R^2	0.408	0.573

*Robustness checks related to **Table 3** about the impact of Internet access on health inequality.*
Standard errors in parentheses.
$^{*}p < 0.10$.
$^{**}p < 0.05$.
$^{***}p < 0.01$.

TABLE 8 | Robustness checks using different samples.

Model	(1)	(2)
Sample	WDI Sample	
Variables	IMR	
Internet	−0.706***	−0.063**
	(0.013)	(0.027)
GDP		0.156
		(0.167)
GDPPC		−10.214***
		(0.432)
TL		−0.001
		(0.007)
GE		−4.371***
		(0.648)
constant	50.581***	111.670***
	(0.548)	(4.692)
Year fixed-effect	Yes	Yes
Observation	2,818	2,818
R^2	0.505	0.624
Adjusted R^2	0.502	0.622

*Robustness checks related to **Table 4** about the impact of Internet access on the IMR.*
Standard errors in parentheses.
$^{*}p < 0.10$.
$^{**}p < 0.05$.
$^{***}p < 0.01$.

disadvantaged groups most severely and goes against the principle of social justice. Reducing health inequalities within and between countries becomes a social, economic and ethical imperative for policy-makers. This paper shows that access to the Internet plays a pivotal role in reducing health inequality across the social gradient. Therefore, governments should increase investments in digital infrastructure and promote the continuous development of the Internet and ICTs, as a means of redressing longstanding inequality in health.

Second, ensuring access to quality healthcare is a crucial component of achieving universal health coverage. The main determinants of healthcare access are the social and economic conditions in which people live that influence health outcomes throughout life (40, 45, 49, 65). By carefully examining the social and economic determinants of healthcare access, this paper points to the moderating role of Internet access on the relationship between income inequality and healthcare access. Since Internet connectivity not only significantly improves healthcare access but also mitigates the negative effect of income inequality, policy-makers aiming to promote access to healthcare should consider the value of the Internet as an important tool to improve healthcare. Governments ought to increase the network coverage and lower barriers to accessing the Internet, especially for disadvantaged groups, which generally have worse health outcomes and suffer from a lack of access to quality healthcare.

Third, given the importance of the Internet in shaping health outcomes through the distributional and aggregate effects (3, 8, 25), ensuring that health outcomes are equitable across different population groups will be as crucial as utilizing new technology in healthcare to improve these outcomes. Policy-makers should pay close attention to the digital divide, which is the uneven distribution in access to, use of, or impact of the Internet and ICTs between different population groups. These distinct groups might be defined based on social, geographical, ethnic, or economic criteria. Thus, bridging the digital divide could reduce disparities in health outcomes and reap the benefits of improving healthcare access (84). Meanwhile, given a vast quantity of inaccurate information online, healthcare misinformation, health-related fake news, and particularly infodemic during a disease outbreak could lead to the spread of ineffective and even harmful public health measures (36–38). It is of vital importance to build up necessary skills needed by public health practitioners to deliver fast, efficient, and cost-effective responses to the challenges of misinformation and health-related fake news. Policy-makers responsible for health communication strategies and social media policies can adopt preventive measures to cope with infodemic during the pandemic (85).

Limitations and Future Research Directions

This study has made considerable contributions to the literature, but there are some limitations to be addressed in future research. First, since the digital economy has developed rapidly over the last few decades, a detailed study of the impact of the digital divide on disparities in healthcare is left for

TABLE 9 | Robustness checks using alternative measures.

	(1)	(2)
Sample	**Full Sample**	
Variables	**HealthcareAccess**	
Internet_server	0.714***	
	(0.179)	
Internet_broadband		0.306***
		(0.101)
IncomeInequality	−0.197	−0.020
	(0.130)	(0.068)
GDP	3.632	1.269
	(2.889)	(1.534)
GDPPC	−1.977	0.298
	(3.048)	(1.630)
TL	−0.012	−0.001
	(0.008)	(0.006)
GE	0.073	1.425***
	(0.842)	(0.537)
constant	4.232	32.210
	(48.236)	(25.934)
Country fixed-effect	Yes	Yes
Year fixed-effect	Yes	Yes
Observation	144	349
R^2	0.999	0.997
Adjusted R^2	0.997	0.996

*Robustness checks related to **Table 5** about the social and economic determinants of access to healthcare; b. Standard errors in parentheses.*
$^{*}p < 0.10$.
$^{**}p < 0.05$.
$^{***}p < 0.01$.
*The WDI reports the worldwide data on the number of secure Internet servers since 2010, and the number of fixed broadband Internet subscribers since 2000. Thus, the sample sizes are smaller than the estimations using Internet access as the key independent variable in **Table 5**.*

TABLE 10 | Robustness checks using subsamples.

	(1)	(2)
Sample	**High Gini Group**	**Low Gini Group**
Variables	**HealthcareAccess**	
Internet	0.075***	−0.002
	(0.017)	(0.009)
GDP	2.483	6.154***
	(1.808)	(1.482)
GDPPC	1.640	−2.909*
	(1.906)	(1.481)
TL	0.047***	0.005
	(0.011)	(0.005)
GE	2.714***	1.775***
	(0.746)	(0.601)
constant	−30.341	−57.874**
	(29.847)	(24.985)
Country fixed-effect	Yes	Yes
Year fixed-effect	Yes	Yes
Observation	361	356
R^2	0.986	0.993
Adjusted R^2	0.981	0.991

*Robustness checks related to **Table 5** about the moderating effect of Internet access. Standard errors in parentheses.*
$^{*}p < 0.10$.
$^{**}p < 0.05$.
$^{***}p < 0.01$.
The high Gini group is defined as the subsample of observations that are greater than the median value of the Gini coefficient (i.e., 38.2), while the low Gini group is defined as the subsample of observations that are less than the median value of the Gini coefficient.

future research. Second, due to data availability, this study could not incorporate the COVID pandemic into the analysis. Future research could further explore the relationship between inequality and healthcare during the COVID pandemic period with updated data. As misinformation concerning health tends to have serious consequences with regard to health risks and outcomes, it is worth examining how people interact with healthcare misinformation online during the COVID pandemic. Exploring practical ways to leverage health communication strategies via the Internet to overcome COVID infodemic deserves further in-depth study. Finally, since this study focuses on a cross-country analysis at the macro-level, it would be interesting to investigate several micro-level (i.e., personal characteristics and/or family characteristics) determinants of income-related health inequalities in the digital era.

CONCLUSION

The Internet has profoundly changed the way in which health information is shared and accessed, which has evolved with the ever-changing needs of both physicians and patients. Health information on the Internet significantly increases people's knowledge of, engagement in, and competence with health decision-making strategies. The Internet has been increasingly used for health-related purposes in the contemporary age and has major implications for public health, including health inequality and healthcare access. Despite the importance of this topic to the field of public health, few comprehensive studies have been conducted to explore their relationships. This paper contributes to the literature by systematically examining the impacts of the Internet on health inequality and healthcare access based on a cross-country study. The major findings of this paper are twofold. First, Internet access significantly reduces health inequality across different income groups and increases the average health condition. Second, access to the Internet significantly facilitates healthcare access and mitigates the negative impact of income inequality on healthcare access. More importantly, the results persist across a wide variety of robustness checks.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: 1. WHO Health Equity Assessment Toolkit: https://www.who.int/data/health-equity/assessment_toolkit. 2. Global Burden of Disease database: https://ghdx.healthdata.

org/gbd-2017. 3. World Bank Database: https://databank.worldbank.org/home.aspx. 4. Standardized World Inequality Database: https://www.wider.unu.edu/project/world-income-inequality-database-wiid.

AUTHOR CONTRIBUTIONS

JY: conceptualization, methodology, validation, and writing—original draft. SM: conceptualization, methodology, visualization, and writing—review and editing. Both authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Associations of Education Level With Survival Outcomes and Treatment Receipt in Patients With Gastric Adenocarcinoma

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Background: It remains largely unclear how education level, an important socioeconomic factor, affects prognoses for patients with gastric adenocarcinoma (GAC). We aimed to demonstrate the associations between education level and clinical outcomes in patients with GAC.

Methods: We included a total of 30,409 patients diagnosed with GAC from the Surveillance, Epidemiology, and End Results 18 registry database. Education level, household income, unemployment rate, poverty rate, insurance status, and marital status were selected as sociodemographic variables for the comprehensive analysis. Cox and logistic regression models, Kaplan–Meier curves, and subgroup analyses were the primary statistical methods employed.

Results: A low level of education was correlated with less income, higher unemployment rates, and higher poverty rates (all $p < 0.001$). The multivariate Cox analysis indicated that a high education level was significantly associated with superior overall survival rates and cancer-specific survival rates in patients with GAC (both $p < 0.001$). We also corroborated favorable survival outcomes by high education level within almost every clinical and demographic subgroup. Furthermore, chemotherapy combined with surgery could markedly prolong the survival for all patients, including patients of stage IV cancer (both $p < 0.001$). By using multivariable logistic models, patients in counties with high education levels had a higher probability of chemotherapy receipt ($p < 0.001$). Contrarily, those in the counties with low levels of education were less likely to receive chemotherapy or undergo surgery ($p < 0.001$).

Conclusions: Education level was identified and confirmed as an independent predictor of treatment and survival for GAC patients. Efforts are needed to provide effective interventions for those whose educational status is adverse.

Keywords: education level, gastric adenocarcinoma, prognosis, treatment receipt, SEER

INTRODUCTION

Gastric cancer (GC) is one of the most frequent cause of tumors in the digestive system, with an estimated 26,560 new cases per year in the United States. It also remains the leading cause of cancer-related deaths (1). Gastric adenocarcinoma (GAC) is the most common type of gastric malignancy, accounting for ∼95% of all types of GC (2). With advancements in therapeutic modalities, an improvement in GC patients' survival rate has been observed, whereas the 5-year overall survival (OS) rate is generally below 30% and the median relative survival rate is just 16 months (3). Moreover, prognoses for patients are highly dependent on the stage at diagnosis. The 5-year OS for those with distant metastases is <5% (3), and chemotherapy remains the preferred choice of treatment for the patients with an advanced GC (4). As a multifactorial disease, the environmental, demographic, and the genetic factors play pivotal roles in the etiology and lead to survival disparities in patients with GC (5). Given the very poor prognosis for patients with GC, the discovery of any factor that predicts better survival outcomes could be highly beneficial.

Socioeconomic status (SES) factors, including insurance status, marital status, income level, and education level, have been reported to influence the morbidity risk, treatment approaches, and long-term prognoses for patients with GC (6–15). Increased survival rates for patients with GC have been observed over the past few decades with a widening SES gap (11). Lower SES is linked to inferior survival rates (7, 11). In addition, patients whose SES is low have a lower probability of curative treatment allocations for gastrointestinal cancers, resulting in dismal prognoses (14). Besides, an adverse marital status (divorced or widowed), living alone, low education level, and low income increase the risks of all GC subtypes (8). A case–control study suggests that the education level could be a reliable and ideal single indicator to measure GC risk among several SES variables (15). Nevertheless, the impact of education level on the GC survival rate remains poorly understood.

Educational attainment is recognized as a crucial social determinant of diseases; it influences health through mechanisms such as biological aging, cognitive ability, and health behaviors (16). Education level has been demonstrated to impact treatment and prognoses in anal cancer, sinonasal cancer, and multiple myeloma (17–19). A nationwide cohort study in Sweden indicated that a high education level was associated with a greater likelihood of improved survival rates and curative treatment in 4,112 patients diagnosed with gastroesophageal cancer (10). Another investigation of 4,709 patients with stomach cancer in Sweden did not show a significant influence of education level on cancer survival rates (20). Considering the lack of such studies in the United States, as well as differences in education systems and patient characteristics between the two countries, we utilized the Surveillance, Epidemiology, and End Results (SEER) database to conduct a large-scale retrospective study in the United States. We investigated the effects of education level and other socioeconomic factors (e.g., income level, unemployment rate, insurance status, marital status) on the treatment receipt and clinical outcomes of patients with GAC.

MATERIALS AND METHODS

Study Population

In this retrospective study, the patient data were extracted from the SEER database (18 cancer registries) *via* SEER*Stat software (version 8.3.9). Patients diagnosed with GAC were defined according to the International Classification of Disease for Oncology, Third Edition (ICD-O-3), histologic codes 8140, 8144, 8145, 8255, 8260, 8480, 8481, and 8490. The ICD-O-3 primary site code was C16 for stomach cancer. The flowchart for screening patients is presented in **Figure 1**. The patients were included preliminarily according to the following criteria: (a) Diagnosed with GAC from 1 January, 2007 to 31 December, 2016; (b) non-autopsy or death certificate only cases; (c) complete information regarding education level; and (d) first primary tumor. The following ineligible cases were excluded: (a) unclear American Joint Committee on Cancer (AJCC) stage; (b) unknown insurance status, marital status, or race; (c) unknown surgery information or metastasis status; (d) non-Hispanic American Indian/Alaska Native (NHAI/AN); and (e) age, <25 years, at diagnosis. Finally, a total of 30,409 patients were enrolled in the study cohort.

Variable Selection

We selected the following sociodemographic and clinicopathological variables from the cohort: Age at diagnosis, sex, race, insurance status, marital status, SEER stage, AJCC stage, tumor grade, metastasis status, treatment approaches, median household income, unemployment rate, poverty rate, and education level. Race was categorized as follows: Non-Hispanic White (NHW), non-Hispanic Black (NHB), non-Hispanic Asian or Pacific Islander (NHAPI), and Hispanic. Marital status was grouped into four categories: Married, divorced, widowed, and single (never married, unmarried, or domestic partner). Insurance status was classified as insured, uninsured, or Medicaid. The SEER database contains county-level rather than patient-level socioeconomic attributes. The county-level household income, unemployment rate, and poverty rate were stratified into the following four quartiles: Quartile 1 (Q1, lowest), quartile 2 (Q2, lower), quartile 3 (Q3, higher), and quartile 4 (Q4, highest). The county-level educational attainment was measured by the percentage of those earning at least a bachelor's degree in the county where a patient was registered and divided into three groups: Q1 (low level, 25th percentile or lower, ≤23.96%), Q2 (moderate level, 25th−75th percentile, 23.96–39.07%), and Q3 (high level, 75th percentile or higher, ≥39.07%). Regarding the primary outcomes, OS was calculated as the interval from diagnosis to death from any cause. Cancer-specific survival (CSS) was calculated as the interval between diagnosis and death from GAC.

Statistical Analyses

All analyses were performed using R 4.0.3 software. The distribution differences in baseline characteristics were compared

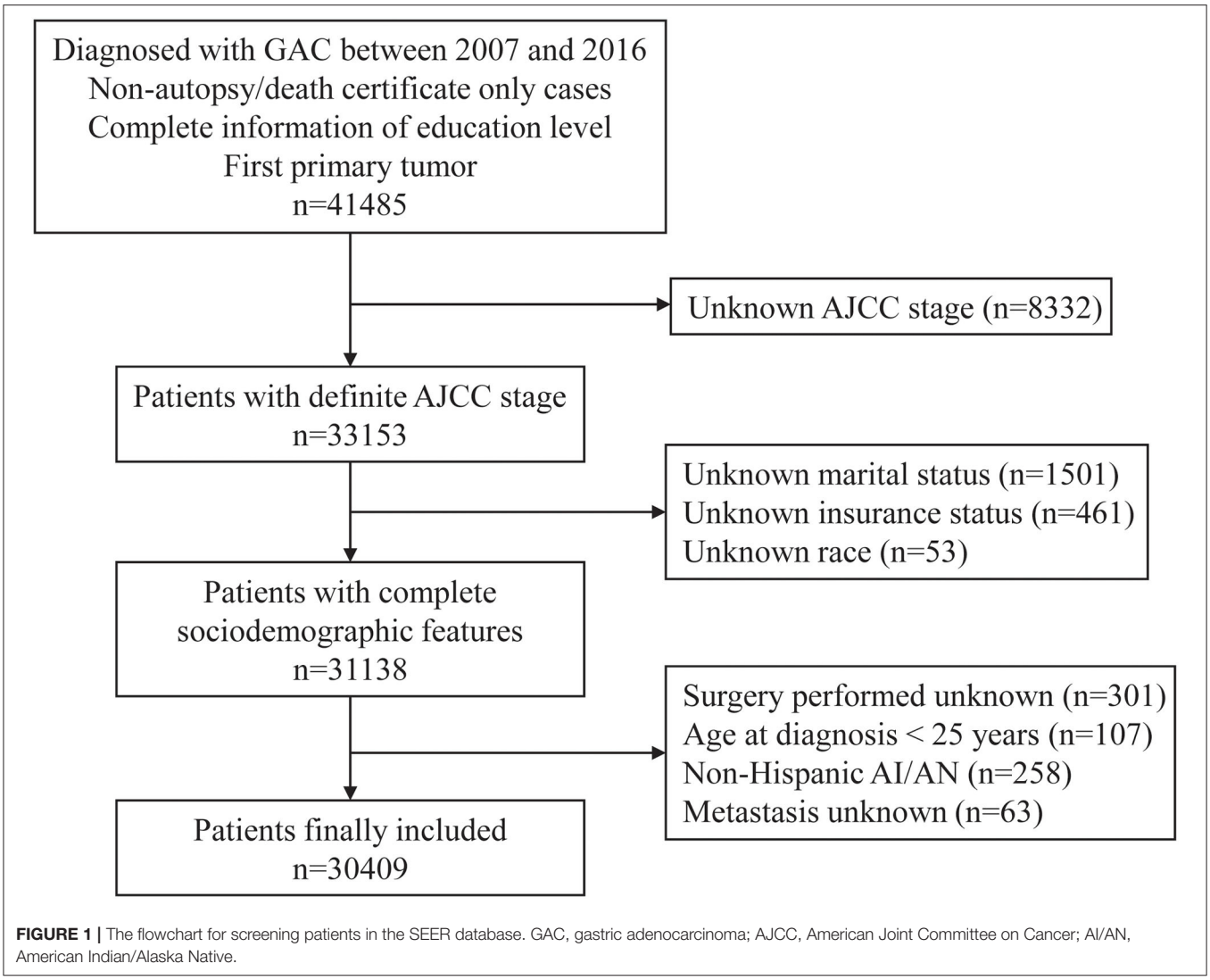

FIGURE 1 | The flowchart for screening patients in the SEER database. GAC, gastric adenocarcinoma; AJCC, American Joint Committee on Cancer; AI/AN, American Indian/Alaska Native.

with the Chi-squared test. Univariate and multivariate Cox regression analyses were conducted to determine the impacts of prognostic factors on survival outcomes. The univariate and multivariate logistic regression models were built to assess the effects of education level on treatment receipt. The hazard ratio (HR), odds ratio (OR), and 95% confidence interval (CI) were estimated for these results. The survival analysis was performed using Kaplan–Meier curves and evaluated by the log–rank test. In the subgroup analyses, forest plots described the influence of a high education level on prognosis compared with the influence of a low education level. A two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

Sociodemographic and Clinical Characteristics of Patients

The baseline characteristics of 30,409 patients are summarized in **Table 1**. The patients were separated into the following three groups according to their education level: 7,626 in the low-level group, 14,823 in the moderate-level group, and 7,960 in the high-level group. The male patients represented a greater proportion than the female patients across the cohort (64.34% vs. 35.66%), and the proportion of males in the group with a low education level (66.39%) was higher than the proportion of males in the other two groups ($p < 0.001$). The percentage of those designated as NHAPI (23.74%) was conspicuously highest among those in the group with a high education level. Additionally, insured status was significantly larger for the patients in counties with high education levels (79.87%, $p < 0.001$), as were cases involving no metastasis (40.69%, $p < 0.037$). The patients in counties with high education levels were more likely to receive chemotherapy (57.83%, $p < 0.001$) and undergo surgery (49.26%, $p < 0.001$). As shown in **Figure 2**, counties with high education levels were associated with greater household income levels (Q4: 77.90%, $p < 0.001$), lower unemployment rates (Q1: 61.80%, $p < 0.001$), and lower poverty rates (Q1: 54.71%, $p < 0.001$), but the differences in marital status were not relatively obvious.

TABLE 1 | Baseline characteristics of patients with GAC grouped by education level.

Characteristics	All *n* = 30,409	Q1 (Low) *n* = 7,626	Q2 (Moderate) *n* = 14,823	Q3 (High) *n* = 7,960	*p*
Age (years)					0.071
<=65	14,367 (47.25%)	3,670 (48.12%)	7,012 (47.30%)	3,685 (46.29%)	
>65	16,042 (52.75%)	3,956 (51.88%)	7,811 (52.70%)	4,275 (53.71%)	
Sex					<0.001
Male	19,566 (64.34%)	5,063 (66.39%)	9,465 (63.85%)	5,038 (63.29%)	
Female	10,843 (35.66%)	2,563 (33.61%)	5,358 (36.15%)	2,922 (36.71%)	
Race					<0.001
NHW	15,564 (51.18%)	4,385 (57.50%)	7,315 (49.35%)	3,864 (48.54%)	
NHB	3,877 (12.75%)	1,408 (18.46%)	1,626 (10.97%)	843 (10.59%)	
NHAPI	4,801 (15.79%)	349 (4.58%)	2,562 (17.28%)	1,890 (23.74%)	
Hispanic	6,167 (20.28%)	1,484 (19.46%)	3,320 (22.40%)	1,363 (17.12%)	
Insurance status					<0.001
Insured	23,648 (77.77%)	5,945 (77.96%)	11,345 (76.54%)	6,358 (79.87%)	
Uninsured	1,375 (4.52%)	321 (4.21%)	726 (4.90%)	328 (4.12%)	
Medicaid	5,386 (17.71%)	1,360 (17.83%)	2,752 (18.57%)	1,274 (16.01%)	
Marital status					0.033
Married	18,723 (61.57%)	4,645 (60.91%)	9,078 (61.24%)	5,000 (62.81%)	
Divorced	2,592 (8.52%)	703 (9.22%)	1,264 (8.53%)	625 (7.85%)	
Single	4,807 (15.81%)	1,194 (15.66%)	2,392 (16.14%)	1,221 (15.34%)	
Widowed	4,287 (14.10%)	1,084 (14.21%)	2,089 (14.09%)	1,114 (13.99%)	
SEER stage					0.008
Distant	13,381 (44.00%)	3,423 (44.89%)	6,544 (44.15%)	3,414 (42.89%)	
Localized	6,862 (22.57%)	1,765 (23.14%)	3,313 (22.35%)	1,784 (22.41%)	
Regional	10,166 (33.43%)	2,438 (31.97%)	4,966 (33.50%)	2,762 (34.70%)	
AJCC stage					0.134
I	8,152 (26.81%)	2,075 (27.21%)	3,920 (26.45%)	2,157 (27.10%)	
II	4,100 (13.48%)	979 (12.84%)	2,010 (13.56%)	1,111 (13.96%)	
III	3,823 (12.57%)	919 (12.05%)	1,891 (12.76%)	1,013 (12.73%)	
IV	14,334 (47.14%)	3,653 (47.90%)	7,002 (47.24%)	3,679 (46.22%)	
Tumor grade					<0.001
I	1,093 (3.59%)	285 (3.74%)	506 (3.41%)	302 (3.79%)	
II	6,910 (22.72%)	1,866 (24.47%)	3,294 (22.22%)	1,750 (21.98%)	
III	17,555 (57.73%)	4,150 (54.42%)	8,803 (59.39%)	4,602 (57.81%)	
IV	488 (1.60%)	132 (1.73%)	236 (1.59%)	120 (1.51%)	
Unknown	4,363 (14.35%)	1,193 (15.64%)	1,984 (13.38%)	1,186 (14.90%)	
Metastasis					0.037
No	17,681 (58.14%)	4,376 (57.38%)	8,584 (57.91%)	4,721 (59.31%)	
Yes	12,728 (41.86%)	3,250 (42.62%)	6,239 (42.09%)	3,239 (40.69%)	
Income					<0.001
Q1 (lowest)	7,749 (25.48%)	5,561 (72.92%)	1,871 (12.62%)	317 (3.98%)	
Q2	8,028 (26.40%)	1,774 (23.26%)	6,197 (41.81%)	57 (0.72%)	
Q3	7,148 (23.51%)	276 (3.62%)	5,487 (37.02%)	1,385 (17.40%)	
Q4 (highest)	7,484 (24.61%)	15 (0.20%)	1,268 (8.55%)	6,201 (77.90%)	
Unemployment rate					<0.001
Q1 (lowest)	8,249 (27.13%)	963 (12.63%)	2,367 (15.97%)	4,919 (61.80%)	
Q2	7,391 (24.31%)	1,093 (14.33%)	4,571 (30.84%)	1,727 (21.70%)	
Q3	7,369 (24.23%)	416 (5.46%)	5,846 (39.44%)	1,107 (13.91%)	
Q4 (highest)	7,400 (24.33%)	5,154 (67.58%)	2,039 (13.76%)	207 (2.60%)	
Poverty rate					<0.001
Q1 (lowest)	7,686 (25.28%)	275 (3.61%)	3,056 (20.62%)	4,355 (54.71%)	

(Continued)

TABLE 1 | Continued

Characteristics	All $n = 30,409$	Q1 (Low) $n = 7,626$	Q2 (Moderate) $n = 14,823$	Q3 (High) $n = 7,960$	*p*
Q2	7,548 (24.82%)	782 (10.25%)	4,102 (27.67%)	2,664 (33.47%)	
Q3	7,714 (25.37%)	1,175 (15.41%)	6,199 (41.82%)	340 (4.27%)	
Q4 (highest)	7,461 (24.54%)	5,394 (70.73%)	1,466 (9.89%)	601 (7.55%)	
Chemotherapy					<0.001
Yes	16,667 (54.81%)	4,084 (53.55%)	7,980 (53.84%)	4,603 (57.83%)	
No/Unknown	13,742 (45.19%)	3,542 (46.45%)	6,843 (46.16%)	3,357 (42.17%)	
Radiation					<0.001
Yes	8,529 (28.05%)	2,333 (30.59%)	3,946 (26.62%)	2,250 (28.27%)	
No	21,880 (71.95%)	5,293 (69.41%)	10,877 (73.38%)	5,710 (71.73%)	
Surgery					<0.001
Yes	14,699 (48.34%)	3,440 (45.11%)	7,338 (49.50%)	3,921 (49.26%)	
No	15,710 (51.66%)	4,186 (54.89%)	7,485 (50.50%)	4,039 (50.74%)	

NHW, non-Hispanic White; NHB, non-Hispanic Black; NHAPI, non-Hispanic Asian or Pacific Islander; AJCC, American Joint Committee on Cancer.
Q1, low education level; Q2, moderate education level; Q3; high education level. p-Value is for comparisons among the three groups: Q1, Q2, and Q3.

Evaluation of Prognostic Indicators

From Kaplan–Meier survival curves stratified by the sociodemographic predictors, education level, income, unemployment, and poverty rate were linked to survival disparities in CSS (all $p < 0.001$, **Figure 3**) and OS (all $p < 0.001$, **Supplementary Figure 1**). Then, a univariate Cox analysis identified the prognostic value of each factor in the entire cohort (**Table 2**). All variables except sex variable proved to be significant in predicting OS and CSS and were further included in the multivariable model (**Table 3**). The multivariate Cox regression analysis confirmed education level as an independent predictor in the survival of patients with GAC. A high education level was significantly associated with superior OS (HR: 0.915, $p = 0.005$) and CSS (HR: 0.907, $p = 0.004$) when compared with a low education level. A moderate education level was also correlated with longer OS (HR: 0.926, $p < 0.001$) and CSS (HR: 0.915, $p < 0.001$) when compared with a low level of education. Compared with the lowest income level, the highest income level was related to better outcomes in both OS (HR: 0.902, $p = 0.016$) and CSS (HR: 0.909, $p = 0.037$). With regard to other sociodemographic factors, age more than 65 years, NHAPI or Hispanic designation, Medicaid status, and unmarried status were independent prognostic indicators of clinical survival. In addition, less mortality risks were observed in patients with localized stage, AJCC stage I, and Grade I tumors (all $p < 0.001$). The patients who did not receive chemotherapy or surgery experienced worse OS and CSS rates (all $p < 0.001$), and radiotherapy showed no significant effect on survival.

Subgroup Analysis for Education Level

To verify the prognostic impacts of education level on survival in different subgroups, Kaplan–Meier curves stratified by education level were exhibited. As expected, a low level of education was distinctly correlated with adverse OS outcomes in subgroups, including age more than 65 years, NHW, unmarried status, uninsured or Medicaid status, distant stage, AJCC stage IV, Grade II–IV tumors, and metastatic status (all $p < 0.001$, **Supplementary Figure 2**). The unfavorable effects of education level on CSS were also pronounced (all $p < 0.001$, **Supplementary Figure 3**). Moreover, we divided education level into a dichotomous variable by the median (31.23%) and further outlined the influence of education level for each subgroup. Forest plots revealed that a higher level of education markedly favored survival prognoses in the vast majority of subgroups (**Figure 4**). Nonetheless, the favorable effects of higher education levels were not appreciable in either OS or CSS for NHBs or patients with Grade IV tumors (both $p > 0.05$).

Influence of Education Level on Treatment

Given the dismal prognosis for GAC, we examined the therapeutic benefits of different treatment modalities, including chemotherapy plus surgery (CS), chemotherapy or surgery alone (C/S), and no chemotherapy or surgery (None). In all patients with GAC, the median survival times for these modalities were 34, 13, and 2 months, respectively, for OS ($p < 0.001$, **Figure 5A**) and 40, 15, and 2 months, respectively, for CSS ($p < 0.001$, **Figure 5B**). Considering that AJCC stage IV tumor confers the poorest survival outcomes, we also performed the same analysis for patients with AJCC stage IV tumor. The median survival months based on the CS, C/S, and "None" modalities were 16, 8, and 1, respectively, for OS ($p < 0.001$, **Figure 5C**) and 17, 8, and 1, respectively, for CSS ($p < 0.001$, **Figure 5D**). Subsequently, a logistic regression model was applied to determine the factors affecting treatment receipt by patients with AJCC stage IV tumor. Through a multivariate analysis (**Table 4**), a lower probability of receiving chemotherapy was correlated with the following indicators: Age, race, insurance status, marital status, metastatic status, poverty rate, and education level. **Table 5** shows that age, insurance status, marital status, SEER stage, metastatic status, poverty rate, and education level could significantly influence the odds of receiving no treatment (no chemotherapy or surgery) in the multivariate model. Notably, a high level of

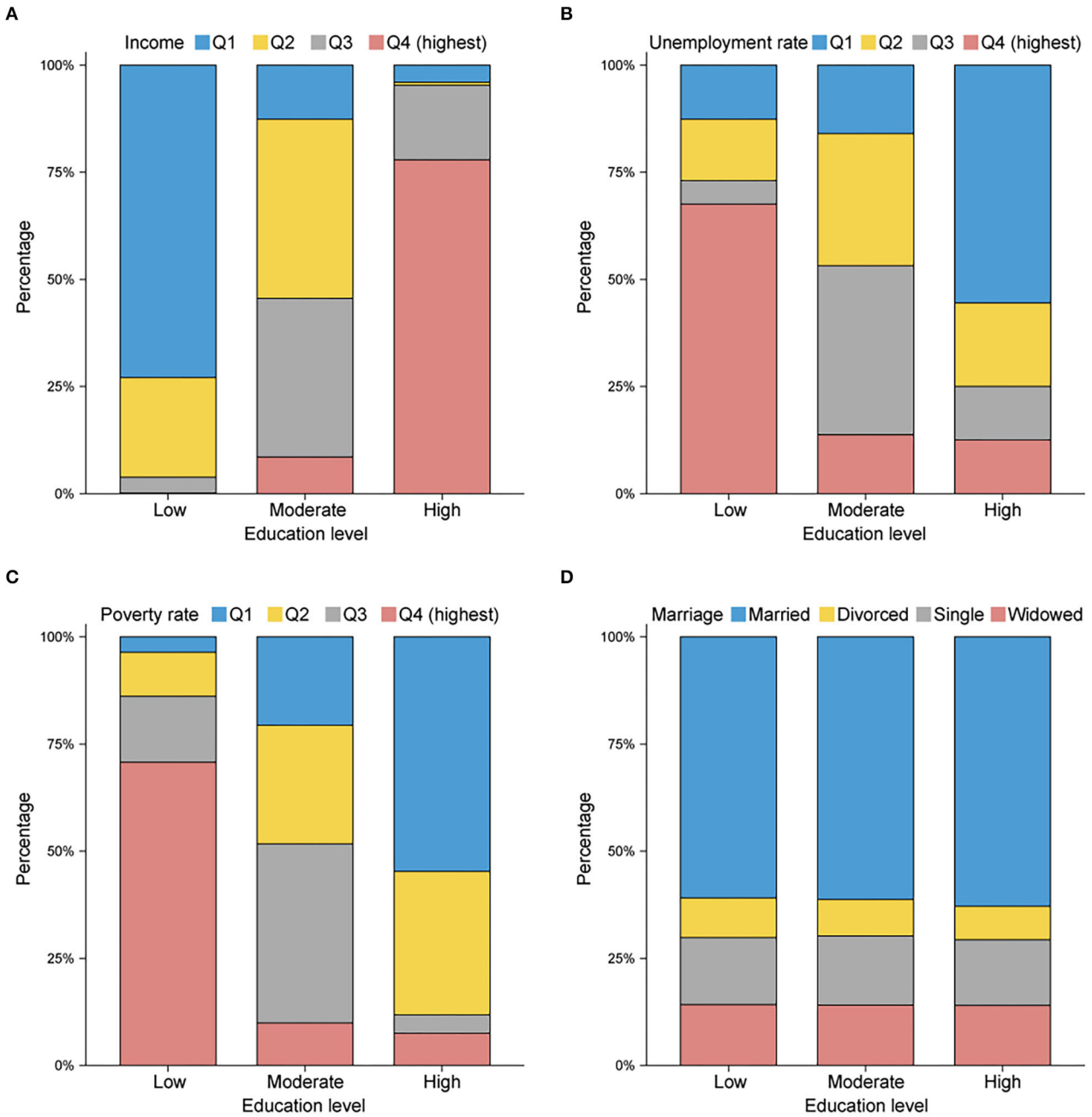

FIGURE 2 | Histogram plots reflecting the proportions in **(A)** median household income, **(B)** unemployment rate, **(C)** poverty rate, and **(D)** marital status, stratified by county education level. Q1, quartile 1 (lowest); Q2, quartile 2 (lower); Q3, quartile 3 (higher); Q4, quartile 4 (highest). Counties with higher education levels tend to have higher average income levels and lower unemployment and poverty rates.

education was independently associated with a higher receipt of chemotherapy (OR: 1.295, $p = 0.002$) and a lower probability of no treatment (OR: 0.814, $p = 0.023$). Even though radiotherapy was not significant in the multivariate Cox analysis, we described the differences in radiotherapy receipt by education level (**Supplementary Table 1**), given the role of radiotherapy in the standard of health care. Our results showed that no statistical significance was observed in the receipt of radiation among different education levels.

DISCUSSION

Of note, SES proved to play a vital role in the pathogenesis of the disease and survival rate of patients with GC (6,

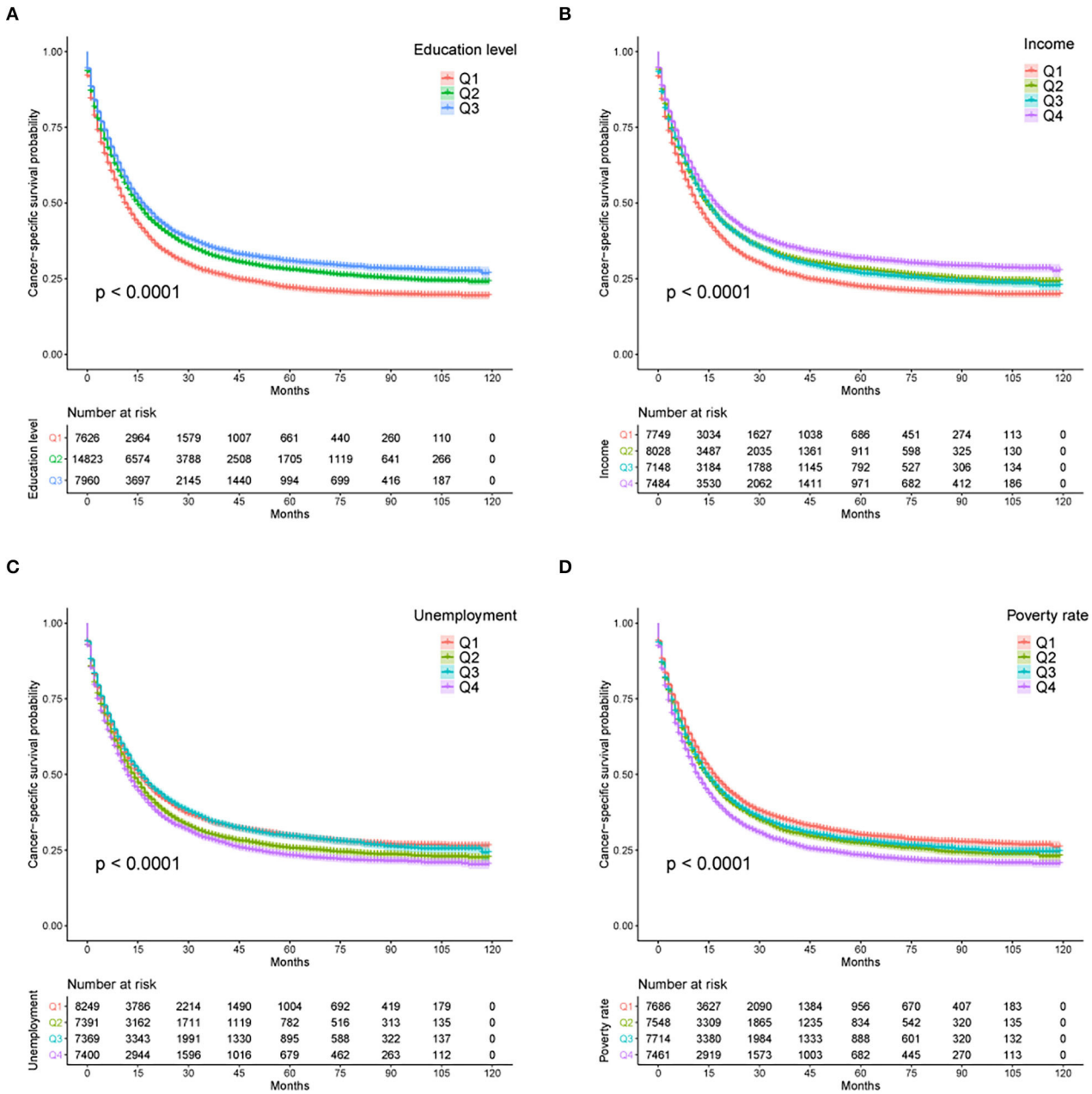

FIGURE 3 | Kaplan–Meier survival curves for CSS according to **(A)** education level, **(B)** income, **(C)** unemployment rate, and **(D)** poverty rate. CSS, cancer-specific survival; U/M, uninsured/Medicaid; NHW, non-Hispanic White; NHB, non-Hispanic Black; NHAPI, non-Hispanic Asian or Pacific Islander.

7, 11), yet there remains a paucity of evidence on the prognostic effects resulting from education level. It is necessary to elaborate on this issue with a large population-based study. Through SEER data, we clarified that low education level was significantly linked to diminished survival rates in patients with GAC, serving as an independent and robust predictor. This view was strengthened by evidence from the subgroup analysis. Moreover, a higher risk for receiving no treatment was observed among patients in counties with low education levels, which explained their poor prognoses to some extent.

Our results confirm that a high level of education confers survival advantages, regardless of other variables. This finding is consistent with that of a previous study on gastroesophageal tumors (10). By contrast, our study included more recently diagnosed patients, larger sample sizes, and a longer follow-up period. The classifications for educational status were determined rationally by referring to a specialized index of educational

TABLE 2 | Univariate cox analysis of OS and CSS.

Characteristics	Levels	OS			CSS		
		HR	95% CI	*p*	HR	95% CI	*p*
Age	≤65 years	Ref			Ref		
	>65 years	1.207	1.176–1.239	<0.001	1.103	1.072–1.134	<0.001
Sex	Male	Ref			Ref		
	Female	1.026	0.999–1.054	0.064	1.028	0.998–1.058	0.067
Race	NHW	Ref			Ref		
	NHB	1.052	1.011–1.094	0.013	1.023	0.980–1.068	0.301
	NHAPI	0.701	0.674–0.730	<0.001	0.684	0.656–0.714	<0.001
	Hispanic	0.972	0.939–1.006	0.103	0.965	0.930–1.001	0.055
Insurance	Insured	Ref			Ref		
	Uninsured	1.276	1.196–1.361	<0.001	1.303	1.217–1.394	<0.001
	Medicaid	1.127	1.089–1.166	<0.001	1.095	1.055–1.136	<0.001
Marriage	Married	Ref			Ref		
	Divorced	1.172	1.118–1.228	<0.001	1.144	1.088–1.203	<0.001
	Single	1.238	1.193–1.284	<0.001	1.215	1.169–1.264	<0.001
	Widowed	1.431	1.379–1.486	<0.001	1.337	1.284–1.392	<0.001
SEER stage	Distant	Ref			Ref		
	Localized	0.198	0.190–0.206	<0.001	0.150	0.143–0.157	<0.001
	Regional	0.329	0.319–0.339	<0.001	0.307	0.298–0.317	<0.001
AJCC stage	I	Ref			Ref		
	II	1.298	1.235–1.364	<0.001	1.520	1.437–1.608	<0.001
	III	1.852	1.765–1.943	<0.001	2.258	2.139–2.382	<0.001
	IV	4.602	1.765–1.943	<0.001	5.866	5.627–6.116	<0.001
Tumor grade	I	Ref			Ref		
	II	1.566	1.435–1.710	<0.001	1.753	1.584–1.941	<0.001
	III	2.101	1.931–2.287	<0.001	2.514	2.278–2.774	<0.001
	IV	1.843	1.612–2.107	<0.001	2.231	1.926–2.585	<0.001
	Unknown	2.869	2.624–3.137	<0.001	3.410	3.076–3.779	<0.001
Metastasis	No	Ref			Ref		
	Yes	3.793	3.689–3.899	<0.001	4.281	4.156–4.410	<0.001
Chemotherapy	Yes	Ref			Ref		
	No/Unknown	1.291	1.258–1.326	<0.001	1.199	1.166–1.234	<0.001
Radiation	Yes	Ref			Ref		
	No	1.442	1.400–1.486	<0.001	1.425	1.381–1.471	<0.001
Surgery	Yes	Ref			Ref		
	No	4.174	4.056–4.295	<0.001	4.562	4.422–4.705	<0.001
Income	Q1 (lowest)	Ref			Ref		
	Q2	0.842	0.812–0.872	<0.001	0.849	0.817–0.882	<0.001
	Q3	0.854	0.824–0.886	<0.001	0.861	0.828–0.895	<0.001
	Q4 (highest)	0.762	0.734–0.791	<0.001	0.765	0.736–0.796	<0.001
Unemployment	Q1 (lowest)	Ref			Ref		
	Q2	1.115	1.075–1.156	<0.001	1.110	1.068–1.154	<0.001
	Q3	1.002	0.966–1.040	0.903	0.990	0.951–1.030	0.606
	Q4 (highest)	1.198	1.156–1.243	<0.001	1.184	1.139–1.231	<0.001
Poverty rate	Q1 (lowest)	Ref			Ref		
	Q2	1.103	1.062–1.144	<0.001	1.100	1.057–1.144	<0.001
	Q3	1.070	1.031–1.111	<0.001	1.076	1.034–1.119	<0.001
	Q4 (highest)	1.262	1.216–1.309	<0.001	1.245	1.197–1.295	<0.001
Education level	Q1 (low)	Ref			Ref		
	Q2 (moderate)	0.843	0.816–0.869	<0.001	0.842	0.815–0.871	<0.001
	Q3 (high)	0.776	0.749–0.805	<0.001	0.778	0.748–0.809	<0.001

HR, hazard ratio; CI, confidence interval; NHW, non-Hispanic White; NHB, non-Hispanic Black; NHAPI, non-Hispanic Asian or Pacific Islander; AJCC, American Joint Committee on Cancer.

TABLE 3 | Multivariate cox analysis of OS and CSS.

Characteristics	Levels	OS			CSS		
		HR	95% CI	*p*	HR	95% CI	*p*
Age	≤65 years	Ref			Ref		
	>65 years	1.275	1.238–1.313	<0.001	1.192	1.156–1.230	<0.001
Race	NHW	Ref			Ref		
	NHB	0.982	0.942–1.024	0.397	0.960	0.917–1.004	0.072
	NHAPI	0.819	0.785–0.855	<0.001	0.813	0.776–0.851	<0.001
	Hispanic	0.940	0.906–0.976	0.001	0.924	0.888–0.961	<0.001
Insurance	Insured	Ref			Ref		
	Uninsured	1.063	0.994–1.136	0.075	1.043	0.972–1.119	0.242
	Medicaid	1.062	1.024–1.101	0.001	1.027	0.988–1.068	0.181
Marriage	Married	Ref			Ref		
	Divorced	1.111	1.059–1.165	<0.001	1.082	1.029–1.139	0.002
	Single	1.113	1.071–1.156	<0.001	1.086	1.043–1.131	<0.001
	Widowed	1.180	1.135–1.228	<0.001	1.155	1.107–1.205	<0.001
SEER stage	Distant	Ref			Ref		
	Localized	0.621	0.550–0.702	<0.001	0.531	0.465–0.606	<0.001
	Regional	1.057	0.962–1.161	0.252	1.035	0.938–1.143	0.493
AJCC stage	I	Ref			Ref		
	II	1.257	1.159–1.364	<0.001	1.305	1.192–1.429	<0.001
	III	1.866	1.722–2.023	<0.001	2.006	1.835–2.193	<0.001
	IV	2.456	2.243–2.690	<0.001	2.670	2.418–2.949	<0.001
Tumor grade	I	Ref			Ref		
	II	1.240	1.136–1.355	<0.001	1.307	1.180–1.448	<0.001
	III	1.644	1.509–1.792	<0.001	1.806	1.635–1.995	<0.001
	IV	1.692	1.479–1.936	<0.001	1.914	1.651–2.219	<0.001
	Unknown	1.450	1.325–1.587	<0.001	1.571	1.415–1.743	<0.001
Metastasis	No	Ref			Ref		
	Yes	1.165	1.056–1.285	0.002	1.155	1.043–1.280	0.006
Chemotherapy	Yes	Ref			Ref		
	No/Unknown	2.373	2.300–2.448	<0.001	2.379	2.301–2.458	<0.001
Radiation	Yes	Ref			Ref		
	No	0.997	0.965–1.030	0.859	0.989	0.955–1.024	0.529
Surgery	Yes	Ref			Ref		
	No	3.112	3.000–3.228	<0.001	3.235	3.110–3.366	<0.001
Income	Q1 (lowest)	Ref			Ref		
	Q2	0.944	0.896–0.993	0.027	0.946	0.895–0.999	0.047
	Q3	0.938	0.880–1.000	0.050	0.944	0.882–1.010	0.097
	Q4 (highest)	0.902	0.829–0.981	0.016	0.909	0.831–0.994	0.037
Unemployment	Q1 (lowest)	Ref			Ref		
	Q2	1.057	1.014–1.102	0.008	1.050	1.005–1.098	0.028
	Q3	0.953	0.907–1.001	0.057	0.935	0.887–0.986	0.013
	Q4 (highest)	0.996	0.946–1.049	0.887	0.979	0.927–1.034	0.453
Poverty rate	Q1 (lowest)	Ref			Ref		
	Q2	1.010	0.968–1.053	0.659	1.015	0.970–1.061	0.529
	Q3	0.993	0.928–1.063	0.840	1.025	0.954–1.102	0.502
	Q4 (highest)	1.057	0.984–1.135	0.126	1.064	0.986–1.148	0.108
Education level	Q1 (low)	Ref			Ref		
	Q2 (moderate)	0.926	0.885–0.969	0.001	0.915	0.872–0.960	<0.001
	Q3 (high)	0.915	0.860–0.973	0.005	0.907	0.849–0.969	0.004

HR, hazard ratio; CI, confidence interval; NHW, non-Hispanic White; NHB, non-Hispanic Black; NHAPI, non-Hispanic Asian or Pacific Islander; AJCC, American Joint Committee on Cancer.

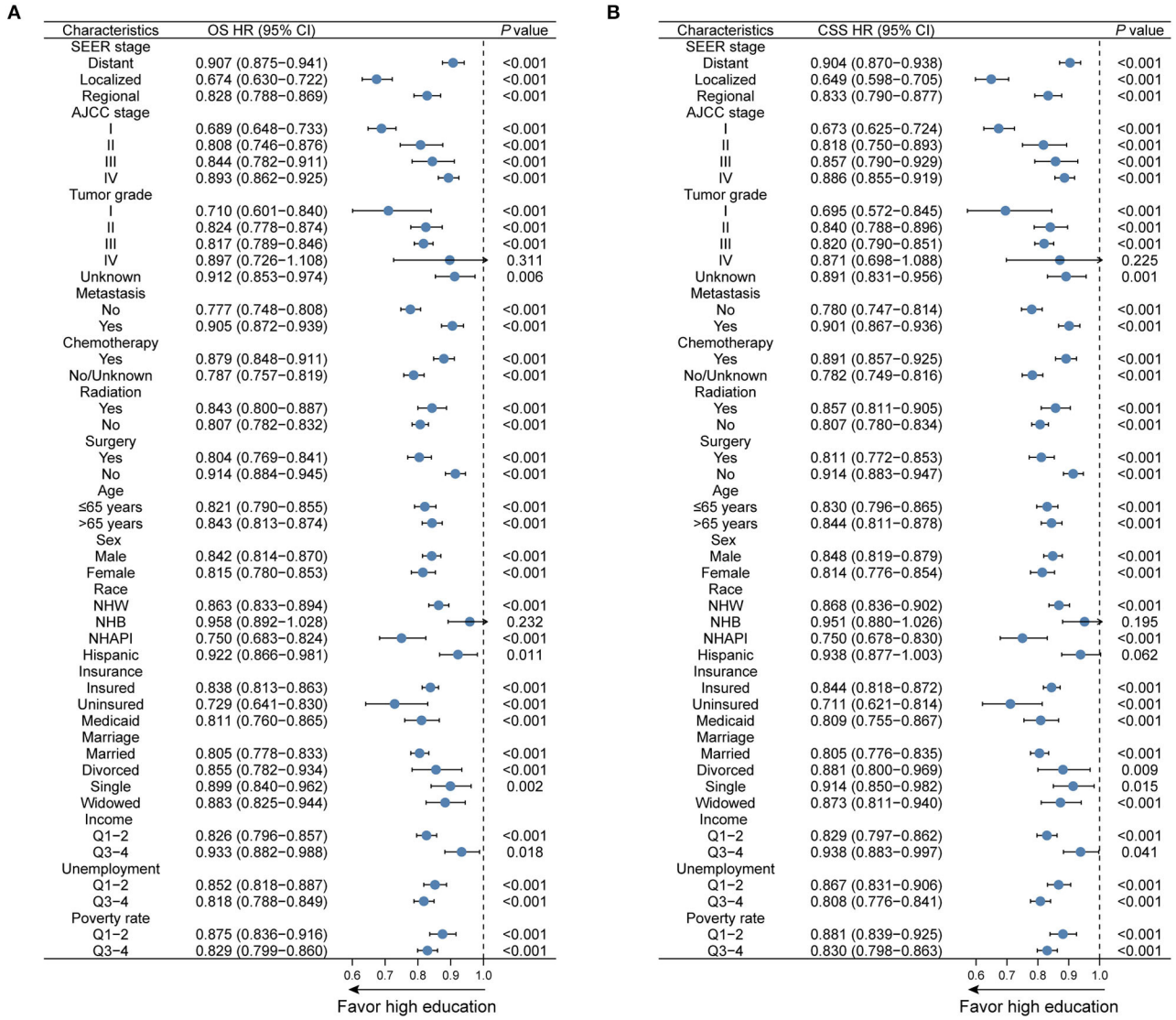

FIGURE 4 | Subgroup analyses regarding education level for **(A)** OS and **(B)** CSS in the overall cohort. OS, overall survival; CSS, cancer-specific survival; HR, hazard ratio; CI, confidence interval; NHW, non-Hispanic White; NHB, non-Hispanic Black; NHAPI, non-Hispanic Asian or Pacific Islander.

degrees. Two earlier studies based on the European population also reported that a higher education level was a favorable prognostic factor in patients with GC (21, 22), which further supports our conclusion. However, these two studies only assessed the impact of simple SES on the survival of patients with GC; clinical factors were not considered. We included detailed clinical variables and confirmed the importance of education level after adjusting for covariates. Moreover, we conducted comprehensive subgroup analyses to fully describe that a low education level carries a higher risk for both OS and CSS in almost every subgroup, highlighting its broad applicability as a prognostic predictor. Nevertheless, we noted that the effect of education category was not so significant for NHB and patients with Grade IV tumor, most likely because of the small sample size of the NHB group. For the latter, a higher tumor grade was positively correlated with the development of a distant metastasis. leading to very poor survival rates for patients with GC (23). This finding could potentially attenuate the effects of education.

A prognosis is largely dependent on treatment modalities and types. As expected, in this study, patients undergoing a combination of surgical resection and chemotherapy experienced the best survival benefits; specifically, gastrectomy performed after chemotherapy led to superior outcomes (24, 25). The survival trends also persisted in stage IV patients, for whom prognoses were quite dismal (as illustrated by the Kaplan–Meier curves). For this population, palliative chemotherapy with supportive care remains the main treatment modality (4,

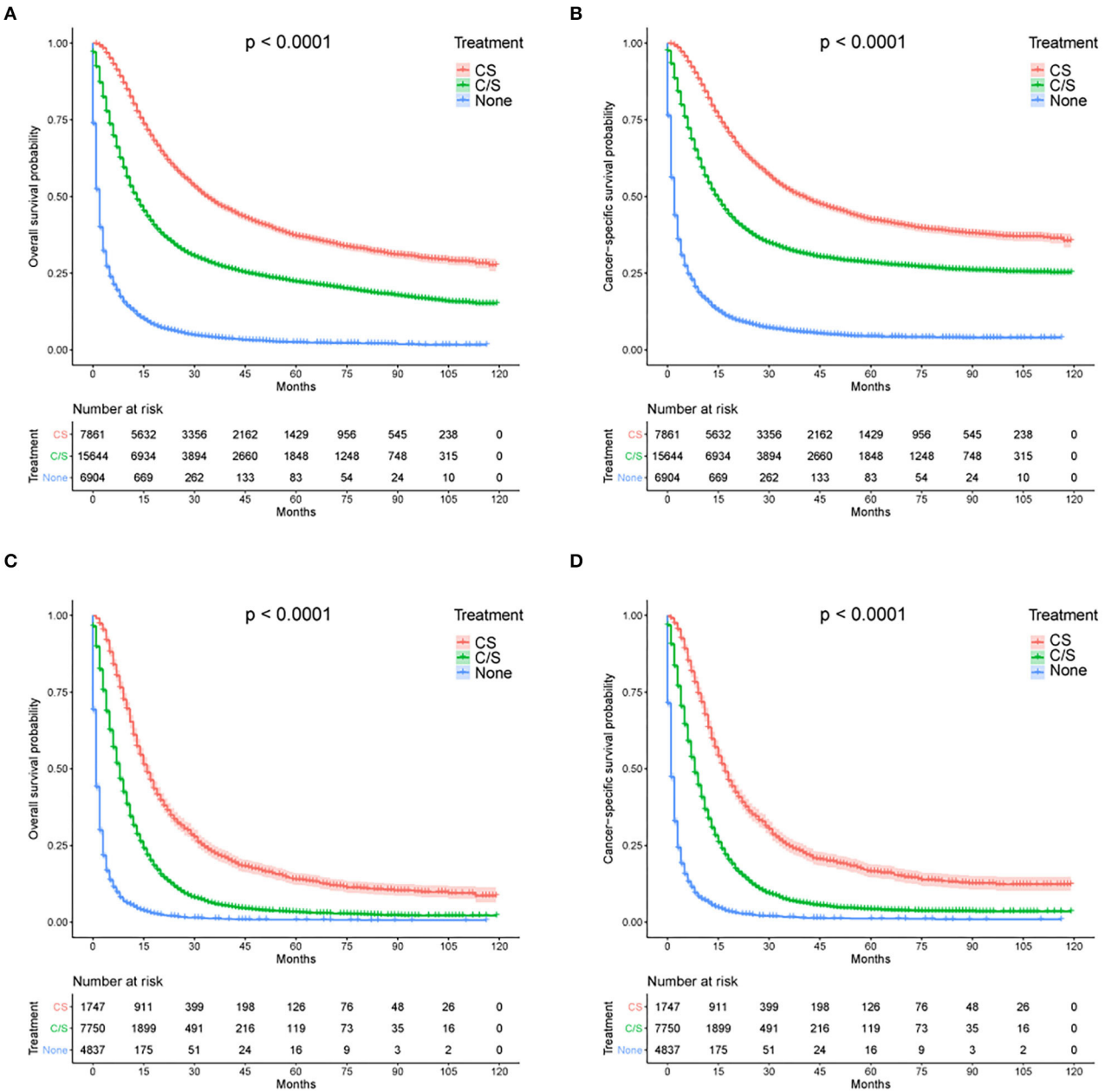

FIGURE 5 | Survival analysis of treatment options for **(A)** OS and **(B)** CSS among all patients with GAC; Survival analysis of treatment options for **(C)** OS and **(D)** CSS among AJCC stage IV tumor patients. CS, chemotherapy combined with surgery; C/S, chemotherapy or surgery alone; None, no chemotherapy or surgery.

26). We performed a logistic regression analysis to validate the role of education in the use of cancer treatments. Here, we report for the first time that a low education level is strongly associated with a lack of therapy in patients with stage IV GC, and this finding complements the two other studies on non-advanced or regional GC (14, 27). However, radiotherapy was not associated with significant survival differences, which is likely due to the low sensitivity of GAC to radiotherapy. Currently, the role of radiotherapy in adjuvant treatment or palliative treatment for GC is less certain (28, 29).

Similar findings have also been reported for other tumor types (10, 17–19), indicating that education disparities are imperative public health concerns. Thus, we were interested in the underlying effects of individual education levels for patients with cancer. First, patients with high education levels tend to be in high SES categories, with easier access to health care and greater financial resources, which typically guarantee better health

TABLE 4 | Univariate and multivariate logistic regression analysis of chemotherapy receipt in AJCC stage IV patients.

Characteristics	Levels	Crude OR	95% CI	*p*	Adjusted OR	95% CI	*p*
Age	≤65 years	Ref			Ref		
	>65 years	0.380	0.355–0.407	<0.001	0.353	0.327–0.381	<0.001
Sex	Male	Ref			Ref		
	Female	0.831	0.776–0.890	<0.001	1.008	0.934–1.088	0.843
Race	NHW	Ref			Ref		
	Hispanic	0.941	0.866–1.024	0.157	0.922	0.837–1.015	0.097
	NHAPI	0.874	0.790–0.967	0.009	0.826	0.737–0.926	0.001
	NHB	0.769	0.694–0.851	<0.001	0.869	0.776–0.972	0.014
Insurance	Insured	Ref			Ref		
	Medicaid	0.731	0.672–0.796	<0.001	0.685	0.623–0.754	<0.001
	Uninsured	0.639	0.557–0.734	<0.001	0.439	0.378–0.509	<0.001
Marriage	Married	Ref			Ref		
	Divorced	0.775	0.687–0.874	<0.001	0.756	0.667–0.858	<0.001
	Single	0.658	0.602–0.720	<0.001	0.617	0.560–0.680	<0.001
	Widowed	0.299	0.269–0.333	<0.001	0.434	0.386–0.488	<0.001
SEER stage	Distant	Ref			Ref		
	Regional	1.258	1.121–1.411	<0.001	0.761	0.552–1.049	0.095
Tumor grade	I	Ref					
	II	0.913	0.692–1.206	0.523			
	III	1.045	0.798–1.369	0.749			
	IV	0.871	0.592–1.281	0.483			
	Unknown	0.819	0.621–1.081	0.159			
Metastasis	No	Ref			Ref		
	Yes	0.758	0.681–0.845	<0.001	0.542	0.400–0.733	<0.001
Income	Q1 (lowest)	Ref			Ref		
	Q2	1.057	0.965–1.158	0.233	1.064	0.927–1.221	0.379
	Q3	1.324	1.204–1.457	<0.001	1.056	0.889–1.256	0.534
	Q4 (highest)	1.355	1.232–1.490	<0.001	0.918	0.731–1.152	0.460
Unemployment	Q1 (lowest)	Ref			Ref		
	Q2	0.940	0.855–1.032	0.195	1.047	0.936–1.170	0.422
	Q3	0.807	0.735–0.886	<0.001	0.999	0.874–1.142	0.990
	Q4 (highest)	0.767	0.699–0.841	<0.001	0.972	0.845–1.118	0.691
Poverty rate	Q1 (lowest)	Ref			Ref		
	Q2	0.841	0.764–0.925	<0.001	0.834	0.744–0.935	0.002
	Q3	0.703	0.640–0.773	<0.001	0.731	0.609–0.879	0.001
	Q4 (highest)	0.698	0.635–0.768	<0.001	0.776	0.639–0.944	0.011
Education level	Q1 (low)	Ref			Ref		
	Q2 (moderate)	1.125	1.038–1.220	0.004	1.079	0.955–1.219	0.220
	Q3 (high)	1.373	1.251–1.508	<0.001	1.295	1.095–1.531	0.002

OR, odd ratio; CI, confidence interval; NHW, non-Hispanic White; NHB, non-Hispanic Black; NHAPI, non-Hispanic Asian or Pacific Islander.

outcomes. Evidence also supports financial income as positively related to health status (30). Second, high educational attainment has positive impacts on vigorous physical exercise regimens and negative impacts on smoking, poor diet, sedentary habits, and other unhealthy behaviors (31). Convincing data show that appropriate diet, physical activities, and normal BMI have survival benefits for cancers (32), as they are associated with such biological hallmarks as immune responses, epigenetic regulation, and rhythm disorders (33). Third, highly educated patients have higher levels of health awareness (i.e., understanding medical information and receiving effective interventions) (34). Fourth, from a psychological perspective, the patients with higher education levels are less likely to become depressed or low-spirited (35). Depression or psychosocial stressors can drive tumor progression and cause worse outcomes through a large number of biobehavioral pathways (36). Fifth, employment rates and income levels are both higher among the better educated patients, which may facilitate their access to advanced treatment regimens with superior continuity and completion. However, the inadequacy is that the examined variable is not the real

TABLE 5 | Univariate and multivariate logistic regression analysis of no treatment (no chemotherapy or surgery) in AJCC stage IV patients.

Characteristics	Levels	Crude OR	95% CI	*p*	Adjusted OR	95% CI	*p*
Age	≤65 years	Ref			Ref		
	>65 years	2.232	2.080–2.395	<0.001	2.556	2.356–2.774	<0.001
Sex	Male	Ref			Ref		
	Female	1.106	1.029–1.188	0.006	0.934	0.861–1.012	0.096
Race	NHW	Ref			Ref		
	Hispanic	0.972	0.890–1.061	0.522	1.045	0.944–1.157	0.396
	NHAPI	0.927	0.833–1.031	0.163	1.054	0.933–1.190	0.397
	NHB	1.223	1.101–1.359	<0.001	1.120	0.996–1.260	0.058
Insurance	Insured	Ref			Ref		
	Medicaid	1.239	1.135–1.354	<0.001	1.353	1.224–1.495	<0.001
	Uninsured	1.680	1.462–1.931	<0.001	2.329	1.997–2.716	<0.001
Marriage	Married	Ref			Ref		
	Divorced	1.338	1.180–1.516	<0.001	1.363	1.194–1.557	<0.001
	Single	1.606	1.465–1.762	<0.001	1.712	1.546–1.895	<0.001
	Widowed	2.779	2.504–3.084	<0.001	2.140	1.900–2.409	<0.001
SEER stage	Distant	Ref			Ref		
	Regional	0.134	0.109–0.164	<0.001	0.451	0.292–0.698	<0.001
Tumor grade	I	Ref			Ref		
	II	1.014	0.761–1.352	0.924	1.063	0.784–1.442	0.695
	III	0.833	0.630–1.102	0.200	1.026	0.763–1.381	0.863
	IV	0.742	0.491–1.123	0.158	0.949	0.611–1.473	0.815
	Unknown	1.476	1.109–1.964	0.008	1.607	1.187–2.177	0.002
Metastasis	No	Ref			Ref		
	Yes	6.605	5.505–7.925	<0.001	3.787	2.576–5.567	<0.001
Income	Q1 (lowest)	Ref			Ref		
	Q2	0.876	0.797–0.963	0.006	0.899	0.777–1.039	0.149
	Q3	0.804	0.728–0.887	<0.001	0.944	0.787–1.133	0.538
	Q4 (highest)	0.754	0.683–0.833	<0.001	1.022	0.805–1.299	0.857
Unemployment	Q1 (lowest)	Ref			Ref		
	Q2	1.014	0.919–1.119	0.780	0.888	0.789–0.998	0.047
	Q3	1.085	0.985–1.196	0.099	0.918	0.798–1.057	0.235
	Q4 (highest)	1.235	1.121–1.359	<0.001	1.023	0.884–1.185	0.759
Poverty rate	Q1 (lowest)	Ref			Ref		
	Q2	1.127	1.020–1.245	0.019	1.140	1.011–1.285	0.032
	Q3	1.219	1.105–1.345	<0.001	1.258	1.037–1.526	0.020
	Q4 (highest)	1.308	1.184–1.444	<0.001	1.155	0.941–1.419	0.168
Education level	Q1 (low)	Ref			Ref		
	Q2 (moderate)	0.885	0.814–0.962	0.004	0.961	0.846–1.092	0.543
	Q3 (high)	0.762	0.692–0.840	<0.001	0.814	0.682–0.972	0.023

OR, odd ratio; CI, confidence interval; NHW, non-Hispanic White; NHB, non-Hispanic Black; NHAPI, non-Hispanic Asian or Pacific Islander.

measure of individual education levels. Our explanations are just based on the putative correlation between county-level education and individual-level education. In county-level terms, counties characterized by high SES have greater medical resources and services compared to those characterized by low SES. Counties with sufficient resources also have greater financial support, more Medicaid funding and programs, and a higher prevalence of academic centers, clinical trials, and collaborations with pharmaceutical companies. Moreover, counties known for high SES have populations that are wealthier, more educated, and more likely to be employed and insured, and these differences in the composition of patient demographics may contribute to the positive effects on survival.

In addition to education level, we identified other demographic factors associated with the treatment and survival for the patients with GAC. Married patients had the lowest rate for no treatment and the highest acceptance rate of chemotherapy compared with the three other unmarried groups. A good marriage may provide adequate economic resources and social support as the basis for treatment regimens. On the

contrary, widowed patients suffered the worst survival rates, possibly because they were less likely to receive treatment and had less social support, higher levels of loneliness, and an inferior insurance status. We also point out that uninsured or Medicaid patients had a significantly higher risk of no treatment. One reasonable explanation for this finding is that an uninsured or Medicaid status is more likely to be linked to poverty, low education levels, and other unfavorable SES factors. Interestingly, those with high income levels tended be less vulnerable to low education levels, according to the forest plots. This means that the adverse effect of a low level of education can possibly be compensated by increasing an individual's revenue. Notably, the beneficial effects of a high education level were the most obvious in the early stages of tumor development, including localized stage, AJCC stage I, and Grade I tumors, and non-metastatic status. The potential reasons for the favorable prognoses of highly educated individuals are advanced health consciousness, earlier diagnosis, and more effective interventions.

The present study has several limitations. First, sociodemographic variables provided by the SEER database were at the county-level rather than the individual level. The principal conclusions were dependent on an investigation at the community level; personal information was lacking. Nevertheless, this is still a reliable measure with practical implications for assessing SES, which has always been widely applied in SEER-based socioeconomic studies. Second, our results only reflect part of the affected population in the United States, and it remains uncertain whether these findings can be applied to other regions of the world. Lastly, we have provided comprehensive evidence of associations between education level and GC but no formal proof of causality. Further statistical methods need to be employed to evaluate casual effects.

While patient knowledge and education levels will remain relatively unchanged among older adults, the adverse sociodemographic status attributed to education levels cannot be ignored. More effective interventions are warranted to mitigate the unfavorable effects from low education levels and SES. Clinicians should enhance health education for patients to promote their health perceptions and behaviors. Governments and medical institutions are also expected to provide equal access to health care resources and services for those vulnerable groups. Income level, insurance status, marital status, and other socioeconomic elements are also involved in multifactor interactions of the disease treatment process. Long-term tracking in the dynamic changes of these factors will be informative for explaining the mechanisms.

To conclude, the education level is sufficiently established as an independent predictor for survival differences in patients with GAC. Our study indicates that the higher education levels may offer greater survival benefits and increase chemotherapy receipt. With predictions based on the education levels, designing personalized and suitable treatment plans in clinical practice is a promising approach.

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

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas. Additionally, all authors took part in drafting, revising, and reviewing the article, giving final approval to the version to be published, agreeing on the journal to which the article has been submitted, and remaining accountable for all aspects of the work.

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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.2022.868416/full#supplementary-material

Supplementary Figure 1 | Kaplan–Meier survival curves for OS according to **(A)** education level, **(B)** income, **(C)** unemployment rate, and **(D)** poverty rate of the patients. OS, overall survival; U/M, uninsured/Medicaid; NHW, non-Hispanic White; NHB, non-Hispanic Black; NHAPI, non-Hispanic Asian or Pacific Islander.

Supplementary Figure 2 | Kaplan–Meier survival analysis for OS in subgroups as follows: **(A)** age > 65 years, **(B)** non-Hispanic White, **(C)** unmarried status, **(D)** uninsured or Medicaid status, **(E)** SEER distant stage, **(F)** AJCC stage IV, **(G)** Grade II–IV tumor, and **(H)** metastatic status, stratified by education level. OS, overall survival; AJCC, American Joint Committee on Cancer; Education level: Q1 (low level, lowest quartile), Q2 (moderate level, 2nd and 3rd quartiles), and Q3 (high level, highest quartile).

Supplementary Figure 3 | Kaplan–Meier survival analysis for CSS in subgroups as follows: **(A)** age > 65 years, **(B)** non-Hispanic White, **(C)** unmarried status, **(D)** uninsured or Medicaid status, **(E)** SEER distant stage, **(F)** AJCC stage IV, **(G)** Grade II–IV tumor, and **(H)** metastatic status, stratified by education level. CSS, cancer-specific survival; AJCC, American Joint Committee on Cancer; Education level: Q1 (low level, lowest quartile), Q2 (moderate level, 2nd and 3rd quartiles), and Q3 (high level, highest quartile).

Supplementary Table 1 | Univariate and multivariate logistic regression analysis of radiotherapy receipt in AJCC stage IV patients. OR, odd ratio; CI, confidence interval; NHW, non-Hispanic White; NHB, non-Hispanic Black; NHAPI, non-Hispanic Asian or Pacific Islander.

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An Assessment Framework for the Training of General Practitioners and Specialists Based on EPAs

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Purpose: The purpose of this study is to explore the practicality and feasibility of EPA (level 4 theory) for establishing medical training and service model in China.

Method: We opted for a mixed qualitative and quantitative research method, considering both explanatory and exploratory sequential designs. The qualitative research comprehended focus groups and interviews conducted with two panels of experts. The quantitative research was conducted to collect data about the applicability of international entrustable professional activities (EPAs) pediatrics standards in the Chinese context by organizing a seminar with a sample of 60 pediatricians. A questionnaire was designed with EPAs and distributed within professional networks. Structural equation modeling and statistical analysis were used to process the data.

Results: In this study, Medical Service-Groups Model (MSGM) with four levels was successfully established to measure the correlation between specialized and general EPAs. As expected, results showed that specialized EPAs were built on top of general EPAs. There may be a mediating mechanism that general EPAs contribute to the lower level of specialization EPAs. In addition, levels 1 and 2 were primarily needed to lay the groundwork for levels 3 and 4, and these higher levels of EPAs were still the most informative for specialized Gastroenterology EPAs.

Conclusions: The diagnosis and treatment level of primary general practitioners, as the basis of the pediatric medical service chain, affected the clinical disposal ability of specialists. The establishment of MSGM provided a theoretical basis for the linkage training of general practitioners and specialist physicians. In future studies, scholars must explore China's EPAs based on unique national conditions.

Keywords: pediatricians, medical service, training, entrustable professional activities, structural model

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INTRODUCTION

Medical development has always been a worldwide subject of research. The World Health Organization (WHO) introduced a basic framework for an integrated health service system in 2016 and made it a global health strategy contributing to sustainable development goals. Despite the rapid development of medical care in China in recent decades, there are still many problems such as the scarcity of medical resources, the imbalance between supply and demand, and the imperfect primary medical system (1, 2). There are many factors contributing to this effect such as a big workload for specialist physicians, an insufficient supply of general physicians, and patients' preferences for community hospitals (3).

There are about 279 million children under the age of 18 years in China, accounting for 15% of children worldwide (4). Therefore, pediatric health care assumes enormous national responsibility, and pediatricians play an important role in China's health care system and constitute a core component of pediatric care resources. The crisis facing pediatric medicine in China, namely the burnout of pediatricians that may place both physicians and patients at risk, (5, 6) has received considerable publicity recently (7). In this context, it is of great significance to integrate regional pediatric medical resources, strengthen the support of primary pediatric medical institutions, improve the ability of pediatric medical services, optimize the allocation of pediatric medical resources, and improve medical efficiency and satisfaction.

Within the profession, the specialty of pediatric gastroenterology is rapidly evolving and increasingly recognized and accepted worldwide (8). The unique characteristics of pediatric gastroenterologists are that they have the potential to be experts in much of the anatomy and physiology of the human body (9). Trainees must have the capacity to analyze and integrate the clinical data, rather than limiting their thought processes to a specific organ or part of the gastrointestinal tract. In addition, the practitioners require routine consulting and collaborating with myriad allied providers and many of the diseases encountered are also related to other subspecialties, necessitating cooperative relationships with these experts. Therefore, the field of pediatric gastroenterology is multidisciplinary and a representative clinical discipline.

To alleviate the contradiction between the increasing demand for medical treatment and the scarcity of pediatrician resources and to better play the radiation effect of medical resources in community hospitals, this study introduced the concept of entrustable professional activities (EPAs) as a tool to assess the competence of pediatric gastroenterologists. EPAs were often used to observe and measure competencies (10, 11). Various courses have been described for suitable EPAs, which involved local or national expert groups (12–14). EPAs are defined as a comprehensive set of responsibilities that physicians (specialists or general practitioners) should be able to perform in their particular field. They must be detailed enough to set the expectations of trainees and guide the assessment and entrustment decisions of supervisors (15). EPAs also provide curriculum developers with tangible goals to align training with clinical practice (16).

In this research, EPAs theory was employed to explore a training model for Chinese pediatricians *via* qualitative and quantitative analysis. The model can be used for the further education of Chinese pediatricians and pediatric skill training for general physicians in communities or the Co-training of general pediatricians and specialist pediatricians. We studied the Co-ordination possibilities between general pediatricians and specialist pediatricians in terms of entrustable professional activities, which served as the prelude for the prospective research of the functional construction of the referral medical system between community, central, and teaching hospitals. The Co-ordination between general and specialist pediatricians can help establish a sound treatment order.

METHOD

Research Design

We opted for a mixed-methods approach as it offers the possibility of joining the strengths of both qualitative and quantitative (17) methods. In designing this mixed-methods study, we considered both explanatory and exploratory sequential designs (18). As our major intention was exploratory in nature, that is, we were motivated first to uncover freely generated interpretations of EPA in pediatrics in China, we deployed the exploratory sequential design from the perspective of an inductive approach. With the insight it provided from qualitative data analysis, we could design a questionnaire that allowed for a comprehensive data collection, thus integrating all variables into a single explanatory model.

Qualitative Research

The focus group and expert interviews were conducted with a semi-structured interview technique. The two kinds of interviews were semi-guided and adopted the same questions, although they could be changed to better capture what the interviewees might be concerned about. This study was organized in a total of two focus group interviews and four expert interviews: all the participants in the first interview are pediatricians (specialists and ordinary pediatricians). The participants in the second interview are nurses, medical technicians, scientific research personnel, management personnel, and social experts.

Quantitative Research

We used the EPAs items that have been widely certified and used to explain, verify, and amend a model through the development of practice activities (sourced from EPAs) among Chinese pediatricians.

Abbreviations: WHO, World Health Organization; EPAs, entrustable professional activities; AAP, American Academy of Pediatrics; KMO, Kaiser–Meyer–Olkin; MSGM, medical service-groups model; APC, average path Co-efficient; ARS, average R-squared; AARS, average adjusted R-squared; AVIF, average block VIF; AFVIF, Average full collinearity VIF; GoF, Tenenhaus GoF; SPR, sympson's paradox ratio; RSCR, R-squared contribution ratio; SSR, software incorporates an index; NLBCDR, non-linear bivariate causality direction ratio; CR, composite reliability; Lev, level; SGEPAs, specialized gastrointestinal EPAs; CITC, corrected item total correlation.

Examining Whether the EPAs Are Consistent With Chinese Pediatricians

The 17 items (Community Pediatricians) of EPAs Theory formulated by the American Academy of Pediatrics (AAP) and the five items (Practice Activities for Pediatric Digestion Specialty) drafted by the managerial level of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and AAP were chosen as a reference for making the questionnaire for investigation and survey. The top priority was to examine where the EPAs were consistent with the daily medical practice activities of Chinese pediatricians and pediatric specialists on digestion.

The researchers promoted a seminar in the form of an enlarged session during an executive meeting of the Shanghai Central Pediatrician Medical Treatment Partnerships with over 60 participants, including authoritative experts at home and abroad, daily clinical teachers who are experienced in both teaching and clinical work, and who hold intermediate professional titles or above. The authors presided over the seminar and briefed on the research background and problems that needed to be solved, introducing the research progress of EPAs and relevant theories. At the meeting, 22 EPAs (covering pediatric general practitioners and specialists on digestion) were given out to the experts to judge whether the items were in accord with the daily practice activities.

To enable these experts to better understand the meaning of practice activities, the full name and specific functions of each practice activity were listed. For the convenience of follow-up classification, the materials distributed to senior professional title experts were color-printed while the materials to physicians with intermediate or lower professional titles were printed in white and black. Each item of the materials issued at the seminar was attached with specific activity notes. After the seminar, supplements and corrections were made based on the feedback of experts.

Questionnaire Design and Measures

The questionnaire (19) covered relevant demographic information, occupational information, types of hospitals, and professional characteristics. The 5-point Likert scale was used to measure specific practice activities of 22 EPAs (pediatricians plus pediatric specialists on digestion).

Entrustable professional activities for general pediatrics were measured using 17 EPAs as found in the qualitative and the first quantitative phase. Participants were requested to answer on a 5-point Likert scale ranging from 1 (not important at all) to five (extremely important) to which extent they agreed that the described EPA should be performed frequently by pediatric gastroenterologists in community hospitals.

Entrustable professional activities for gastroenterological pediatricians were measured with five EPAs as found in the qualitative and the first quantitative phase. Participants were requested to answer on a 5-point Likert scale ranging from 1 (not important at all) to 5 (extremely important) to which extent they agreed that the described specialized EPA should be performed frequently by pediatric gastroenterologists in community hospitals.

Considering the professionalism of the contents in the questionnaires, the eligible respondents should be pediatricians, pediatric specialists on digestion, and other groups closely related to pediatrics. Therefore, the questionnaire was sensibly distributed to the groups in this industry by using special channels. To ensure the quality of the sample collected, the questionnaires were handed to members of China's pediatric academic organizations and participants in the academic meetings.

Finally, with guaranteed validity and reliability, we will show the test results: (a) if the EPA levels of complexity operate in parallel or in a hierarchical way, (b) which EPA levels predict each specialized EPAs, and (c) which individual EPAs predict each specialized EPAs, so to uncover the competencies that leverage EPAs. In this way, we intend to understand if the EPAs apply to pediatrics in China. The final model will offer a structural view for the linkage training of general practitioners and specialists.

Statistical Analysis

We confirmed data suitability using the Kaiser–Meyer–Olkin (KMO) index of sampling adequacy, adopted Covariance Base SEM (CB-SEM) and Partial Lease Square SEM (PLS-SEM) Structural Equations Modeling, and tested with PROCESS macro available in SPSS (20) and PLS-SEM software (Warp-PLS) (21). Statistical analyses were performed using IBM SPSS Statistics 20 and AMOS 17.0. For all tests, the statistical significance level was set at $P < 0.05$.

RESULTS

Data Description of the Sample

The sample comprises 776 valid answers originating from almost all the Chinese provinces with about two-thirds of the participants being from Hebei, Shanghai, Hubei, Jiangsu, Hainan, Hainan, Liaoning, and Guangdong (**Supplementary Figure 1** and **Supplementary Table 1**).

The type of pediatrician crossed with the type or nature of hospital is depicted in the following tables (**Supplementary Tables 2, 3**). It is clear that specialists are mostly working in community hospitals and that the largest sample comes from such hospitals.

Reflective vs. Formative Nature of EPAs

The opinions of experts holding a title of a senior professional post were mainly taken into consideration. Among the reviewed materials, research on the suggestions of doctors holding a title of a senior professional post was conducted. It was found that all 22 EPAs (pediatric general practitioners plus pediatric specialists on digestion), through expert review, were basically in line with the practice activities of Chinese pediatricians.

Validity analysis was used to know if the items under study were reasonably and meaningfully treated as reflecting a latent construct (22). Validity can be approached using a factor analysis where KMO value, commonalities, explained variance, and factor-loading Co-efficients are considered to judge the suitability of the analysis. KMO serves to identify if the data intercorrelation is high enough to allow the factor analysis. Commonalities should

attain at least the 0.5 threshold. When a given item does not do this, it does not converge with the other items in the factor analysis and should be excluded.

The variance explanation rate represents the information extraction quality and should be at least 60. Finally, factor loadings measure the magnitude in which a given item value reflects the corresponding latent construct.

The factor analysis validity indicators suggested that there was enough high level of intercorrelations to allow it (KMO = 0.993). However, there were many cases of insufficient commonalities (**Supplementary Table 4**) and the explained variance was below the comfortable level ($R^2 = 48.5\%$).

By sequentially removing items that showed lower commonality, we were able to obtain an efficient two-factor solution that had good KMO (.829) with commonality above.500 for all items, despite explaining only 58.5% of the total variance after rotation (Varimax). The remaining items corresponded to only seven EPAs, but one of them (EPAs #16) should be deleted based on cross-loading analysis. Therefore, the final factor rotation matrix contained only six EPAs (KMO = 0.771, commonalities all above.576, $R^2 = 60.9\%$) and had been organized in pediatricians' minds into a two-factor reflective structure (**Supplementary Table 5**).

This was relevant information, as it pertained to how extensively professionals integrated EPAs into a set of cognitive categories but is not workable for this research. These findings indicated that pediatricians had a common understanding of these six EPAs as organized around two major categories (data-based actions and intervention actions), but it leaves out very important EPAs. Because this research emphasizes performed activities, it was not a requirement that EPAs were organized around reflective constructs. Therefore, we concluded that EPAs should be considered as a formative structure. The reflective structure is the unobservable construct, which consists of the reflective indicators and the error term for each indicator. For formative structure, the items describe and define the construct rather than vice versa. The constructs comprised of these causal indicators along with a disturbance term. A paralleled scenario occurred for specialized gastrointestinal EPAs (SGEPAs) with the exploratory factor analysis showing a high level of intercorrelations (KMO = 0.824), except one case that had insufficient commonality (**Supplementary Table 6**) and explained variance below the comfort level ($R^2 = 56.1\%$).

Following the same rationale, we concluded that the construct for SGEPAs was in line with the previous choice for treating EPAs as formative. For such purposes, we will treat general EPAs and SGEPAs in the same way.

Reliability and Validity Analyses for General and Specialized Gastrointestinal EPAs

Since validity is based on the formative nature of constructs, we need to verify if the measures are reliable. Reliability concerns the extent to which a given questionnaire measures the same construct. It was commonly expressed by Cronbach's alpha, which attained the value of 0.70 (22). Findings were shown in **Supplementary Table 7**.

As may be seen in the above table, the reliability Co-efficients of General EPAs and SGEPAs were 0.883 and 0.801, respectively. Regarding the item deleted, α Co-efficient, the reliability Co-efficient of both cases has no significant improvement. As for CITC, there were many cases where the value fell below 0.60, indicating problems. In conclusion, the overall scale is reliable, but there are problems with specific items, probably because of its formative nature.

Testing the Hierarchical Model of EPAs

We speculated that general EPAs followed some sort of sequential structure, from simple to complex, from early to late, and from general to specialized. To uncover a meaningful structure, we reasoned that clinical learning processes took place in stages: (1) to gather all required information to reach a good diagnosis; (2) to understand macro-level dimensions that may impact the accuracy of the diagnosis; (3) to be capable of bridging with other services; and finally, (4) to deliver a best practice-based treatment while being able to lead clinically.

The first phase: when faced with any clinical situation, pediatricians need to properly use screening tools to gather information. This information will be more accurate when the physician can establish a positive relationship with the patient's family as well as colleagues. A family that is trusting and willing to Co-operate will disclose more information. Likewise, colleagues with whom one can have an open communication channel will also contribute to triangulating and clarifying doubtful situations.

The second phase: when faced with an emergency, pediatricians must be able to consider macro information related to risk groups, epidemiology, and understand services for referring emergency cases to pediatricians.

The third phase: many cases will require the intervention of other medical area professionals. These cases require a sense of importance and know how to transfer to other services to provide for clinical needs that may fall outside the scope of pediatricians.

The fourth phase: delivering best practice service implies knowing and observing referral guidelines while keeping a focus not only on treatment but also on the need to lead oneself into learning more while leading others. This level is the most complex as it comprehends practices that are usually allocated only to pediatricians in community hospitals.

Because such logic might not resonate with all pediatricians, we have subjected this proposal to the validation of expert pediatricians. We elected three senior-level experts and three more experts but with the medium position. The results may be found in **Supplementary Table 8**.

The interpretation allows the attribution of the following objectives linked to each EPA level:

1st level: establishing conditions to gather information for diagnosis
2nd level: first diagnosis and treatment
3rd level: bridging/referring to other services
4th level: observing best practices and leading

The four levels, named as Medical Service-Groups Model (MSGM), had an expected contribution to the overall job performance of a pediatrician while simultaneously being linked

in a sequence from the simplest to the more complex. This configured a sequential mediation model with three paths. The sequential mediation model is single-input and single-output, with one path leading to the end. There is an only adjacent relationship between layers and no cross-layer connection. The first path linked to level 1 with level 2, the second path linked to level 2 with level 3, and the third path linked to level 3 with level 4. We believed that it is also reasonable to expect relations between these levels that bypass the sequential mediation making it partial. We assumed that there is a partial mediation between levels 1 and 4, which occurs through a sequential positive relationship between levels 2 and 3.

Based on this rationale, we hypothesized that:

Hypothesis 1: Level 2 mediated the positive relationship between Levels 1 and 3 ($1 \overset{2}{\longleftrightarrow} 3$)

Hypothesis 2: Level 3 mediated the positive relationship between Levels 1 and 4($1 \overset{3}{\longleftrightarrow} 4$)

Hypothesis 3: There was a sequential mediation by Level 2 and Level 3 in the positive relationship between Levels 1 and 4 ($1 \overset{2}{\underset{3}{\longleftrightarrow}} 4$).

Hierarchical EPAs Structure of MSGM With CB Models

The MSGM was depicted in **Supplementary Figure 2**, where X was Level 1, Y was Level 4, and M1 and M2 were Levels 2 and 3, respectively. The results showed that there were six direct effects and three indirect effects between X and Y operating simultaneously.

The relation between Levels 1 and 2 had considerable power that the explained variance was 37.1% corresponding to a significant F (1,774) value of 458.1993 ($P < 0.01$). The direct effect of Level 1 on Level 2 had a Co-efficient of.659.

The joint relation of Levels 1 and 2 on Level 3 also had considerable, with an explained variance of 49.4% corresponding to a significant F (2,773) value of 377.6766 ($P < 0.01$). The direct effect of Levels 1 and 2 was also significant, with a magnitude of.301 and.423, respectively.

The join relation of all preceding levels on Level 4 was slightly stronger than the previous with an explained variance of 50% corresponding to a significant F (3,772) value of 258.2555 ($P < 0.01$). The direct effects of Levels 1, 2, and 3 were all significant with a magnitude of 0.102, 0.180, and 0.342, respectively.

The totally standardized indirect effect of Level 1 on Level 3 through Level 2 was significant with a magnitude of 0.1508. This supported Hypothesis 1($1 \overset{2}{\longleftrightarrow} 3$).

The totally standardized indirect effect of Level 1 on Level 4 through Level 3 was significant with a magnitude of 0.1312. This supported Hypothesis 2($1 \overset{3}{\longleftrightarrow} 4$).

The totally standardized indirect effect of Level 1 on Level 4 through both Levels 2 and 3 was significant with a magnitude of 0.1215. This supported Hypothesis 3($1 \overset{2}{\underset{3}{\longleftrightarrow}} 4$).

Supplementary Table 9 summarized the findings from mediation testing and its respective classification. The results pertaining to mediation were shown in **Supplementary Figure 3**.

Hierarchical EPAs Structure of MSGM With PLS Models

The Average path Co-efficient (APC) (23) should be statistically significant ($P < 0.05$) and expressed the average association Co-efficients for direct effects established between latent variables. The Average R-squared (ARS) (24) and Average adjusted R-squared (AARS) should also be statistically significant, and the difference between the two should be no more than 5%. Other sets of indices are multicollinearity. The software offers calculations on the Average block VIF (AVIF) (25) and Average full collinearity VIF (AFVIF) that ideally should fall below 3.3 (values up to 5 are also within the acceptance range). These indicators are particularly important as they can show if common method bias occurred (26). Another important indicator is the Tenenhaus GoF (GoF) (27) which is expressed as being small ($0.01 \leq$ GOF < 0.25), medium ($0.25 \leq$ GOF < 0.36), or large (GOF over 0.36) and measures the explanatory power of the model. Other issues that may hamper the quality of a PLS-SEM model concern specific patterns of association between the values of two variables in such a way that false negatives may emerge. Sympson's paradox ratio (SPR) is useful to detect these. It should not fall below 0.70.

In addition, the R-Squared Contribution Ratio (RSCR) verifies if the model has any case of negative R-squared contribution, which would indicate the wrongly designed dependence direction of the hypotheses. Values over 0.9 indicate no problem with this issue. Also, statistical suppression is a problem that may occur when the absolute beta value is higher than the correlation between the two latent variables (28) and the software incorporates an index (SSR) that indicates the extent to which this might have occurred. Values of 0.70 or above indicate that statistical suppression did not occur. Finally, the non-linear bivariate causality direction ratio (NLBCDR) indicates how much beta Co-efficients between two latent variables may change when using non-linear algorithms and inverting the direction of causality. Perfect situations are indicated by a value of NLBCDR of 1, but the acceptable threshold is set to 0.70.

In the case of the current sequential mediation model, all values excluded validity and quality problems associated with the model. Correlation degree and explanatory variance were significant (APC = 0.369, ARS = 0.465, AARS = 0.464; $P < 0.001$). Likewise, there was no obvious multicollinearity problem (AVIF = 1.795, AFVIF = 2.101), and the model fitted the data well (GOF = 0.480). The SPR was 1 and Sympson's paradox was thus not a matter of concern, which was consistent with the SSR value of 1. In the direction of influence, the improvement was not observed in RSCR and NLBCDR (1 for both values) from reversing direction.

Variables also had high reliability. Composite Reliability (CR) reached threshold of 0.70 for all EPA levels (CR Level 1–4: 0.792, 0.782, 0.819, 0.814). The distributions were unimodal in both Rohatgi–Szekely and Klaassen–Mokveld–van ES tests, indicating

TABLE 1 | OLS regression for GI EPA 1[a].

Model	B (unstandardized)	Standard error	Beta (standardized)	t	Sig.	Collinearity statistics	
						Tolerance	VIF
(Constant)	0.005	0.202		0.024	0.981		
EPA GI Lev1	0.003	0.055	0.002	0.060	0.952	0.551	1.815
EPA GI Lev 2	0.095	0.056	0.072	1.713	0.087	0.465	2.151
EPA GI Lev 3	0.340	0.064	0.231	5.293	0.000	0.428	2.337
EPA GI Lev 4	0.687	0.074	0.377	9.340	0.000	0.499	2.004

[a]*Dependent Variable: B18 (GI EPA 1). Care acute/chronic GI disease.*

TABLE 2 | OLS regression for GI EPA 2[a].

Model	B (unstandardized)	Standard error	Beta (standardized)	t	Sig.	Collinearity statistics	
						Tolerance	VIF
(Constant)	0.324	0.222		1.454	0.146		
EPA GI Lev1	–0.040	0.061	–0.027	–0.659	0.510	0.551	1.815
EPA GI Lev 2	0.096	0.061	0.070	1.567	0.117	0.465	2.151
EPA GI Lev 3	0.329	0.071	0.216	4.658	0.000	0.428	2.337
EPA GI Lev 4	0.638	0.081	0.338	7.880	0.000	0.499	2.004

[a]*Dependent Variable: B19 (GI EPA 2). Care acute/chronic hepatobiliary disease.*

that the results were reliable. Results showed that all direct paths were statistically significant (**Supplementary Figure 4**).

The indirect effects of the two-path and the three-path were significant. The relationship mediation between Levels 1 and 3 *via* Level 2 presented a significant value of 0.287 ($P < 0.01$). Likewise, the relationship mediation between Levels 1 and 4 *via* Level 3 presented a significant value of 0.310 ($P < 0.01$). Finally, the three-path mediation model through Levels 2 and 3 also presented a significant value of 120 ($P < 0.01$) (**Supplementary Table 10**).

These results also supported all three hypotheses. Comparatively, although the path Co-efficients (and consequently indirect effects) in the PLS-SEM model were substantially larger than those in the CB-Process, the statistical significance remained equivalent for all studied paths. This ensured that the existing paths were not affected by data analysis technique options.

Specialized EPAs Dependence on General EPAs

Another issue of relevance to uncover the structure of EPAs was how they relate to the SGEPAs. Because specialized learning goals cannot be achieved at the expense of previously acquired learning and skills, we assume that:

> Hypothesis 4: All EPA levels are positively associated with each of the SGEPAs.

We derived six sub-hypotheses from H4a to H4f, one per each. Furthermore, we speculated that the magnitude of association between general EPAs and SGEPAs differed in the sense of being stronger in the more complex general EPAs.

Therefore, we hypothesize that:

> Hypothesis 5: There will be stronger associations between higher complexity EPA levels and SGEPAs than those found between the lower level and SGEPAs.

In this case, six sub-hypotheses were also derived from H5a to H5f. The CB-SEM method is used to analyze the covariance structure of variables. It mainly tests the applicability of theories and is suitable for testing theoretical models (validation), while the PLS-SEM method is used to analyze the principal component structure of variables. Mainly in the interpretation of variance (testing whether causality has a significant relationship), suitable for the construction of the theoretical model (exploratory), but also used to verify the causal relationship discussed. Because CB-SEM and PLS-SEM were previously used for analysis, we repeated this procedure for the new predictive models of SGEPAs, using multiple OLS regression with SPSS 24 and WarpPLS-SEM 6.0.

Specialized EPA Dependence on General EPA With CB Models

The results showed that each of the dependent regression analyses was separated. For GI EPA 1-5, the OLS multiple regression explained an adjusted variance of 36.9, 28.9, 28.0, 25.9, and 17.7%, respectively, where Levels 3 and 4 were significant predictors (**Tables 1**–**5**). This supported both Hypotheses 4 and 5.

Overall, hypothesis 4 was fully supported, thus suggesting that there was empirical evidence that SGEPAs were built on top of general EPAs. Likewise, Hypothesis 5 suggests that an established stronger association between higher general EPA levels (3 and 4) with SGEPAs was globally supported to the exception of GI

TABLE 3 | OLS regression for GI EPA 3[a].

Model	B (unstandardized)	Standard error	Beta (standardized)	t	Sig.	Collinearity statistics	
						Tolerance	VIF
(Constant)	0.839	0.207		4.049	0.000	0.551	1.815
EPA GI Lev1	0.037	0.057	0.027	0.652	0.515	0.465	2.151
EPA GI Lev 2	–0.008	0.057	–0.007	–0.147	0.883	0.428	2.337
EPA GI Lev 3	0.328	0.066	0.232	4.983	0.000	0.499	2.004
EPA GI Lev 4	0.588	0.075	0.336	7.797	0.000		

[a]*Dependent Variable: B20 (GI EPA 3). Diagnose and manage common GI/hepatobiliary diseases.*

TABLE 4 | OLS regression for GI EPA 4[a].

Model	B (unstandardized)	Standard error	Beta (standardized)	t	Sig.	Collinearity statistics	
						Tolerance	VIF
(Constant)	0.391	0.223		1.755	0.080		
EPA GI Lev1	0.137	0.061	0.094	2.253	0.025	0.551	1.815
EPA GI Lev 2	0.186	0.061	0.138	3.033	0.003	0.465	2.151
EPA GI Lev 3	0.276	0.071	0.184	3.900	0.000	0.428	2.337
EPA GI Lev 4	0.348	0.081	0.188	4.288	0.000	0.499	2.004

[a]*Dependent Variable: B21 (GI EPA 4). Assess and provide counseling regarding nutrition.*

TABLE 5 | OLS regression for GI EPA 5[a].

Model	B (unstandardized)	Standard error	Beta (standardized)	t	Sig.	Collinearity statistics	
						Tolerance	VIF
(Constant)	0.881	0.259		3.406	0.001		
EPA GI Lev1	0.026	0.071	0.016	0.368	0.713	0.551	1.815
EPA GI Lev 2	0.036	0.071	0.024	0.500	0.617	0.465	2.151
EPA GI Lev 3	0.218	0.082	0.132	2.652	0.008	0.428	2.337
EPA GI Lev 4	0.609	0.094	0.299	6.471	0.000	0.499	2.004

[a]*Dependent Variable: B22 (GI EPA 5). Using endoscopy.*

EPA 4. Furthermore, there was no indication of multicollinearity, meaning that the explained variance was not exaggerated due to inter EPA correlations.

Interestingly, the dependence of SGEPAs was stronger in the simplest GI EPAs, suggesting a possible mediating mechanism by which general EPAs contributed directly or indirectly through the lower levels of SGEPAs.

Specialized EPA Dependence on General EPA With PLS-SEM Models

In the first model (General EPA levels and SGEPAs 1), APC = 0.290 ($P < 0.001$), ARS = 0.443 ($P < 0.001$), and AARS = 0.441 ($P < 0.001$) (**Table 6**), indicating that it matched the requirements of validity and quality.

Multicollinearity was also ruled out (AVIF = 1.926, AFVIF = 2.064). The model fitted well (Tenenhaus GoF = 0.514), without Sympson's paradox problem (SPR = 1.000). SPR and SSR were both equal to 1, so there were no Simpson paradoxes problems due to data distortion. And both RSCR and NLBCDR were equal to 1, indicating that the reversal direction had not been improved.

TABLE 6 | Association Co-efficients general EPAs-GI EPA 1 for PLS-SEM.

	EPA_level 1	EPA_level 2	EPA_level 3	EPA_level 4
EPA_level 1				
EPA_level 2	0.610*			
EPA_level 3	0.313*	0.470*		
EPA_level 4	0.107	0.295*	0.417*	
EPA_GI 1	0.011	0.056	0.242*	0.374*

*$P < 0.001$.

For analysis purposes, the most informative findings concerned the existence or not of significant relationships between general EPA levels and the SGEPAs under focus. In the case of GI EPA 1, only two significant path Co-efficients

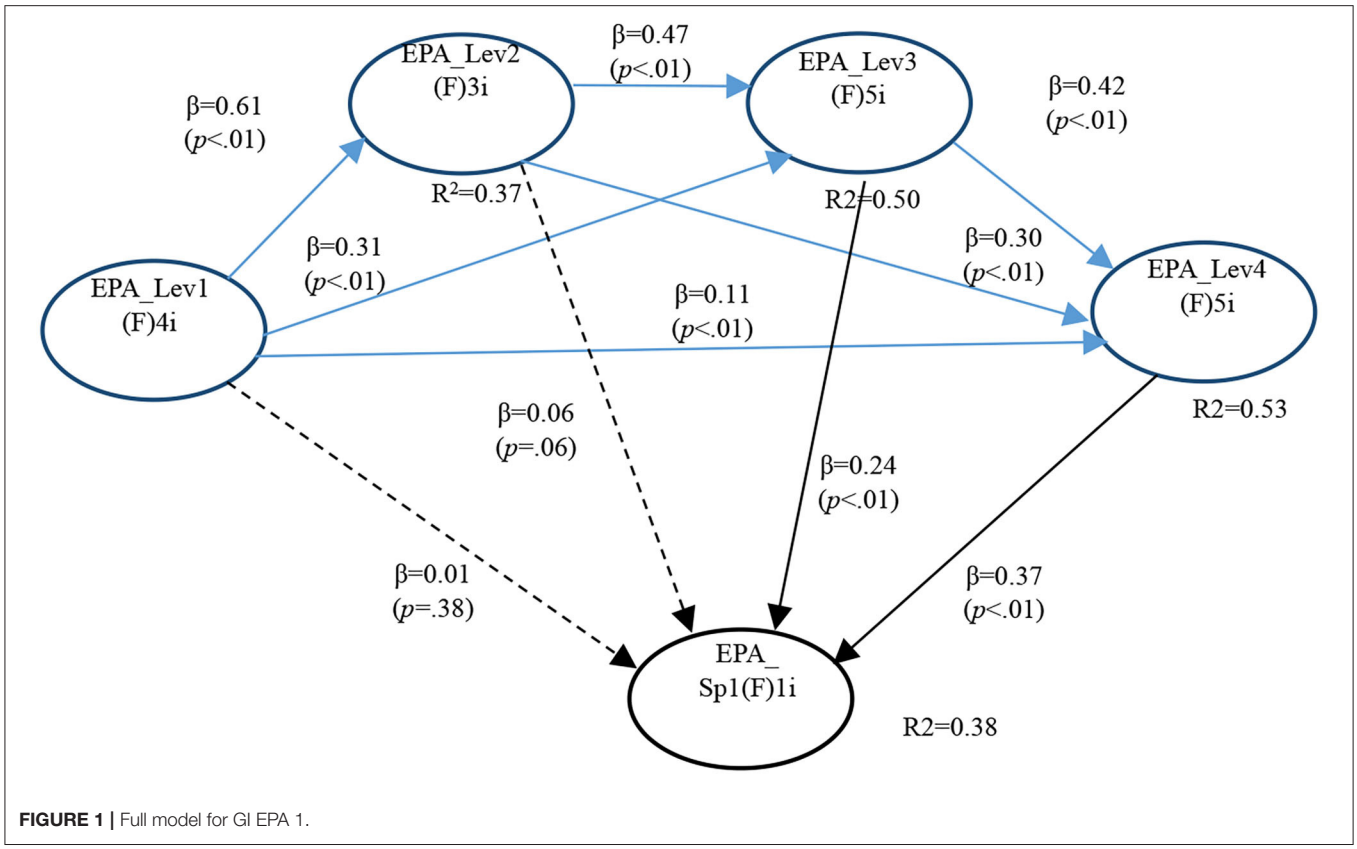

FIGURE 1 | Full model for GI EPA 1.

were found, one with Level 3 ($P < 0.001$) and the other with Level 4 ($P < 0.001$). This supported both Hypotheses 4a and 5a (**Figure 1**).

In the second model (General EPA levels and SGEPAs 2), APC = 0.283 ($P < 0.001$), ARS = 0.425 ($P < 0.001$), and AARS = 0.423 ($P < 0.001$), indicating that it matched the requirements of validity and quality.

Multicollinearity was also ruled out (AVIF = 1.945, AFVIF = 2.012). The model fitted well (Tenenhaus GoF = 0.503) without Sympson's paradox problem (SPR = 1.000) or data distortion (SSR = 1.000). Both RSCR and NLBCDR were 1, indicating that the reversal direction had not been improved.

There were also only two significant path Co-efficients for GI EPA 2. Again, one with Level 3 ($P < 0.001$) and the other with Level 4 ($P < 0.001$). This supported both Hypotheses 4b and 5b (**Figure 2** and **Table 7**).

In the third model (General EPA levels and SGEPAs 3), APC = 0.279 ($P < 0.001$), ARS = 0.415 ($P < 0.001$), and AARS = 0.413 ($P < 0.001$), indicating that it matched the requirements of validity and quality.

Multicollinearity was also ruled out (AVIF = 1.930, AFVIF = 1.998). The model fitted well (Tenenhaus GoF = 0.497) without Sympson's paradox problem (SPR = 0.900). A better value was found for SSR that equals 1. Finally, causality direction is the most suited as seen by both RSCR (0.998) and NLBCDR (1.0) (**Table 8**).

GI EPA 3 results followed precisely the same pattern of the previous specialized EPAs with the variant that both betas are of similar magnitude. Therefore, one with Level 3 ($P < 0.001$) and the other with Level 4 ($P < 0.001$). This supports both Hypotheses 4c and 5c (**Figure 3**).

In the fourth model (General EPA levels and SGEPAs 4), APC = 0.283 ($P < 0.001$), ARS = 0.420 ($P < 0.001$), and AARS = 0.418 ($P < 0.001$), indicating that it matched the requirements of validity and quality. Multicollinearity was also ruled out (AVIF = 1.955, AFVIF = 1.982). The model fitted well (Tenenhaus GoF = 0.500) without Sympson's paradox problem (SPR = 1.000) or data distortion (SSR = 1.000). The designed causality direction was also the most suited (RSCR = 1.000 and NLBCDR = 1.000) (**Table 9**).

There are three statistically significant path Co-efficients of modest magnitude for GI EPA 4. Namely with EPA Level 2 ($P < 0.001$), EPA Level 3 ($P < 0.001$), and EPA Level 4 ($P < 0.001$). This supported Hypothesis 4d (**Figure 4**).

In the last model (General EPA levels and SGEPAs 5), APC = 0.270 ($P < 0.001$), ARS = 0.395($P < 0.001$), and AARS = 0.393($P < 0.001$), indicating that it matched the requirements of validity and quality. Multicollinearity was also ruled out (AVIF = 1.897, AFVIF = 1.947). The model fitted well (Tenenhaus GoF = 0.485) without Sympson's paradox problem (SPR = 1.000) or data distortion (SSR = 1.000). The causality direction designed is also the most suited as indicated by both RSCR and NLBCDR achieving a value of 1.0 (**Table 10**).

In the case of GI EPA 5, the predominant pattern is observed with the two more complex general EPA levels showing statistically significant path Co-efficients, namely, with EPA Level

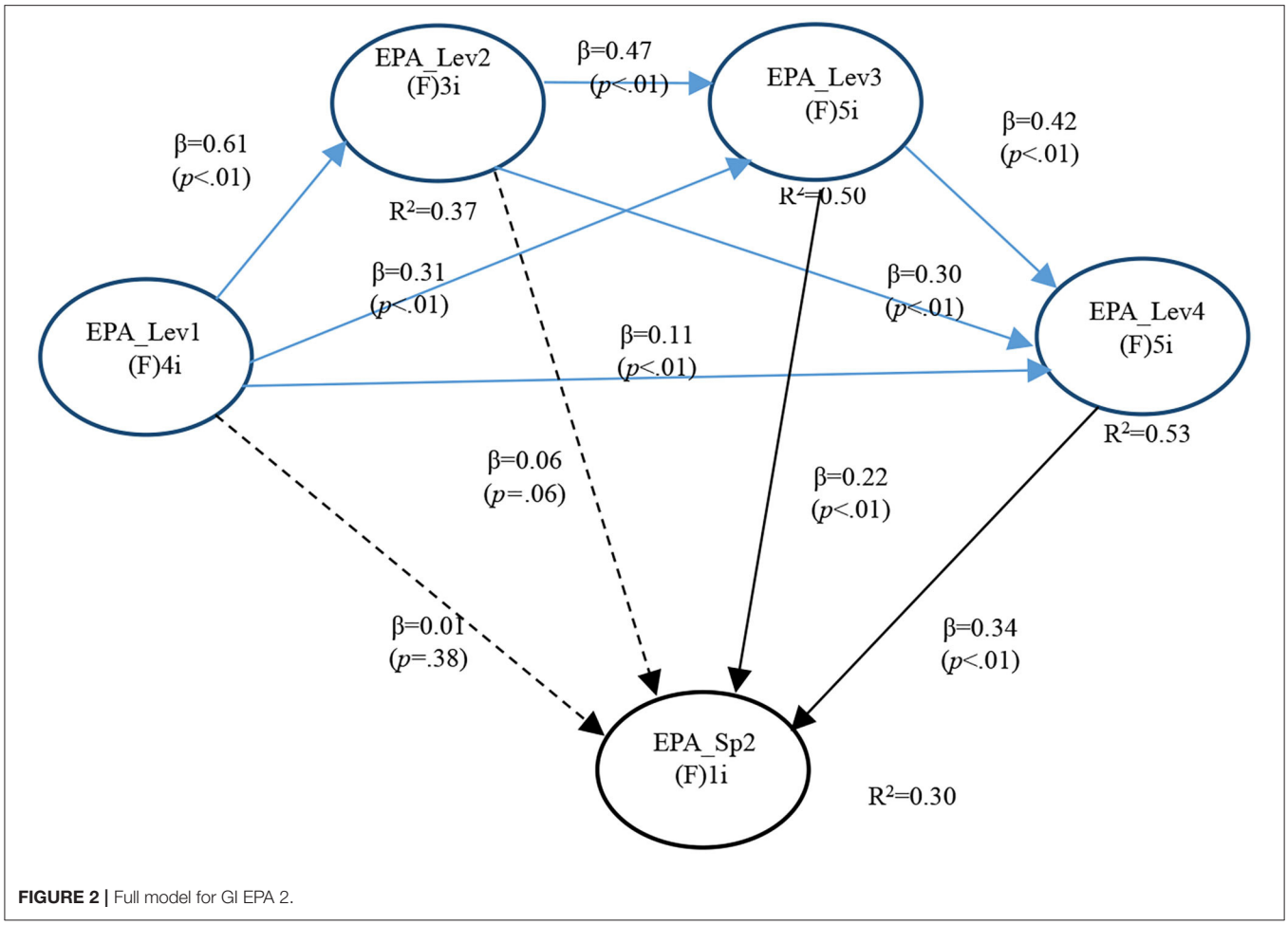

FIGURE 2 | Full model for GI EPA 2.

TABLE 7 | Association Co-efficients general EPAs-GI EPA 2 for PLS-SEM.

	EPA_level 1	EPA_level 2	EPA_level 3	EPA_level 4
EPA_level 1				
EPA_level 2	0.610*			
EPA_level 3	0.313*	0.470*		
EPA_level 4	0.107	0.295*	0.417*	
EPA_GI 2	0.013	0.057	0.215*	0.338*

*$P < 0.001$.

TABLE 8 | Association Co-efficients general EPAs-GI EPA 3 for PLS-SEM.

	EPA_level 1	EPA_level 2	EPA_level 3	EPA_level 4
EPA_level 1				
EPA_level 2	0.610*			
EPA_level 3	0.313*	0.470*		
EPA_level 4	0.107	0.295*	0.417*	
EPA_GI 3	0.038	–0.007	0.260*	0.277*

*$P < 0.001$.

3 ($P < 0.001$) and EPA Level 4 ($P < 0.001$). This supported both Hypotheses 4f and 5f (**Figure 5**).

Overall, the results of testing prediction models between general and SGEPAs supported the hypothesis. As expected, all statistically significant associations were positive, thus suggesting that specialized EPAs were built on top of general EPAs. Likewise, this significant association was mainly seen at levels 1 and 2. This indicated that levels 1 and 2 were primarily needed to lay the groundwork for levels 3 and 4, and that these higher levels of EPAs were still the most informative for SGEPAs. Given that general EPA levels are designed by consensus as a formative construct, we consider it necessary to explore each general EPA separately to determine which measurement results express homogeneous behavior within each level.

DISCUSSION

At present, all community hospitals in China are part of the medical consortium project (29). These hospitals act as trainers of general practitioners and health popularizers. Such roles will become mandatory for physicians in these hospitals, and will soon become part of physicians' routine. Therefore, they have to receive relevant training and continue education after graduation to be competent for the new job requirements (30). Before

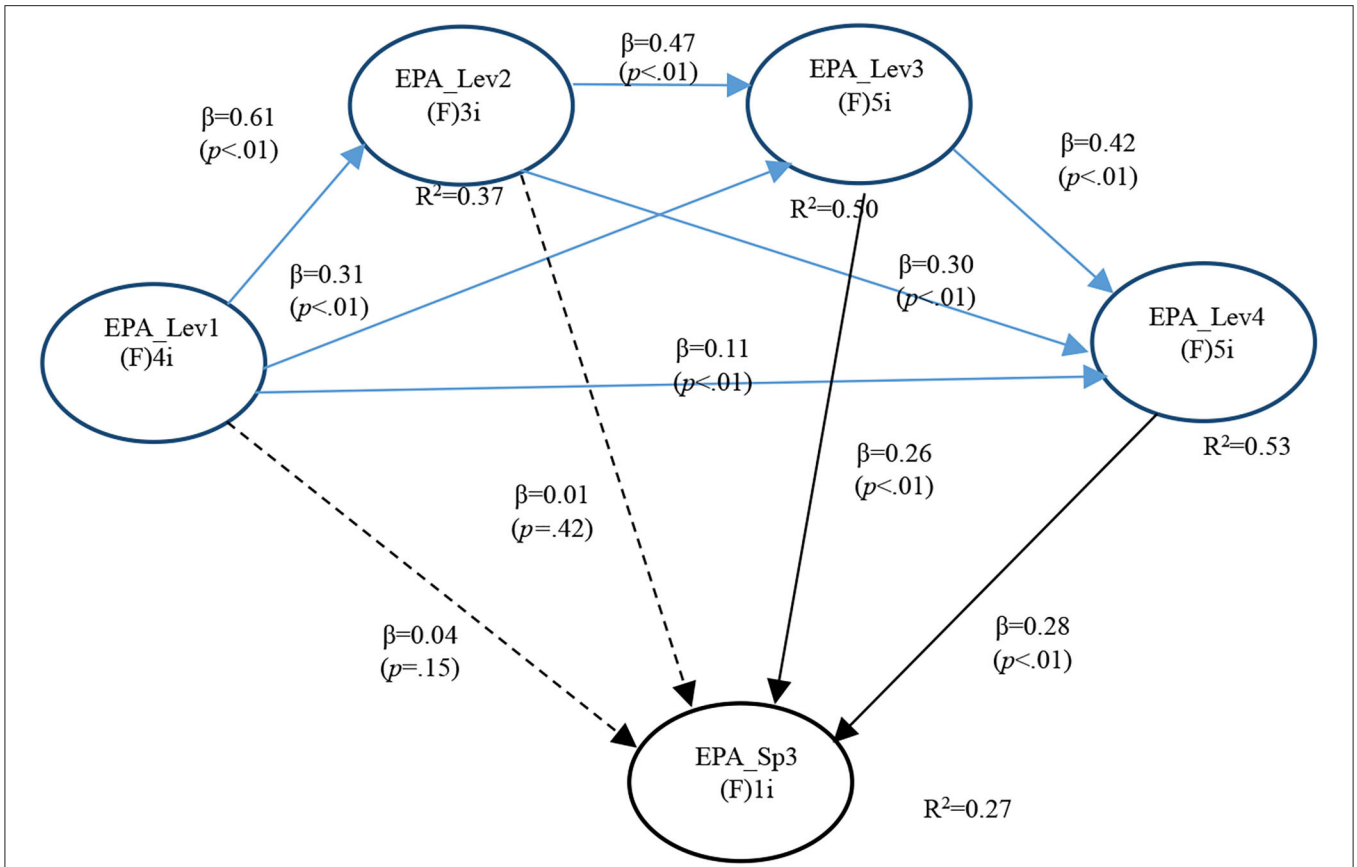

FIGURE 3 | Full model for GI EPA 3.

TABLE 9 | Association Co-efficients general EPAs-GI EPA 4 for PLS-SEM.

	EPA_level 1	EPA_level 2	EPA_level 3	EPA_level 4
EPA_level 1				
EPA_level 2	0.610*			
EPA_level 3	0.313*	0.470*		
EPA_level 4	0.107	0.295*	0.417*	
EPA_GI 4	0.100	0.121*	0.186*	0.214*

*$P < 0.001$.

becoming a specialist, one must train as a general practitioner to acquire a full range of medical knowledge (31). Then, combining clinical practice, personal development, and other factors, general practitioners decide whether to pursue further specialist careers. Hospital requirements will in turn become part of the competency model.

To maximize the role of general practitioners in pediatric medical care, optimize and integrate medical resources, and ultimately improve the medical level and patient satisfaction, the EPAs of the AAP and NASPGHAN were used to test whether the MSGM was in line with the practice of pediatrics in China in this study. Medical behavior is the key to measure the competence of doctors. The EPAs theory is closely related to post-competency theory. EPAs include basic practical activities required to train a medical professional, such as pediatric emergency treatment, critical illness identification, and harmonious doctor–patient relationship. The correct implementation of these key clinical practice activities is conducive to improving the work ability and post-competency of doctors.

In China, general pediatricians work in secondary hospitals or community hospitals, and their responsibilities are the diagnosis and treatment of common diseases and child care. Most pediatric gastroenterologists work in tertiary hospitals (general hospitals and children's hospitals), undertake the diagnosis and treatment of pediatric complicated and difficult children with digestive diseases, and are equipped with the operation skills of digestive endoscopy. Therefore, EPAs for general pediatrics and pediatric gastroenterology are different in terms of educational practices, with higher requirements for pediatric gastroenterology doctors than for general pediatricians.

In our study, 776 pediatricians in China were surveyed by questionnaire on EPAs of general pediatricians and pediatric gastroenterology. The qualitative and quantitative statistical analysis, CB model, and PLS-SEM model were conducted on

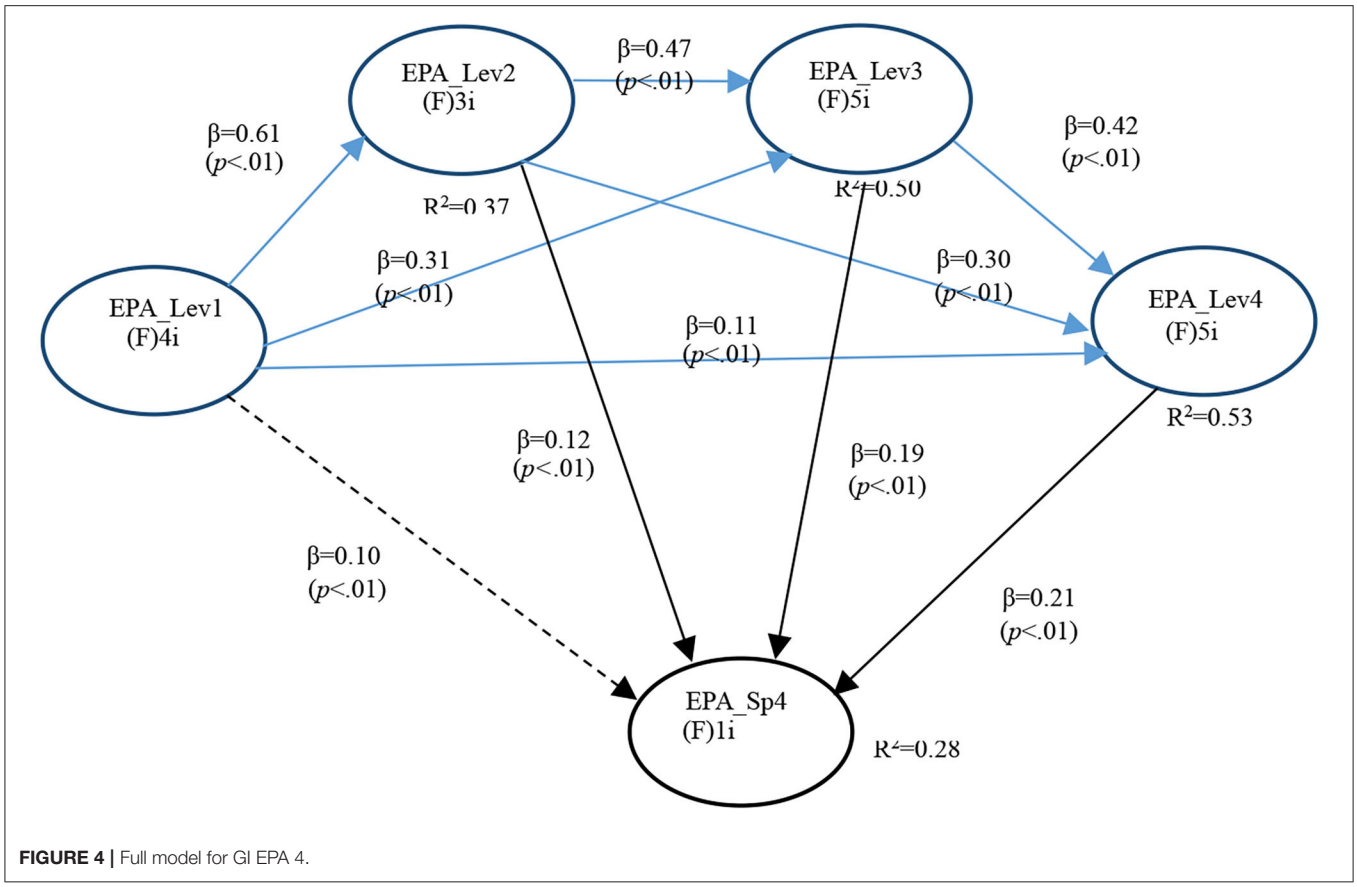

FIGURE 4 | Full model for GI EPA 4.

TABLE 10 | Association Co-efficients general EPAs-GI EPA 5 for PLS-SEM.

	EPA_level 1	EPA_level 2	EPA_level 3	EPA_level 4
EPA_level 1				
EPA_level 2	0.610*			
EPA_level 3	0.313*	0.470*		
EPA_level 4	0.107	0.295*	0.417*	
EPA_GI 5	0.068	0.007	0.133*	0.282*

*$P < 0.001$.

the questionnaire results. The results showed that specialized EPAs depended on general EPAs. A seminar was delivered before the research upon which it was demonstrated that these items reflect the reality of Chinese pediatrics. These EPAs are cleverly broken down into detailed activities according to different medical tasks. Through the quantitative study, we found a positive correlation and complementarity among pediatrician EPAs. EPAs of general pediatricians and digestive pediatricians were also complementary and positively correlated. They also enhanced and reinforced performance indicators. If there is no general practice and skill training of EPAs in the early stage as the basis, the medical ability of pediatric gastroenterology specialty may not be achieved in the later stage. This study also found that "professionalism" and "medical knowledge" were significantly positively correlated with EPAs of general pediatricians and pediatric gastroenterology, suggesting that these two competencies are the basis of other competencies.

This research focused on the approaches and methods of post-graduate medical education and continuing education and studied the growth patterns of digestive pediatricians, a professional group that is in short supply in China's medical industry (7). The study confirmed that the number of pediatricians is declining significantly due to a variety of reasons, including government policies, hospital management, department performance, compensation, and education patterns (32, 33). This study attempts to establish MSGM for community hospitals based on EPAs, which is helpful to relieve the pressure of pediatricians' loss through this new and effective training method in China's medical reform.

This thesis is a prospective study of the digestive pediatrician education system, an exploration of the digestive endoscopy pediatrician panel of the National Health Commission of the People's Republic of China. MSGM serves as a way toward the improvement and exploration of the education system for pediatricians after graduation and for continuing education. Meanwhile, it also helps lay the foundation for a clinical pediatrician's career after graduation and for continuing education.

Entrustable professional activities have a close relationship with the actual clinical and teaching environment and national

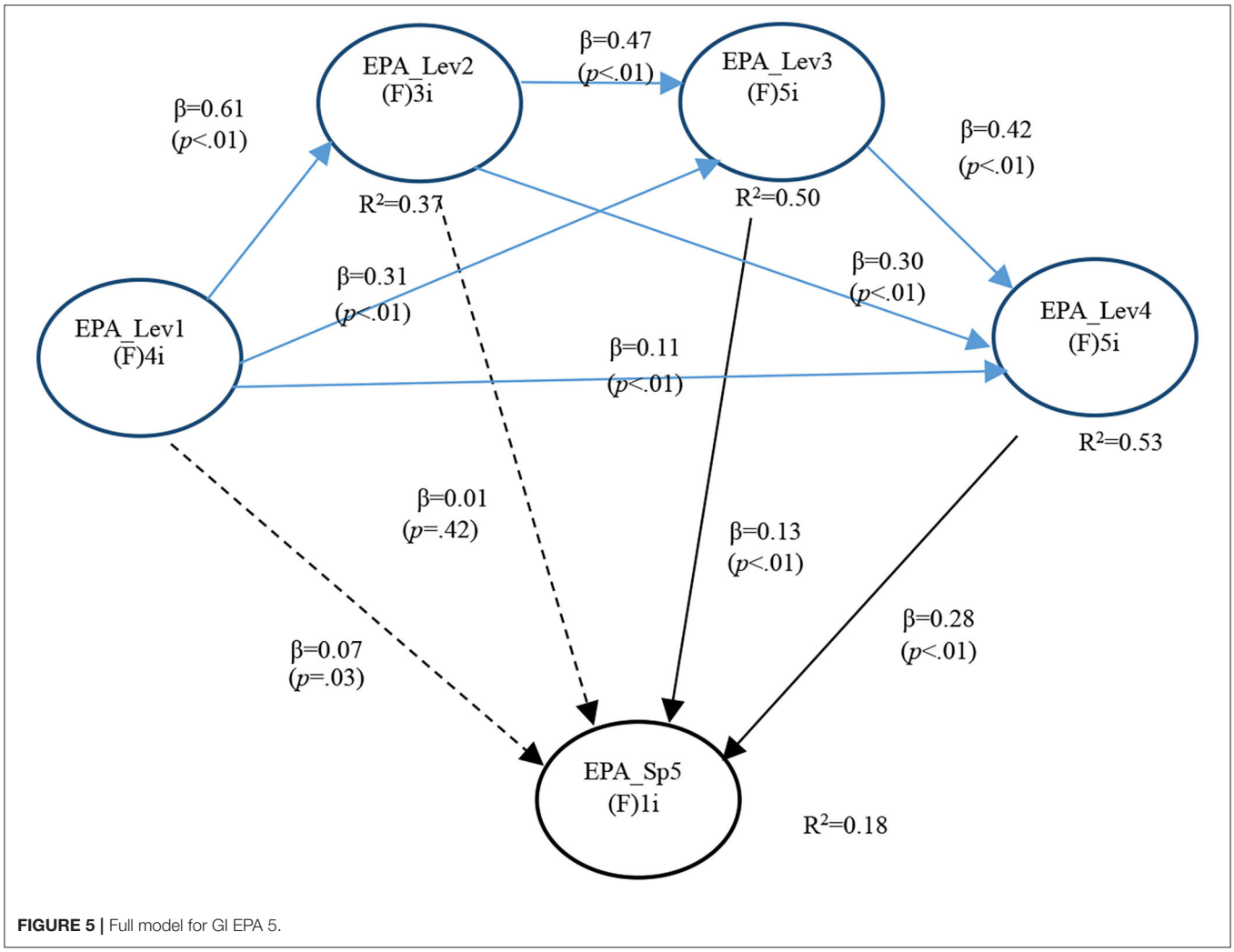

FIGURE 5 | Full model for GI EPA 5.

conditions. Although the MSGM established according to EPAs has certain theoretical significance and reference value for the improvement and exploration of post-graduation and continuing education system of Pediatricians in China, in view of the differences in a clinical teaching environment and national conditions between China and the United States, it is imperative to establish a Chinese EPAs suitable for pediatricians. In future studies, it is necessary for scholars to explore China's own EPAs based on unique national conditions.

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.

ETHICS STATEMENT

Ethics review and approval/written informed consent was not required as per local legislation and institutional requirements.

AUTHOR CONTRIBUTIONS

NCR directed the entire research process. VT and RZ designed the study. SG and NL drafted the manuscript. XW carried out the data collection. YY participated in the data processing. All authors reviewed and approved the final version of the 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.2022.896097/full#supplementary-material

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The Effect of Health on the Elderly's Labor Supply in Rural China: Simultaneous Equation Models With Binary, Ordered, and Censored Variables

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In this study, we examined the effect of health on the elderly's labor supply in rural China based on the data of the Chinese Health and Nutrition Survey (CHNS) from 1997 to 2006. We used simultaneous equations to address the endogeneity problem of health and estimate the models with censored data of labor supply by the full information maximum likelihood estimation. We found that the failing health does not significantly decrease the elderly's labor supply in rural areas when using both the subjective (self-reported health status) and objective (hypertension diagnosed or not) health indicators. Our finding indicates the phenomenon of "ceaseless toil" for the elderly in rural China, i.e., the elderly almost work their whole life even if they are not physically capable. The results remain robust when using a two-stage limited information maximum likelihood estimation.

Keywords: The elderly's labor supply, hypertension, self-reported health, simultaneous equation models, binary Probit model, ordered Probit model, censored data

INTRODUCTION

With the decreasing fertility rate and rising life expectancy, the pace of population aging in China is much faster than that in the past (1). The aging problem may impose a heavy burden on society, and the easing of the burden mostly depends on when the elderly decide to retire (2). Although people eventually will be too sick to work, they may retire far before then. There are two possibilities of the retirement timing for the elderly, leading to different fiscal pressures. On the one hand, the elderly choose to retire and begin to receive pensions once they feel just slightly ill. This way of old-age care requires the government to allocate a great amount of fiscal budget to support the high level of social welfare. On the other hand, the elderly tend to work their whole life even if they are not physically capable to make a living as Benjamin et al. (3) found in China. Such a way of old-age care reduces the toil of the government but comes at the cost of reducing the welfare of the elderly. Therefore, it is a challenge for the government to find a balance between the welfare of the elderly and the growing pension burden when determining the retirement policy (4).

The key to addressing this policy challenge is to investigate how the elderly's labor supply will respond to their failing health. Therefore, this study examined the effect of health on the elderly's labor supply in rural China and investigated the retirement choice patterns of the elderly in rural China. We wanted the answer to whether the elderly in rural China retire in time when they feel just slightly ill, as the first pattern, or will work their whole life even if they are not physically capable, as the latter pattern. Holding other factors constant, if health has no significant effect on the elderly's labor, it means they follow the first pattern, but if there is a significantly negative effect, it is the second one.

Theoretically, the impact of health on the elderly's labor supply is uncertain. On the one hand, failing health will lead to lower labor productivity, which in turn results in unemployment (5). The less healthy a person is, the more likely he or she is to drop out of the labor market (6). On the other hand, poor health also has an income effect, which may increase the labor supply. Poorer health requires more medical care and health services (7). Therefore, the elderly need to provide more labor to afford the health services if they are limited in economic conditions, especially when the social security system is not well ensured. In this study, we attempted to test the theory that explains the elderly's labor supply with the data from rural China.

The data in China are suitable research sample to investigate the impact of health on the elderly's labor supply in developing countries. The economic conditions and retirement patterns differ remarkably in urban and rural China due to China's unique urban–rural dual social structure. The old-age security system in cities is relatively complete, while in rural areas, the system has not been fully established. In some poor families in rural areas, where the adult children cannot afford to support their parents, the older parents need to earn their own living by heavy farming work all their life, which leads to the phenomenon of "ceaseless toil" (3, 8). Therefore, the data on the elderly in rural China provide us with sufficient variations in the sample for estimation.

However, an empirical challenge lies in the measurement of health. In the current literature, scholars often use subjective and objective indicators to measure health. Subjective indicators include self-reported health status, self-reported days of disability, or limitations in activities. Objective health indicators are constructed based on medical tests of health conditions, such as height, weight, body mass index (BMI), grip strength, blood pressure, and limitations in activities of daily living (ADLs) (9–11). Nevertheless, both indicators have the endogeneity problem, which may cause biased estimation results when examining the effect of health on labor supply (12–14).

The endogeneity problem comes from several aspects: First, the reverse causation, which means that the health will affect people's labor supply, while the labor supply may also affect the health status. For example, the justification bias will lead to an endogeneity problem of reverse causation, which indicates that people may deliberately undervalue their health status for the excuse of their withdrawal from the labor market (15–17); second, the omitted variables, which means that health is often related to an individual's economic and social conditions, which also affect the labor supply behavior. If the factors of economic and social conditions are omitted in regressions, it will lead to biased estimation results. Compared to subjective health indicators, the objective health indicators do not have the endogeneity problem caused by justification bias but still have the reverse causality and omitted variable problems. Third, objective health indicators are more susceptible to measurement errors, which may lead to endogeneity as well (11). Since the measurements of objective health indicators mostly depend on medical instruments, people's emotions will sometimes be influenced by those instruments and then cause measurement errors.

In this study, we used simultaneous equations to solve the endogeneity problem in the health and labor supply model. The estimation of simultaneous equations not only reduces the difficulty of searching for proper instruments to address the endogeneity problem but also gets a more asymptotically efficient estimated result.

We contribute to the literature in three ways: First, this study adds to the literature on the causal effect of health on the elderly's labor supply and in particular to the few studies that examine the effect in developing countries (6, 18–20). The effect of health on the elderly's labor supply is controversial in the literature. Some studies find that health has a significant positive impact on labor supply, but some conclude that there is no such effect (3, 21–24). The reason for the controversy lies in the endogeneity problem of health variables and the measurements of labor supply. Therefore, in this study, we used the simultaneous-equation Tobit models with both the subjective and objective health indicators to achieve more robust and efficient estimated results. Our results help to resolve the controversy in supporting the conclusion of Benjamin et al. (3) that there is a phenomenon of "ceaseless toil" among the elderly in rural areas in China.

Second, to reveal the impact of health from different aspects, we used both the objective and subjective health indicators to measure the health level of the elderly and considered the objective indicator (hypertension diagnosed or not) as a binary variable and the subjective indicator (self-reported health status) as an ordered variable in estimation, which enriches the measures of health in literature. Using hypertension as a health indicator has several advantages. Hypertension can be accurately measured and has fewer measurement errors. In addition, hypertension is a common chronic disease in older adults, which is mostly diagnosed when people who are not yet retired face the decision of retirement, so there are sufficient variations in the sample of older people with different decisions (25–27).

Third, in this study, we first derived a logarithmic likelihood function of the joint distribution for the simultaneous equations including both a Tobit-type limited dependent variable and a binary choice (or an ordered) variable and then used the full information maximum likelihood (FIML) estimation method to obtain a more asymptotically efficient estimated result. There is no previous research deriving the likelihood function of simultaneous equations in this type and using FIML to estimate them, which can be used for further research of relevant models. Besides the better asymptotically efficiency, another advantage of the FIML estimation is that the correlation coefficient of residuals in labor and health equations can be directly estimated.

Therefore, we can test the significance of the correlation coefficient directly to verify the existence of endogeneity and address the endogeneity by FIML estimation.

The rest of this study is organized as follows: Section "MATERIALS AND METHODS" introduces the data, variable modeling and estimation strategies. Section "RESULTS" shows the results, and section "DISCUSSION" discusses our results compared with other related findings. The final section presents the concluding points.

MATERIALS AND METHODS

Data

We used the data from China Health and Nutrition Survey (CHNS) to investigate the effect of health on the labor supply of the elderly in rural China. Our sample includes individuals with rural household registration, comprising men aged 60 and above and women aged 55 and above. We gathered 3,535 observations from 1997, 2001, 2004, and 2006 with complete data on hypertension, self-reported health status, and working hours[1].

For the age criteria of the sample, we used 60 years for men and 55 years for women, because the working-age population is defined as men aged 16–59 and women aged 16–54 as the benchmark in China[2]. The age criteria of the retirement policy for urban workers are the same as above, but there is no specific standard of retirement for many self-employed workers in rural areas. Therefore, we focused on the rural elderly who have reached the same age as urban workers and explored their health and labor hours.

Our sample from CHNS is representative of the elderly living in rural China for several reasons. First, the data from CHNS cover nine provinces (Guangxi, Guizhou, Heilongjiang, Henan, Hubei, Hunan, Jiangsu, Liaoning, and Shandong) in China, which vary greatly in economy and geography of rural areas. Second, the samples from CHNS were selected by a multistage and random cluster design. Selected counties were stratified into three different levels of income, and a weighted random sampling technique was used to choose four counties in each province. Finally, during our research period from 1991 to 2006, China experienced large-scale social and economic reforms; the living standards of Chinese rural families changed a lot and related questions were included in the questionnaires of CHNS. Thus, the dataset in CHNS could cover the most representative population in rural China.

Variables

The Explained Variable: Labor Supply

From the data of CHNS, the annual working hours of the elderly in rural China are composed of three parts: the employed working hours, the self-employed agricultural working hours (including home gardening, collective and household farming, raising livestock and poultry, and collective and household fishing), and the self-employed non-agricultural working hours. We summed up these three parts of annual working hours to measure the variable of labor supply (*Laborhour*) and took it as the logarithmic form in regressions.

In our sample, about 31.5% (1,112/3,535 equals 31.5%) observations' annual working hours are zero, which means that, if some elderly quit the labor market after retirement, their labor supply will censor to zero, and the Tobit model addressing the censored data is more suitable for estimation than ordinary least square regressions. If we focus on the labor participation rate as a binary variable, it will underestimate the labor supply of the elderly. Therefore, we emphasized the detailed working hours of the elderly as censored data in estimation and used the Tobit model to reduce the estimation bias.

Figure 1 shows the average working hours of the rural elderly in different age groups. The working hours decline along with the increase of age. Before the age of 70, the average working hours stay over 800, but there are almost no elderly who participate in the labor market after their 80s.

The Explanatory Variable: Health

In this study, we used both objective and subjective health indicators to investigate the effect of health on the elderly's labor supply from different perspectives. The objective indicator is hypertension diagnosed or not, and the subjective indicator is self-reported health status. Meanwhile, we emphasize the different data types of the indictors in estimation, i.e., hypertension as a binary variable and self-reported health as an ordered variable.

The Objective Indicator of Health: Hypertension

We used hypertension diagnosed or not (*Hypertension*) as an objective health indicator to measure health. The definition of the variable *Hypertension* is based on the benchmark of the World Health Organization (WHO) in 1999. If an individual's systolic blood pressure is not $<$140 mm Hg or diastolic blood pressure is not $<$90 mm Hg or "has been diagnosed as hypertension by the doctor," we then define that the binary variable *Hypertension* equals to one but is otherwise zero. In the survey of CHNS, the doctor measured blood pressure three times, both systolic and diastolic, for each respondent. Since the first measurement is more likely to be affected by emotional fluctuations, we chose the average of the last two measurements to calculate the systolic and diastolic blood pressures.

Using hypertension to measure health has two advantages. One advantage is that hypertension can be accurately measured with fewer measurement errors and justification bias (25, 26). Another advantage is that hypertension is a common chronic disease in older Chinese, which provides sufficient variations in the sample (27, 28).

Figure 2 displays the elderly's average working hours of different age groups in rural China with hypertension diagnosed or not. The solid line presents the working hours of the elderly without hypertension and the dashed line presents those of the

[1]We used the above four years because the questions of self-reported health status were surveyed only in these four years.

[2]China has implemented a compulsory regulation of retirement age in urban areas since the 1950s, with 60 for male and 55 for female professionals or cadres (including teachers, medical personnel, other professionals, and administrators), and 50 for the rest of the female workers (2). Correspondingly, in this study, we used a narrower sample by defining the age 55 or above as the elderly for women in rural areas.

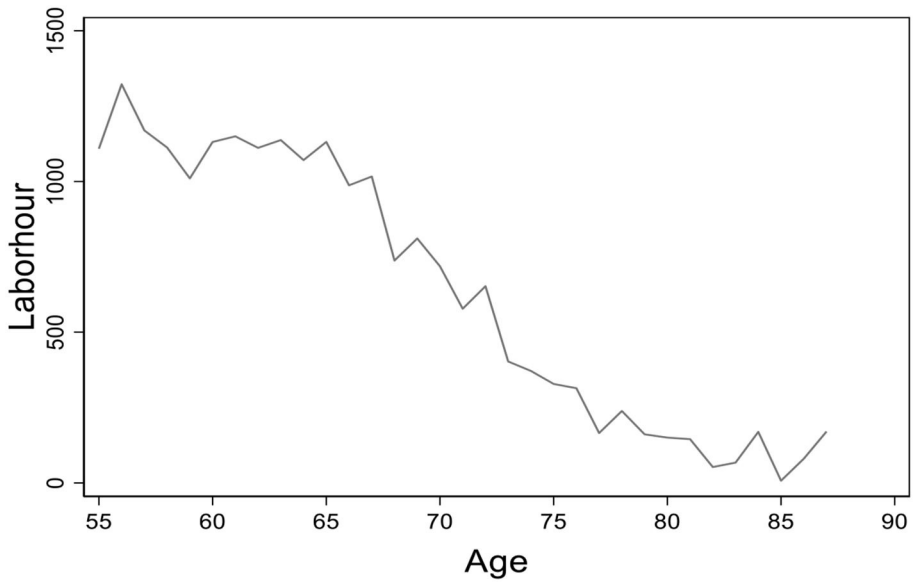

FIGURE 1 | The age distribution of average working hours. Data from the China Health and Nutrition Survey (CHNS) database. The figure presents the age distribution of average working hours for the elderly in rural China.

elderly diagnosed with hypertension. We found that the average working hours of the two sub-samples are close, which implies that hypertension may not affect the elderly's working hours across different ages.

The Subjective Indicator of Health: Self-Reported Health

We also used the self-reported health status (*Selfhealth*) as a subjective health indicator to measure health. The CHNS questionnaire includes the question: "Right now, how would you describe your health compared to that of other people at your age?" We defined the variable *Selfhealth* as an ordered variable, which equals to one if the respondent chooses the answer "excellent" or "good," equals to two if the choice is "fair," and equals to three if the choice is "poor."

In **Figure 3**, we present a graph of the elderly's average working hours of age groups with different self-reported health statuses. We found that the elderly's working hours are virtually the same between the groups of "good" and "fair," and there is a little gap between "good" and "poor." **Figures 2**, **3** provide preliminary descriptive evidence that the elderly in rural China may continue to work regardless of their failing health.

Other Control Variables

To examine the effect of health on the elderly's labor supply, the social and economic factors related to health and working hours are necessary to be controlled in regressions. Our control variables are from three aspects. First, for the individual characteristics, we controlled the age (*Age, Age2*), gender (*Male*), education levels (*Edu*), marital status (*Marr1, Marr2, Marr3*) of the elderly, and the year dummies. *Age2* is the square of an individual's age (*Age*) to control a non-linear effect in regression. *Male* is a dummy variable, which equals to one if the individual is a man but is otherwise zero. *Edu* is the total number of years of education, *Marr1* represents the marital status as divorced or separated, *Marr2* as widowed, and *Marr3* as married, respectively. We set the married individuals as the benchmark group in regressions.

Second, for the family factors, we controlled the family income (*Hhinc*) and wealth (*Hwealth*). *Hhinc* is defined as the annual household income and *Hwealth* is the accumulated family wealth, which were adjusted by CPI in 2009 and in the logarithmic form in regressions.

Third, according to the model settings of simultaneous equations, it is necessary to identify at least one variable only included in the health equation but not in the labor supply equation, which means that the identifying variables should affect health but not affect an individual's labor supply from other channels besides health. In this study, we used three variables, the amount of salt intake per person per meal (*Salt*), the square of the salt intake per person per meal (*Salt2*), and the alcohol consumption frequency (*Alcohol_fre*) as the identifying variables. Dahl (29) and MacMahon (30) indicated that high intake of salt and long-term alcohol consumption are positively correlated with hypertension.

Specifically, about the measurements, the nutrition survey of CHNS records the 3-day total actual salt consumption of the household, the 3-day total number of meals eaten at home per person, and the 3-day total number of persons who ate at home. Therefore, we divided the first value by the last two values to obtain the average amount of salt consumption per person per meal (*Salt*). In addition, the adult survey of CHNS records the

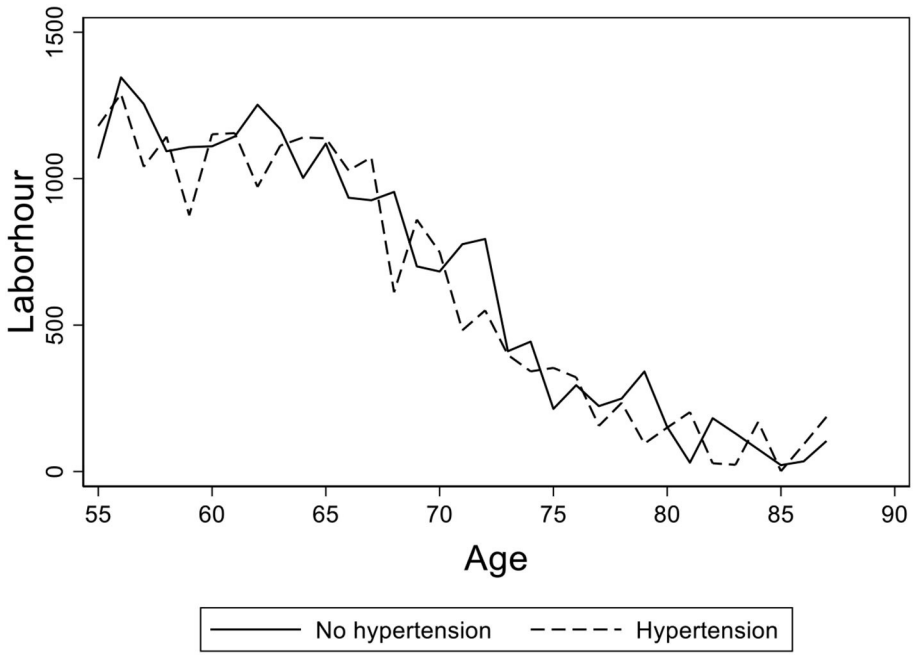

FIGURE 2 | The age distribution of average working hours for the elderly with hypertension diagnosed or not. Data from the China Health and Nutrition Survey (CHNS) database. The figure shows the age distribution of average working hours for the elderly with hypertension diagnosed or not in rural China. The solid line shows the age path of the elderly without hypertension and the dashed line shows the ones with hypertension diagnosed.

FIGURE 3 | The age distribution of average working hours for the elderly with different self-reported health statuses. Data from the China Health and Nutrition Survey (CHNS) database. The figure shows the age distribution of average working hours for the elderly with different self-reported health statuses in rural China. The solid line shows the age path of the elderly with "excellent" or "good" health, the dashed line shows the ones with "fair" health, and the dash-dotted line shows the ones with "poor" self-reported health status.

frequency of alcohol consumption. We define the values of the variable *Alcohol_fre* as follows: 0 for never, 1 for not more than one time a month, 2 for one time or two times a month, 3 for once or twice a week, 4 for three to four times a week, and 5 for almost every day.

Descriptive Statistics

The definitions and descriptive statistics of variables are shown in **Table 1**. The number of years of schooling is small, with an average of only 2.7 years, and about one-third of the elderly did not receive any formal education in our sample. The mean value of the annual working hours of the sample is about 869.4 h, which is relatively small because more than half of the elderly in the sample do not work. The zero values indicate that the explained variable is censored, so the results obtained by ordinary least squares will be biased, and the Tobit model is more suitable to address the censored data.

Further, we compare the mean values of the variables grouped by different health levels (hypertension diagnosed or not) in **Table 2** and report the *t*-test results. The average annual working hours of rural elderly of the two groups are 343.3 and 278.1 h, respectively. **Table 2** shows that there is a significant yet small difference between these two groups, which may be different from the data seen in **Figure 2**. Therefore, we need to investigate the effect of health on labor supply in regression by holding other confounding factors fixed as well as addressing the endogeneity problem of health.

Compared with those who are not diagnosed with hypertension, the elderly with hypertension are averagely older and poorer and there are more men than women. The frequency of alcohol consumption does not differ significantly between the hypertension and non-hypertension samples. However, the salt consumption is significantly higher in the hypertension group at the 1% level, which suggests that salt consumption is a proper identifying variable.

In **Table 3**, we compare the mean values of variables grouped by different self-reported health statuses as "excellent" or "good," "fair," and "poor," and the results are consistent with **Table 2**. The elderly in rural areas evaluated their own health to be worse as they became older, and the women with lower household income and less education evaluated their own health status as significantly worse. In particular, the higher the frequency of drinking, the better the self-reported health is. The higher the salt consumption, the lower the self-evaluated health status, which suggests that drinking frequency and salt consumption are proper identifying variables.

Modeling and Estimation Strategies

Simultaneous Equations of Health and Elderly's Labor Supply

The Equation of Labor Supply

For the labor supply equation in simultaneous equations, we set the Tobit model as follows:

$$Laborhour = \max\{0,\ Laborhour^*\} = \max\{0,\ \gamma_0 + Controls^{'}\delta_1 + a_1 Health + \mu_1\} \quad (1)$$

Where $Laborhour^*$ is a latent variable, which can be interpreted as the elderly's actual willingness to work. We define the explained variable *Laborhour* as the observed labor supply, which is the actual working hours when $Laborhour^* > 0$, while *Laborhour* is 0 when $Laborhour^* \leq 0$, since we observe no actual working hours in this condition. In this sense, the data of the elderly's labor supply are censored to zero and the variable *Laborhour* is the Tobit-type limited dependent variable.

The variable *Health* representing an individual's health level is the key explanatory variable. We focused on the core coefficient α_1, which indicates the effect of health on the elderly's labor supply. If $\alpha_1 > 0$, it means that the worse the health condition of the elderly, the more working hours they provide, since the higher value of the variable *Health* indicates a worse health condition (individual with hypertension or poorer self-reported health).

The vector *Controls* includes variables such as the age and its square (*Age, Age2*), gender (*Male*), education levels (*Edu*), two dummies of marital status (*Marr1, Marr2*), household income (*Hhinc*) and household wealth (*Hwealth*) of the elderly, and 3-year dummies, which meets the assumption $Cov(Controls,\ \mu_1) = 0$. δ_1 is the vector of coefficients of *Controls*, and $\gamma_0$is the constant term. $\mu_1$is the random disturbance term, which meets the assumption $Var(\mu_1) = \sigma_1^2$.

The variable *Health* may be endogenous due to its correlation with the disturbance term μ_1, since the health status may be related to some unobservable factors affecting the elderly's willingness to work. Therefore, we cannot use the general method to estimate the Tobit model because the results will be biased and inconsistent.

The Equation of Health (Hypertension)

For the health equation in simultaneous equations, we set the health as a binary variable as in model (2). We used *Hypertension* to represent $Health_1$ of model (2) in estimation.

$$Health_1 = 1\{Health_1^* > 0\} = 1\{\beta_0 + Controls^{'}\delta_{21} + Identify^{'}\delta_{22} + v_2 > 0\} \equiv 1\left\{\beta_0 + Varbs^{'}\delta_2 + v_2 > 0\right\} \quad (2)$$

Where 1 {.} is the characteristic function, which means that, when $Health_1^* > 0$, $Health_1$ equals to 1 but is otherwise 0. $Health_1^*$ is the latent variable, which can be interpreted as the actual health condition, and $Health_1$is the observed health. If $Health_1^*$ is >0, we can observe that the individual has hypertension diagnosed as 1 but is otherwise 0.

The vector of control variables *Varbs* includes the vectors *Controls* and *Identify*, which satisfies the assumption $Cov(Varbs,\ v_2) = 0$. *Controls* represents the individual and family factors, which is the same as that in the labor equation as Equation (1). *Identify* represents the identifying variables that affect health but not an individual's labor supply. Including these variables in the health equation will ensure the parameters in simultaneous equations are identified and could be estimated. δ_{21} and δ_{22} are the vector of coefficients *Controls* and *Identify*, respectively, and $\beta_0$is the constant term. $v_2$is the random disturbance term, and for convenience, we set that it meets the assumption $Var(v_2) = 1$.

TABLE 1 | Descriptive statistics.

Variable	Definition
Laborhour	The annual working hours of each older person
Hypertension	Dummy variable. Equals to 1 if the individual is diagnosed with hypertension, otherwise is 0
Self-health	Ordered variable. Equals to 1 if the individual's self-reported health is "excellent" or "good", 2 for the "fair", and 3 for the "poor"
Age	The age of each older person
Male	Dummy variable. Equals to 1 if the individual is a man and 0 for women
Edu	Number of years of schooling
Marr1	Dummy variable. Equals to 1 if the marital status is divorced or separated, otherwise is 0
Marr2	Dummy variable. Equals to 1 if the marital status is widowed, otherwise is 0
Marr3	Dummy variable. Equals to 1 if the marital status is married, otherwise is 0
Hhinc	The annual household income adjusted by CPI in 2009
Hwealth	The accumulated household wealth adjusted by CPI in 2009
Drink_fre	The alcohol consumption frequency. Equals to 0 if the individual never drinks, 1 for not more than one time a month, 2 for once or twice a month, 3 for one time or two times a week, 4 for three to four times a week, and 5 for almost every day
Salt	The average amount of salt consumption per person per meal

Variable	Observations	Mean value	Standard deviation	Minimum	Median	Maximum
Laborhour	3,535	869.437	1,175.701	0	390	5,824
Hypertension	3,535	0.566	0.496	0	1	1
Self-health	3,535	1.76	0.684	1	2	3
Age	3,535	66.008	7.545	55	65	87
Male	3,535	0.386	0.487	0	0	1
Edu	3,535	2.718	3.244	0	1	12
Marr1	3,535	0.029	0.167	0	0	1
Marr2	3,535	0.23	0.421	0	0	1
Marr3	3,535	0.728	0.445	0	1	1
Hhinc_cpi	3,535	9.068	1.146	5.055	9.177	11.17
Hwealth	3,535	0.419	0.972	0	0.114	6.308
Drink_fre	3,535	0.523	1.121	0	0	5
Salt	3,535	5.28	2.712	1.389	4.63	17.778

Descriptive statistics of the sample, including 3,535 individuals with rural household registration in China from 1997, 2001, 2004, and 2006. The sample contains men aged 60 and above and women aged 55 and above.

TABLE 2 | *T*-test for the differences between the elderly with hypertension diagnosed or not.

	(1) No hypertension	(2) Hypertension	(3) Diff. (1)–(2)
Laborhour	343.323	278.109	65.214***
Age	64.075	67.492	−3.417***
Male	0.345	0.416	−0.071***
Edu	2.915	2.567	0.348***
Marr1	0.027	0.030	−0.004
Marr2	0.198	0.255	−0.057***
Marr3	0.764	0.700	0.064***
Hhinc_cpi	9.154	9.003	0.151***
Hwealth	0.444	0.400	0.044
Drink_fre	0.511	0.532	−0.021
Salt	5.104	5.415	−0.31***

The differences between the elderly with hypertension diagnosed or not in the sample. The variables are introduced in ***Table 1****.*
****Indicate statistical significance at the 10, 5, and 1% levels, respectively.*

TABLE 3 | *T*-test for the differences in the various groups of self-reported health status in the elderly.

	(1) Excellent or good	(2) Fair	(3) Poor	(4) Diff. (1)–(3)	(5) Diff. (1)–(2)	(6) Diff. (2)–(3)
Laborhour	330.461	317.605	204.914	125.547***	12.855	112.692***
Age	65.215	66.167	67.606	−2.391***	−0.952***	−1.439***
Male	0.420	0.364	0.364	0.055**	0.055***	0
Edu	2.997	2.635	2.244	0.753***	0.362***	0.391**
Marr1	0.033	0.024	0.036	−0.003	0.009	−0.012
Marr2	0.234	0.218	0.263	−0.03	0.016	−0.046**
Marr3	0.719	0.748	0.681	0.038	−0.029*	0.067***
Hhinc_cpi	9.136	9.079	8.852	0.284***	0.058	0.226***
Hwealth	0.469	0.387	0.396	0.073	0.082**	−0.009
Drink_fre	0.591	0.513	0.374	0.216***	0.077*	0.139**
Salt	5.192	5.304	5.436	−0.244*	−0.112	−0.132

The differences in the various groups of self-reported health status in the elderly. The variables are introduced in ***Table 1****.*
**, **, and ***indicate statistical significance at the 10, 5, and 1% levels, respectively.*

Therefore, when health is a binary variable, combining Equations 1, 2, we can obtain the following simultaneous equations:

$$\begin{aligned} &Laborhour = \max\{0,\ Laborhour^{*}\} \equiv \\ &\max\{0,\ \gamma_0 + Controls^{'}\delta_1 + a_1 Health_1 + \mu_1\} \\ &Health_1 = 1\{\beta_0 + Controls^{'}\delta_{21} + \\ &Identify^{'}\delta_{22} + \nu_2 > 0\} \equiv 1\left\{\beta_0 + Varbs^{'}\delta_2 + \nu_2 > 0\right\} \end{aligned} \tag{3}$$

In Equation (3), the existence of endogeneity of $Health_1$ is determined by the correlation between μ_1 and ν_2. If μ_1 and ν_2 are not correlated, there is no endogeneity in model (3); otherwise, the variable $Health_1$ is endogenous. Therefore, we set μ_1 and ν_2 as jointly normal distributions with zero mean value and their covariance matrix is as follows:

$$Var\begin{pmatrix}\mu_1\\ \upsilon_2\end{pmatrix} = \begin{pmatrix}\sigma_1^2 & \rho_1\\ \rho_1 & 1\end{pmatrix} \tag{4}$$

We also set $\mu_1 = \rho_1\nu_2 + e_1$, where $\rho_1 = cov(\mu_1,\ \nu_2)$. When $\rho_1 = 0$, $Health_1$ is exogenous, otherwise $Health_1$ is endogenous in model (3). In this way, the omitted variables and potential reverse causality, which may lead to the endogeneity problem, are addressed in the model settings. We assume that e_1 is independent to ν_2, and then, it can be derived that $e_1 \sim N(0, \sigma_1^2 - \rho_1^2)$.

Therefore, in Equation (3), we need to estimate the coefficients γ_0, α_1, β_0, ρ_1, and σ_1, as well as the coefficient vectors δ_1 and δ_2. The core coefficient α_1 is what we focus on most, which indicates the effect of hypertension on the rural elderly's working hours.

The Equation of Health (Self-Reported Health)

In the health equation, we set the health level of the elderly as an ordered variable as in model (5). We use *Selfhealth* to represent $Health_2$ of model (5) in estimation.

$$\begin{aligned} &Health_2^{*} = \chi_0 + Controls^{'}\eta_{21} + Identify^{'}\eta_{22} + \varepsilon_2 \equiv \\ &\chi_0 + Varbs^{'}\eta_2 + \varepsilon_2 \\ &Health_2 = \begin{cases} 1, & -\infty < Health_2^{*} \le \tau_1 \\ 2, & \tau_1 < Health_2^{*} \le \tau_2 \\ 3, & \tau_2 < Health_2^{*} < +\infty \end{cases} \end{aligned} \tag{5}$$

Where $Health_2^{*}$ is the latent variable. Similar to Equation (2), $Health_2^{*}$ can be interpreted as the actual health condition, and $Health_2$ is the correspondingly observed ordered variable with three values: 1 means the health condition is good, 2 means normal, and 3 means poor. ε_2 is the random disturbance term, and for convenience, we set that it meets the assumption $Var(\varepsilon_2) = 1$. The other settings are the same as in Equation (2).

Therefore, when health is an ordered variable, combining Equations 1, 5, we can obtain the following simultaneous equations:

$$\begin{aligned} &Laborhour = \max\{0,\ Laborhour^{*}\} \equiv \\ &\max\{0,\ \gamma_0 + Controls^{'}\delta_1 + a_1 Health_2 + \mu_1\} \\ &Health_2^{*} = \chi_0 + Controls^{'}\eta_{21} + \\ &Identify^{'}\eta_{22} + \varepsilon_2 \equiv \chi_0 + Varbs^{'}\eta_2 + \varepsilon_2 \\ &Health_2 = \begin{cases} 1, & -\infty < Health_2^{*} \le \tau_1 \\ 2, & \tau_1 < Health_2^{*} \le \tau_2 \\ 3, & \tau_2 < Health_2^{*} < +\infty \end{cases} \end{aligned} \tag{6}$$

In model (6), we also set μ_1 and ε_2 as jointly normal distribution with zero mean value, and their covariance matrix is as follows:

$$Var\begin{pmatrix}\mu_1\\ \varepsilon_2\end{pmatrix} = \begin{pmatrix}\sigma_1^2 & \rho_2\\ \rho_2 & 1\end{pmatrix} \tag{7}$$

Similarly, as model (4), we set $\mu_1 = \rho_2\varepsilon_2 + e_2$, where $\rho_2 = cov(\mu_1, \varepsilon_2)$. When $\rho_2 = 0$, $Health_2$ is exogenous, otherwise, it is

$$
\begin{aligned}
&f(Laborhour, Health_1|Varbs)\\
&=\left[\frac{1}{\sigma_1}\phi\left(\frac{Laborhour-\gamma_0-Controls^{'}\delta_1-\alpha_1 Health_1}{\sigma_1}\right)\right]^{1\{Laborhour>0\}}\\
&\cdot\left[\Phi\left(\frac{\sigma_1^2(\beta_0+Varbs^{'}\delta_2)+\rho(Laborhour-\gamma_0-Controls^{'}\delta_1-\alpha_1 Health_1)}{\sigma_1\sqrt{\sigma_1^2-\rho_1^2}}\right)\right]^{1\{Laborhour>0\}\times 1\{Health_1=0\}}\\
&\cdot\left[1-\Phi\left(\frac{\sigma_1^2(\beta_0+Varbs^{'}\delta_2)+\rho(Laborhour-\gamma_0-Controls^{'}\delta_1-\alpha_1 Health_1)}{\sigma_1\sqrt{\sigma_1^2-\rho_1^2}}\right)\right]^{1\{Laborhour>0\}\times 1\{Health_1=1\}}\\
&\cdot\left[1-\Phi\left(\beta_0+Varbs^{'}\delta_2\right)-\int_{-\infty}^{-\beta_0-Varbs^{'}\delta_2}\Phi\left(\frac{\gamma_0+Controls^{'}\delta_1+\alpha_1 Health_1+\rho_1 v_2}{\sqrt{\sigma_1^2-\rho_1^2}}\right)\phi(v_2)dv_2\right]^{1\{Laborhour=0\}\times 1\{Health_1=0\}}\\
&\cdot\left[\Phi\left(\beta_0+Varbs^{'}\delta_2\right)-\int_{-\beta_0-Varbs^{'}\delta_2}^{+\infty}\Phi\left(\frac{\gamma_0+Controls^{'}\delta_1+\alpha_1 Health_1+\rho_1 v_2}{\sqrt{\sigma_1^2-\rho_1^2}}\right)\phi(v_2)dv_2\right]^{1\{Laborhour=0\}\times 1\{Health_1=1\}}
\end{aligned}
\tag{10}
$$

$$
\begin{aligned}
&f(Laborhour, Health_2|Varbs)\\
&=\left[\phi\left(\frac{Laborhour-\gamma_0-Controls^{'}\delta_1-\alpha_1 Health_2}{\sigma_1}\right)\right]^{1\{Laborhour>0\}}\\
&\cdot\left[1-\Phi\left(\frac{\sigma_1^2(\chi_0+Varbs^{'}\eta_2-\tau_1)+\rho(Laborhour-\gamma_0-Controls^{'}\delta_1-\alpha_1 Health_2)}{\sigma_1\sqrt{\sigma_1^2-\rho_2^2}}\right)\right]^{1\{Laborhour>0\}\times 1\{Health_2=1\}}\\
&\cdot\left[\begin{array}{l}\Phi\left(\frac{\sigma_1^2(\tau_2-\chi_0-Varbs^{'}\eta_2)+\rho(Laborhour-\gamma_0-Controls^{'}\delta_1-\alpha_1 Health_2)}{\sigma_1\sqrt{\sigma_1^2-\rho_2^2}}\right)\\ -\Phi\left(\frac{\sigma_1^2(\tau_1-\chi_0-Varbs^{'}\eta_2)+\rho(Laborhour-\gamma_0-Controls^{'}\delta_1-\alpha_1 Health_2)}{\sigma_1\sqrt{\sigma_1^2-\rho_2^2}}\right)\end{array}\right]^{1\{Laborhour>0\}\times 1\{Health_2=2\}}\\
&\cdot\left[1-\Phi\left(\frac{\sigma_1^2(\tau_2-\chi_0-Varbs^{'}\eta_2)+\rho(Laborhour-\gamma_0-Controls^{'}\delta_1-\alpha_1 Health_2)}{\sigma_1\sqrt{\sigma_1^2-\rho_2^2}}\right)\right]^{1\{Laborhour>0\}\times 1\{Health_2=3\}}\\
&\cdot\left[\Phi(\tau_1-\chi_0-Varbs^{'}\eta_2)-\int_{-\infty}^{\tau_1-\chi_0-Varbs^{'}\eta_2}\Phi\left(\frac{\gamma_0+Controls^{'}\delta_1+\alpha_1 Health_2+\rho_2\varepsilon_2}{\sqrt{\sigma_1^2-\rho_2^2}}\right)\phi(\varepsilon_2)d\varepsilon_2\right]^{1\{Laborhour=0\}\times 1\{Health_2=1\}}\\
&\cdot\left[\Phi(\tau_2-\chi_0-Varbs^{'}\eta_2)-\Phi(\tau_1-\chi_0-Varbs^{'}\eta_2)-\int_{\tau_1-\chi_0-Varbs^{'}\eta_2}^{\tau_2-\chi_0-Varbs^{'}\eta_2}\Phi\left(\frac{\gamma_0+Controls^{'}\delta_1+\alpha_1 Health_2+\rho_2\varepsilon_2}{\sqrt{\sigma_1^2-\rho_2^2}}\right)\phi(\varepsilon_2)d\varepsilon_2\right]^{1\{Laborhour=0\}\times 1\{Health_2=2\}}\\
&\cdot\left[1-\Phi(\tau_2-\chi_0-Varbs^{'}\eta_2)-\int_{\tau_2-\chi_0-Varbs^{'}\eta_2}^{+\infty}\Phi\left(\frac{\gamma_0+Controls^{'}\delta_1+\alpha_1 Health_2+\rho_2\varepsilon_2}{\sqrt{\sigma_1^2-\rho_2^2}}\right)\phi(\varepsilon_2)d\varepsilon_2\right]^{1\{Laborhour=0\}\times 1\{Health_2=3\}}
\end{aligned}
\tag{11}
$$

endogenous in model (6). We also assume that e_2 is independent of ε_2 and derive that $e_2 \sim N(0, \sigma_1^2 - \rho_2^2)$. The same as above, in Equation (6), we will estimate the coefficients γ_0, α_1, χ_0, ρ_2, and σ_1, as well as the coefficient vectors δ_1 and η_2. We focus mostly on α_1, since it reveals how self-reported health affects the rural elderly's labor supply.

The Estimation

There are two main methods to estimate simultaneous equations as model (3) and model (6). The first is the full information maximum likelihood (FIML) estimation method. By maximizing the logarithmic likelihood function of the joint distribution $f\left(Labor,\ Health\middle|Varbs\right)$, we obtained the consistent and efficient estimation results of the parameters. Another method is the limited information maximum likelihood (LIML) method as a two-stage estimation. We will introduce the two methods, respectively, in the following sections.

Full Information Maximum Likelihood (FIML) Estimation

We used the binary variable and the ordered variable to measure health; therefore, we derived the FIML functions of these two cases, respectively.

When we set health as a binary variable, we have $e_1 \sim N(0, \sigma_1^2 - \rho_1^2)$, and

$$
\begin{aligned}
Laborhour^{*} &= \gamma_0 + Controls^{'}\delta_1 + a_1 Health_1 + \mu_1\\
&= \gamma_0 + Controls^{'}\delta_1 +\\
&a_1 Health_1 + \rho_1 v_2 + e_1
\end{aligned}
\tag{8}
$$

Then, we arrive at:

$$
\begin{aligned}
Laborhour^{*}|_{Varbs,v_2}\tilde{}N(\gamma_0 + Controls^{'}\delta_1 + a_1 Health_1 +\\
\rho_1 v_2, \sigma_1^2 - \rho_1^2)
\end{aligned}
\tag{9}
$$

Given *Varbs*, we can derive the joint distribution of *Laborhour* and $Health_1$ as follows:

When we set the health as an ordered variable, following the similar excise as above, we can derive the joint distribution of *Laborhour* and $Health_2$ as follows:

Appendixes A1 and A2 show the detailed probability definitions and derivation process of models (10) and (11),

respectively. We wrote a GAUSS program to estimate the parameters (coefficients γ_0, α_1, β_0, ρ_1, σ_1, and the coefficients vectors δ_1, δ_2) in model (10) and in model (11) (coefficients γ_0, α_1, χ_0, ρ_2, σ_1, and the coefficients vectors δ_1, η_2), since the standard econometric packages do not include this type of model.

Two-Stage Limited Information Maximum Likelihood (Two-Stage LIML) Estimation

Besides the FMIL method, we also used the two-stage LIML method as a robustness check. Using the two-stage LIML method, we can avoid the difficulties of the convergence of the estimation and the derivation of the joint distribution, while the estimation results are still consistent.

For example, when the health is a binary variable as Equation (3), compared with the FIML method, we no longer estimated the joint distribution of *Laborhour* and $Health_1$ directly but estimated the distributions of $f_2\left(Health_1 \middle| Varbs, \beta_0, \delta_2, \sigma_1\right)$ and $f_1\left(Laborhour \middle| Varbs, \beta_0, \delta_2, \sigma_1, \gamma_0, \alpha_1, \delta_1, \rho_1\right)$ by two steps. In the first step, we used the maximum likelihood method to get the estimated parameters in the health equation ($\hat{\beta_0}$, $\hat{\delta_2}$, $\hat{\sigma_1}$), The conditional likelihood function is:

$$ll_2 = \sum_{i=1}^{N} \ln f_2(Health_1 \,|\, Varbs, \beta_0, \delta_2, \sigma_1) \tag{12}$$

In the second step, we took $\hat{\beta_0}$ and $\hat{\delta_2}$ to construct $\hat{Health_1}$ and used the maximum likelihood method to estimate parameters in the labor equation, and the conditional likelihood function is:

$$ll_1 = \sum_{i=1}^{N} \ln f_1(Laborhour \,|\, Varbs, \beta_0, \delta_2, \sigma_1, \gamma_0, \alpha_1, \delta_1, \rho_1) \tag{13}$$

It can be proved that all the estimated parameters are consistent estimators. However, the problem with the two-stage LIML method is that, in the second step, the predicted value of health ($\hat{Health_1}$) is taken into the labor equation, and then the prediction error will affect the disturbance term of the labor equation and cause bias; thus, we need to correct the prediction error. Specifically, we estimated the covariance matrix (V) following Murphy and Topel (31), which presents a correction method of the asymptotic covariance matrix in the two-stage estimation. We set the unknown parameter vector $\theta_1 = (\gamma_0, \alpha_1, \delta_1, \rho_1)'$ and $\theta_2 = (\beta_0, \delta_2, \sigma_1)'$, and then the asymptotic covariance matrix (V) of θ_1 is:

$$V = V_1 + V_1(CV_2C' - RV_2C' - CV_2R')V_1 \tag{14}$$

where $V_2 = Asy.Var(\hat{\theta_2})$, which is obtained by the estimation of ll_2, $V_1 = Asy.Var(\hat{\theta_1})$ obtained by the estimation of ll_1, $C = E\left\{(\frac{\partial u1}{\partial \theta_1})(\frac{\partial u1}{\partial \theta_2'})\right\}$ and $R = E\left\{(\frac{\partial u1}{\partial \theta_1})(\frac{\partial u2}{\partial \theta_2'})\right\}$. The detailed proofs are in Murphy and Topel (31).

Besides, according to Cameron and Trivedi (32), we used another bootstrap method to correct the standard error in the two-stage estimation. The bootstrap method is based on the empirical distribution; so it is easier to obtain a consistent estimation of the standard error without the correction step in non-linear models (32). When estimating Equation (6) where the health is an ordered variable, we used the same LIML estimation method.

RESULTS

We first tested the endogeneity of the variables $Health_1$ and $Health_2$ to decide whether we need to address the endogeneity problem when estimating the simultaneous equations. Then, we analyzed the results to see the impact of health on the elderly's labor supply in rural areas.

The Endogeneity Test

Whether the variables $Health_1$ and $Health_2$ in models (3) and (6) are endogenous can be determined by testing the significance of ρ_1 and ρ_2, which represents the correlations of the disturbance terms in the labor equation and the health equation. For example, in model (3), if the null hypothesis $\rho_1 = cov(\mu_1, \nu_2) = 0$, it means that there is no endogeneity; otherwise, $Health_1$ is endogenous. Following Wooldridge (33), the test of model (3) includes two steps: First, we estimated the health equation and got the predicted residual $\hat{\nu_2}$. Second, we estimated the labor equation by taking $\hat{\nu_2}$ into it and then using t-test to determine whether ρ_1 is significantly different from zero.

The test results show that when health is the binary variable as hypertension diagnosed or not, the t-value is -2.16 and the p-value is 0.031. For the ordered variable as self-reported health, the t-value is -3.55 and the p-value is 0. This implies that the variables $Health_1$ and $Health_2$ in models (3) and (6) are endogenous. Therefore, in the following section, we will use the FIML and LIML estimation methods to examine the effect of health on the elderly's labor supply.

The Effect of Health on the Elderly's Labor Supply

Table 4 shows the estimation results of the simultaneous equations using the binary variable $Health_1$. We found that the coefficients of $Health_1$ are all negative but not significant in the labor equations [columns (2), (4), (5) and (6)], which means that the failing health does not significantly decrease the elderly's labor supply in rural China. Our finding indicates the phenomenon of "ceaseless toil" for the elderly in rural China, i.e., the elderly almost work their whole life even if they are not physically capable.

For the robustness of the results, we provided both the FIML and two-stage LIML estimation results with three kinds of corrected standard errors. For the size of the standard errors with three methods [column (4)–(6)], the original standard error without correction and the standard error corrected following the method of Murphy and Topel (31) were similar, while the standard error corrected by the bootstrap method seems significantly greater than the other two ones. However, the differences in standard errors do not affect the robustness of our results.

TABLE 4 | The effect of health on the elderly's labor supply (using the objective indicator of health: Hypertension diagnosed or not).

	(1) FIML Health equation	(2) FIML Labor equation	(3) LIML Health equation	(4) LIML Labor equation (Original std.)	(5) LIML Labor equation (MT std.)	(6) LIML Labor equation (Bootstrap std.)
Hypertension		−0.198		−0.084	−0.084	−0.084
		(1.672)		(1.569)	(1.567)	(2.032)
Age	0.036	0.824	0.109**	0.894***	0.894***	0.894***
	(0.112)	(0.846)	(0.049)	(0.185)	(0.185)	(0.216)
Age2	0.000	−0.000*	−0.001	−0.008***	−0.008***	−0.008***
	(0.001)	(0.000)	(0.000)	(0.001)	(0.001)	(0.002)
Male	0.054	0.850***	0.098*	0.893***	0.893***	0.893***
	(0.122)	(0.160)	(0.056)	(0.180)	(0.179)	(0.194)
Edu	−0.005	−0.061***	−0.011	−0.119***	−0.119***	−0.119***
	(0.017)	(0.022)	(0.008)	(0.026)	(0.026)	(0.029)
Marr1	0.011	−0.231	0.035	−0.224	−0.224	−0.224
	(0.303)	(0.378)	(0.133)	(0.427)	(0.426)	(0.437)
Marr2	0.014	−0.528***	0.028	−0.837***	−0.837***	−0.837***
	(0.129)	(0.168)	(0.057)	(0.186)	(0.186)	(0.250)
Hhinc	−0.017	0.195***	−0.013	0.482***	0.482***	0.482***
	(0.048)	(0.060)	(0.021)	(0.069)	(0.069)	(0.076)
Hwealth	−0.033	−0.044	−0.005	−0.344***	−0.344***	0.344***
	(0.052)	(0.072)	(0.023)	(0.076)	(0.076)	(0.081)
Drink_fre	0.004		0.000			
	(0.045)		(0.021)			
Salt	−0.068		−0.099***			
	(0.066)		(0.028)			
Salt2	0.006		0.008***			
	(0.004)		(0.002)			
Constant	−1.523	−20.577***	−4.579***	−21.661***	−21.661***	−21.661***
	(3.823)	(4.964)	(1.684)	(6.269)	(6.266)	(7.161)
Year effect	Yes	Yes	Yes	Yes	Yes	Yes
N	3,535	3,535	3,535	3,535	3,535	3,535

The estimates of the effect of health on the elderly's labor supply using the objective indicator hypertension. Columns (1) and (2) present the results of the FIML estimation and columns (3) to (6) are the results of the two-stage LIML estimation. The standard errors in column (4) are the original ones in estimation, in column (5) are corrected following the method of Murphy and Topel (31), and in column (6) are corrected by the bootstrap method. The explained variable is the annual working hours of the elderly in rural China (lnLaborhour). The explanatory variables are introduced in ***Table 1****. Standard errors are reported in parentheses below the coefficients.*

**, **, and ***indicate statistical significance at the 10, 5, and 1% levels, respectively.*

For the control variables, first, the coefficients of *Age2* were significantly negative, which means that the relationship between age and labor supply is non-linear as the inverted U shape. Second, the coefficients of *Male* are significantly positive in labor equations, which reveal that elderly men work more hours than women. This is consistent with the studies of Wang (34), Ling and Chi (35). For this reason, the elderly men in rural areas spend more working hours in family agricultural production. Third, the significantly negative coefficients of the variable *Edu* in labor equations indicate that the elderly with higher education levels work less. They may have better jobs and positions and enjoy higher welfare, so they tend to spend less time working when getting older. Forth, for the coefficients of household income (*Hhinc*) and wealth (*Hwealth*), we found that the income significantly increases the labor supply while the wealth lowers it. It means that the elderly work more to increase family income, but if the family is rich in assets, they may work less.

Table 5 shows the estimation results of the effect of self-reported health on the elderly's labor supply. In column (2), it shows that health does not significantly affect the working hours of the elderly in rural China when using the FIML estimation method. We found that there is a positive correlation between self-reported health and working hours, which means the poorer the self-evaluated health, the longer the working hours. Although the positive correlation is not statistically significant, it also indicates the phenomenon of "ceaseless toil" of the elderly from a subjective measurement of health.

However, the results of the two-stage LIML estimation are shown inconsistently in columns (4) to (6). It is worth mentioning that if we use the original standard error in column

TABLE 5 | The effect of health on the elderly's labor supply (using the subjective indicator of health: Self-reported health).

	(1) FIML Health equation	(2) FIML Labor equation	(3) LIML Health equation	(4) LIML Labor equation (Original std.)	(5) LIML Labor equation (MT std.)	(6) LIML Labor equation (Bootstrap std.)
Selfhealth		5.345		7.465**	7.465	7.465
		(5.513)		(2.933)	(7.478)	(5.781)
Age	0.040***	0.063	0.097**	1.165***	1.165	1.165***
	(0.009)	(0.120)	(0.042)	(0.219)	(0.767)	(0.341)
Age2	−0.000	−0.001**	−0.001**	−0.010***	−0.010*	−0.010***
	(0.001)	(0.000)	(0.000)	(0.002)	(0.005)	(0.002)
Male	−0.066***	0.810***	−0.121**	0.466*	0.466	0.466
	(0.023)	(0.172)	(0.049)	(0.247)	(1.008)	(0.427)
Edu	−0.008	−0.054**	−0.022***	−0.180***	−0.180**	−0.180
	(0.030)	(0.022)	(0.007)	(0.035)	(0.080)	(0.068)
Mar1	−0.018	−0.377	−0.016	−0.260	−0.260	−0.26
	(0.501)	(0.347)	(0.117)	(0.426)	(0.588)	(0.678)
Mar2	−0.050	−0.306*	−0.106**	−1.144***	−1.144	−1.144***
	(0.240)	(0.165)	(0.050)	(0.238)	(0.731)	(0.343)
Hhinc	−0.047	0.217**	−0.051***	0.332***	0.332	0.332***
	(0.089)	(0.087)	(0.018)	(0.098)	(0.289)	(0.142)
Hwealth	−0.007	−0.101***	−0.011	−0.379***	−0.379***	−0.379***
	(0.094)	(0.004)	(0.021)	(0.081)	(0.120)	(0.097)
Drink_fre	−0.018**		−0.040**			
	(0.007)		(0.018)			
Salt	−0.016		−0.034			
	(0.096)		(0.023)			
Salt2	0.001**		0.003**			
	(0.000)		(0.001)			
Cut1	2.001***		3.114**			
	(0.771)		(1.448)			
Cut2	4.171***		4.521***			
	(1.101)		(1.449)			
Constant		15.109		−34.265***	−34.265	−34.265
		(15.018)		(8.130)	(27.961)	(13.604)
Year effect	Yes	Yes	Yes	Yes	Yes	Yes
N	3,535	3,535	3,535	3,535	3,535	3,535

The estimates of the effect of health on the elderly's labor supply using the subjective indicator self-reported health. Columns (1) and (2) present the results of the FIML estimation and columns (3) to (6) are the results of the two-stage LIML estimation. The standard errors in column (4) are the original ones in estimation, in column (5) are corrected following the method of Murphy and Topel (31), and in column (6) are corrected by the bootstrap method. The explained variable is the annual working hours of the elderly in rural China (lnLaborhour). The explanatory variables are introduced in ***Table 1****. Standard errors are reported in parentheses below the coefficients.*

**, **, and ***indicate statistical significance at the 10, 5, and 1% levels, respectively.*

(4) to make a statistical inference, the effect of health on labor supply is significant at a 5% level. However, we cannot give enough credit to this empirical result because the standard error has not been corrected. As we introduced in Section "The Estimation", the problem of the two-stage LIML method is that the prediction error will affect the disturbance term of the labor equation and cause estimation bias. If we do not correct the prediction error, the hypothesis tests based on the estimated covariance matrix of the second-step estimator are biased (31).

Therefore, in columns (5) and (6), we use the Murphy and Topel (31) standard error and the bootstrapped standard error, respectively, and the significance disappears. This also indicates that the correction and robustness check are necessary in two-stage estimation.

DISCUSSION

The Effect of Health on the Elderly's Labor Supply

The effect of health on the elderly's labor supply is controversial in the literature. While some studies found that health has a significant positive impact on labor supply (6, 18–20, 36), some other studies found that there is no significant effect (3, 21–24).

Benjamin et al. (3) and Tan and Zhou (22) hold that there is the phenomenon of "ceaseless toil" existing among the elderly in rural China. French (21) found that the declining health explains only a small fraction of retirement, and the number of unhealthy adults above age 55 is far smaller than the number of those who drop their employment. Coile et al. (23) also found that the declines in health are much too small to explain the declines in the employment of older people.

The reason for the controversy is two-fold. One is that the literature varies in the ways in dealing with the endogeneity problem of health variables. In Section "The Endogeneity Problem of the Health," we will discuss it in detail. The second is about the measurements of labor supply. Most studies focus on labor participation rather than labor hours (18–20, 37). Since people always choose to work either full time or not at all, this may lead to a significant effect of health on labor participation but not on labor hours. In this study, we addressed this issue in two ways. First, the sample we used is the rural older adults who are mainly self-employed and therefore they have a more flexible working hours. Second, the equation of labor supply we used is a Tobit model, which takes into account both the continuous working hours and zero working hours to avoid the estimation bias.

Therefore, by using the simultaneous-equation Tobit model with both the subjective and objective health indicators, this study adds to the literature on the causal effect of health on the elderly's labor supply and in particular to the few studies that examine the effect in developing countries. We found that failing health does not significantly decrease the elderly's labor supply in rural areas. The results further support the conclusion of Benjamin et al. (3) that there is a phenomenon of "ceaseless toil" among the elderly in rural areas in China. That is to say that the rural elderly almost work their whole life even if they are not physically capable.

The Endogeneity Problem of the Health

Alleviating the endogeneity problem of health variables is essential for examining the effect of health on the elderly's labor supply. Some studies used self-reported health status to measure health and found that it is strongly associated with early retirement (38–41). However, as a subjective health indicator, the self-reported health status is susceptible to the influence of an individual's heterogeneous characteristics, which may cause omitted variables and measurement errors (25).

Other studies used objective health indicators as the instrumental variables for health, such as hospital stay, BMI index, parental health indicators, and health behaviors, such as current or past smoking experience, physical exercise frequency, and alcohol abuse (9, 10). However, the information advantage of subjective health indicators may be lost and lead to a weak-instruments problem. In addition, some studies directly investigate the impact of objective health indicators on labor supply. Kalwij and Vermeulen (11) used the physical function limitations to measure health, but the study has some drawbacks as the physical function limitations tend to occur in the senior elderly. The young elderly, however, as the main participants of the elderly's labor supply, are less likely to have physical function limitations.

Some scholars used both objective and subjective health indicators in their studies. Mete and Schultz (6) analyzed the effect of health on the elderly's labor participation in Taiwan using three types of health indicators as self-reported health, ADLs, and specific diseases. Besides, some researchers used principal component analysis to construct composite health indicators (42, 43). However, such composite indicators may lack economic meaning and become inaccurate when single indicators are not highly correlated.

In this study, we used both objective and subjective health indicators, i.e., hypertension and self-reported health status. In the simultaneous-equation Tobit model, we emphasized hypertension as a binary variable by setting the equation of health as a Probit model and self-reported health as an ordered variable by setting an ordered Probit model. In this way, we investigated the effect of health on the elderly's labor supply from different perspectives and enriched the measures of health in the literature.

The Estimation Strategies

To address the endogeneity problem of the variable health in estimation, some studies used the method of instrumental variables. However, it is very difficult to find a proper instrumental variable that can affect health but not affect labor supply through channels except health. Scholars mainly used objective health indicators as the instrumental variables for subjective health indicators. For example, Campolieti (9) studied the impact of physical disability on labor force participation among the Canadian elderly using specific disease indicators and BMI as the instrumental variables for physical disability. Sheran (44) used regional prices of food and health service as instrumental variables for subjective health indicators. Latif (45) used health information as diabetes diagnosed or not of the individual's father, mother, and siblings as the instrumental variables for the individual's own diabetes.

Some studies used simultaneous equations to address the endogeneity problem (10, 46–48). Different from the single equation model usually estimated by two-stage least squares, in simultaneous equations, the correlation of the residuals between the labor equation and the health equation is sufficiently considered. Therefore, the omitted variables and reverse causality that may lead to the endogeneity problem are addressed in simultaneous equations.

In general, the simultaneous equations are usually estimated by the two-stage LIML or the FIML method. Essentially, the two-stage LIML method is the instrumental variable method, and each equation is estimated separately using exogenous instruments. We can obtain a consistent but not efficient estimator using this method because the correlation of residuals in simultaneous equations is not fully taken into consideration. However, the FIML method fully considers the correlation of residuals, i.e., the unobserved factors affect both labor and health simultaneously. Thus, the estimation results are not only consistent but also efficient.

In addition, using the FIML method, the correlation coefficient of residuals in the labor equation and the health

equation can be directly estimated, and we can test the significance of the correlation coefficient directly to verify the existence of endogeneity. If we used the two-stage LIML estimation, the endogeneity can only be partially tested based on the second step in the labor Equation (10). Using the FIML method, Cai and Kalb (10) estimated the simultaneous equations of the binary variable (labor participation) and the ordered variable (health) and analyzed the impact of self-reported health on labor participation of Australian adults. Zhang et al. (46) estimated the simultaneous equations of five simultaneous binary variables using the FIML method and investigated the effect of diabetes, cardiovascular disease, mental illness, and other chronic diseases on labor force participation in Australia.

The difference between our simultaneous equations model and the previous ones is that, in the labor equation, our explained variable is a Tobit-type limited dependent variable rather than a binary variable. In the health equation, we used two types of variables to measure the health level, the binary variable (hypertension diagnosed or not) and the ordered variable (self-reported health status). Based on these variables, we derived the logarithmic likelihood function of joint distribution and then used the FIML method to estimate the results. As we could not find the literature that use FIML method to estimate simultaneous equations of this type, our study is a beneficial supplement to current literature.

CONCLUSION

In this study, we used the four-period CHNS data in the years 1997, 2001, 2004, and 2006 to estimate the impact of health on the working hours of the elderly in rural China. The results showed that neither the objective indicator (hypertension diagnosed or not) nor the subjective indicator (self-reported health status) has a significant impact on the labor supply of the rural elderly. This means that the rural residents have to keep working even if they are suffering from chronic diseases or failing health. We focused on the endogeneity of health variables in the Tobit model of working hours and used the FIML and two-stage LIML estimation methods to conduct simultaneous estimations of labor supply (Tobit model) and health (Probit model and Ordered-Probit model) equations. Our estimation strategy can be used for further empirical research of relevant models.

The split between the urban and rural social security systems in China has lasted for a long time. The conflict between labor supply and the health welfare of the elderly living in rural China raises a lot of compelling questions. For instance, how to better design the social security system in rural China? Due to the reduced fertility rates and increasing medical costs, many countries have great fiscal pressures and seek policy reforms for the later retirement of older people (24). In rural China, these policy reforms may not be applicable. Our study is meaningful to policymakers for the medical and retirement policies in China.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://www.cpc.unc.edu/projects/china.

AUTHOR CONTRIBUTIONS

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

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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.2022.890374/full#supplementary-material

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Time tracking and multidimensional influencing factors analysis on female breast cancer mortality: Evidence from urban and rural China between 1994 to 2019

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Background: There are huge differences in female breast cancer mortality between urban and rural China. In order to better prevent breast cancer equally in urban and rural areas, it is critical to trace the root causes of past inequities and predict how future differences will change. Moreover, carcinogenic factors from micro-individual to macro-environment also need to be analyzed in detail. However, there is no systematic research covering these two aspects in the current literature.

Methods: Breast cancer mortality data in urban and rural China from 1994 to 2019 are collected, which from China Health Statistical Yearbook. The Age-Period-Cohort model is used to examine the effects of different age groups, periods, and birth cohorts on breast cancer mortality. Nordpred project is used to predict breast cancer mortality from 2020 to 2039.

Results: The age effect gradually increases and changes from negative to positive at the age of 40–44. The period effect fluctuates very little and shows the largest difference between urban and rural areas in 2019. The birth cohort effect gradually decreases with urban-rural effects alternating between strong and weak. In the predicted results, the urban-rural mortality gap becomes first narrow and then wide and shows a trend of younger death.

Conclusions: From the perspective of a temporal system, the changing trend of breast cancer mortality is highly consistent with the history of social and economic structural changes in China. From the perspective of the theory of social determinants of health, individuals, families, institutions and governments need to participate in the prevention of breast cancer.

KEYWORDS

breast cancer, urban areas, rural areas, Age-Period-Cohort model, prediction, the theory of social determinants of health

Introduction

Breast cancer (BC) always ranks in the top 10 among Chinese woman's cancer deaths, and its ranking is still rising at the beginning of the new century (1). According to the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO), the morbidity of BC (19.9%) ranks first of cancer among Chinese women, and the mortality rate (9.9%) ranks fourth among all cancers in 2020 (2), women live in fear of BC. On the one hand, BC has many causative factors, including congenital heredity (3–6), acquired habits or lifestyle (4, 7–9), and living environment (4, 10–12), crises surrounding everywhere. On the other hand, after experiencing the multiple shocks of economic, psychological and medical conditions (4), the probability of diagnosed patients surviving has been reduced. This anxiety is exacerbated by the huge disparity between China's urban and rural areas (13).

The urban-rural dual system is a major feature of China's development. Rural areas are dominated by agriculture, while urban areas are more inclined toward higher-paying service industries. As a result, the development of the two regions is not always balanced. The display in Table 1 proves this. Based on the statistics of differences in population and facility quality, the values of some health indicators (health workers, number of beds in medical institutions, and maternal and child health hospitals) are higher in rural areas than in urban areas. But the overall narrowing trend of the development gap of health indicators between urban and rural areas. Also, the growth rate of the gap in the per capita disposable income of residents has decreased gradually, especially after the rural revitalization strategy was proposed in 2017.

Additionally, the China Health Statistical Yearbook announced that the mortality rates of BC for urban and rural women in China were 9.34/100,000 and 6.92/100,000 in 2019 (1), an increase of 14.69 and 47.55% respectively compared to the end of the 1990's. Rural women worry that local medical resources are limited and that cancer is found in the late stage without effective treatment (14). Urban women worry that their immunity would continue to decline due to the strange vision and huge psychological pressure that come with the diagnosis (15). To reduce the mortality rates of BC, it is necessary not only to find causative factors for "prevention" but also to focus on the fairness of resources for "treatment," so that more women can escape the shadow of BC.

Research on carcinogenic factors has been very rich so far. Global burden of disease (GBD) research divides risk factors into four dimensions, mainly focusing on the extraction of population characteristics, namely environmental and occupational, behavioral, metabolic and dietary risks (16–18). However, based on the theory of social determinants of health, the influencing factors of disease occurrence cover more dimensions. If a person eats too much high-fat diets, the steroids in it will be converted into estrogen in the body, which promotes the formation of BC cells (19); Increasing spending power is a sign of wealthier people, and disease prevention is more effective among themselves (20); Agriculture has been the backbone of China's economy for a long time in history, women often worked on the farmland, and more exercise could change the way estrogen is metabolized and reduce the risk of BC (21); Aromatic hydrocarbon receptors mediate the effects of many endocrine disruptors in polluted environments and have implications for BC in young or premenopausal women (22), and so on.

Coincidentally, Age-Period-Cohort (APC) analysis may be used to better depict the entire complex of social, historical, and environmental factors that simultaneously impact individuals or social groups (23). Therefore, it is widely used to assess the characteristics and quality of the epidemic trend of various diseases. At present, there are three major breakthroughs in BC related literature using the APC model: the expansion of regional scope (24), the long traceability of time (21), and the focus on causative factors (25). Wang et al. distinguished between Chinese urban and rural areas and compared with South Korea, Japan, and the United States, finally they summarized the similarities on pursuing health and the differences on cultural habits in different ages and periods of eastern and western society. Ding et al. used the net effect of the birth cohort in the APC model to measure the risk of cancer death for the time where no death data were collected (1906–1990), it verified that its trend was consistent with major political and socioeconomic events in China since the 20th century. Based on the fact that the impact of educational inequality on the mortality rate of BC in Korea changed from positive to negative, Bahk et al. conducted APC analysis by focusing on educational level. The result demonstrated that an increasing trend in BC mortality among Korean women between 1983 and 2012 was due to the increased mortality of the lower education groups, not the highest education group. This also shows that the application of the APC model has a huge space for meticulous processing.

Nevertheless, there are still some deficiencies in the previous literature. First, the comparative analysis of BC deaths focusing on urban and rural areas is not rich enough, but China has a vast territory and a large population, and the problem of urban-rural dual structure is prominent (26). Failure to make a comprehensive and precise distinction may exacerbate the inequity between urban and rural areas (27). Second, the time horizon is concentrated on the past, but rarely on the future. The cohort effect in the APC model is useful for understanding the development of relevant BC over a long period of time in the past, ignoring predict its change in the future that we cannot see. However, the predicting trend has an important guiding role. For example, Yasmeen F predicted a continued increase in

Abbreviations: BC, Breast Cancer; IARC, the International Agency for Research on Cancer; GBD, Global Burden of Disease; APC, Age-Period-Cohort; IE, intrinsic estimator; WHO, World Health Organization.

TABLE 1 Development differences between urban and rural China in 2010–2019.

	Population (10,000 people)		Per capita disposable income of residents (Chinese Yuan ¥)		Health workers (1,000 people)		Number of beds in medical institutions (1,000)		Maternal and child health hospitals (one)		Infant mortality (1/1,000)	
	Urban Areas	Rural Areas	Urban Areas	Rural Areas	Urban Areas	Rural Areas	Urban Areas	Rural Areas	Urban Areas	Rural Areas	Urban Areas	Rural Areas
2010	66,978	67,113	19,109.4	5,919.0	3,647.861	4,549.641	2,302.297	2,484.534	1,042	1,983	5.8	16.1
2011	69,079	65,656	21,809.8	6,977.3	3,844.201	4,761.839	2,475.222	2,684.667	1,042	1,994	5.8	14.7
2012	71,182	64,222	24,564.7	7,916.6	4,141.058	4,967.647	2,733.403	2,991.372	1,058	1,986	5.2	12.4
2013	73,111	62,961	26,467.0	9,429.6	4,488.500	5,291.983	2,948.465	3,233.426	1,096	2,048	5.2	11.3
2014	74,916	61,866	28,843.9	10,488.9	4,770.661	5,453.652	3,169.880	3,431.334	1,096	2,002	4.8	10.7
2015	77,116	60,346	31,194.8	11,421.7	5,127.704	5,556.177	3,418.194	3,597.020	1,120	1,958	4.7	9.6
2016	79,298	58,973	33,616.2	12,363.4	5,487.317	5,675.628	3,654.956	3,755.497	1,145	1,918	4.2	9.0
2017	81,347	57,661	36,396.2	13,432.4	5,892.116	5,846.856	3,922.024	4,018.228	1,160	1,917	4.1	7.9
2018	83,137	56,401	39,250.8	14,617.0	6,263.898	6,026.427	4,141.427	4,262.661	1,166	1,914	3.6	7.3
2019	84,843	55,162	42,358.8	16,020.7	6,665.163	6,253.172	4,351.540	4,455.416	1,168	1,903	3.4	6.6

Data from China Statistical Yearbook and China Health Statistical Yearbook.

the morbidity of BC in U.S. for black and white women over the next 15 years, and this increase would be faster in black women, thus making recommendations to improve high-quality care for black people (28). Katayama and Narimatsu predicted that BC cases in the urban area of Kanagawa, Japan, among people over 65 years old would be peak by 2040 (31.2% increase from 2010), such a high increase in demand for BC treatment naturally required a lot of medical resources (29). Third, the attribution dimension of BC deaths in urban and rural areas is limited. The four dimensions of risk factors summarized by GBD ignored the role of the macro environment. Moreover, most studies explained the phenomenon that the deaths in urban areas increased more slowly than in rural areas from the perspective of better access to health care (24). There are also studies on the goal of reducing mortality rates by curbing high morbidity. They point out that urban lifestyles such as high-fat diets, less exercise, and later childbirth tend to be more westernized, so urban women have higher morbidity rates (19). However, these studies lack emphasis on a more comprehensive perspective from other factors. This causes people to ignore other equally important lethal factors and reduce their chances of surviving.

In such a context, our study has some outstanding innovations. On the one hand, considering history as a mirror, we apply the APC model to trace the historical trend of BC mortality rate changes in urban and rural China to avoid the recurrence of high levels of the risk factors in the past. At the same time, we also pay attention to the future, Nordpred project is used to predict the future, which can obtain more precise results by correlating mortality with age structure and population scale (30). That is to say, we characterize BC deaths in a long time context from the past to the future. To our knowledge, no study has been published covering such a long temporal system. Moreover, in order to make up for the lack of comprehensive discussion on non-pathological factors such as economic and social factors in previous studies, the analysis of BC causative or lethal factors in urban and rural areas are widely covered. Supported by the theory of social determinants of health, comprehensive determinants of BC are covered from personal biological characteristics to group living environment, social environment and social development perspectives. It is expected to provide a theoretical reference for intervening in the future trend of continued increase in BC mortality, and also to provide suggestions for resource allocation under the mortality turning trend, which is of great significance for providing BC the prevention evidence for countries with urban-rural differences like China.

Materials and methods

Data sources and processing

Following the data requirements of the APC model, this paper collects data on BC mortality in the age group of 20–84 years old women in urban and rural China from 1994 to 2019. The mortality rate (1/100,000) is calculated as the proportion of BC deaths in the total population, and these data are obtained from China Health Statistical Yearbook (1995–2020). Moreover, these data are processed as follows: (1) About age: due to the rare occurrence of cancer in the population before the age of 20, and the patients over the age of 85 have low immunity and usually die from other complex causes. What's more, the APC model cannot handle the open age group (31), only rates for those within the age range of 20–84 are considered here, yielding 13 5- year age groups. (2) About period: 5-year average data commonly used

in previous APC modeling studies (32, 33), the dilemma is that people in the 5-year-old age group in 5- year period end up being born over a 10-year period, and continuing to estimate the birth cohort effect this way reduces the temporal resolution by a half (34). Therefore, this paper uses single-year data with an interval of 5 years. Specifically, we analyze age-group mortality data for 1994, 1999, 2004, 2009, 2014, and 2019 to ensure that women in the 5-year-old age group within 1 year were all born within the 5 years in the past. (3) About birth cohort: according to different age groups in the specific study period, we can trace the earliest date of birth to 1910–1914 (year 1994 – age 84 = birth year 1910; and year 1994 – age 80 = birth year 1914); and the latest to 1995–1999 (year 2019 – age 24 = birth year 1995; and year 2019– age 20 = birth year 1999), yielding 18 birth period groups. Further, the "unidentifiable" problem in the APC model should be solved, so this paper uses the intrinsic estimator (IE) algorithm (31) to identify the three variables of age, period, and cohort, which can be used to estimate linear and nonlinear components.

There are stringent requirements for data processing by using the Nordpred project to predict future female BC mortality rates. First, the project predicts the mean BC mortality rate for women in different age groups in the unknown period group based on the mean number of BC deaths by the existing period group. We choose 1996–2019 from the existing 1994–2019 data to ensure evenly grouping, yielding 6 4-year groups, and we plan to predict 2020–2039, a total of 5 groups of data. Second, BC mortality is calculated based on the female population structure. So we collect the population forecast data of 18 age groups of urban and rural women from 1996 to 2039 and divide them into a group every 4 years to take the average. Population forecast data comes from the Department of Economic and Social Affairs of the United Nations (35). Finally, population age standardization is performed. The data comes from the WHO World Standard (36) publicity. All data above processing is performed in Excel 2010 software.

Age-Period-Cohort model

Traditional methodologies are often unable to overcome the problem of interaction between time-related influencing factors when describing the epidemiological characteristics of diseases. The APC model just makes up for this shortcoming. It controls to some extent the interaction among the effect of age, period, and birth cohort on trends in disease mortality (37), making the trend of cancer clearer. The mathematical theory of the APC model is based on the Poisson distribution (38), and the basic expression of the Poisson log-linear model is as follows:

$$ln(M_{ijk}) = ln\left(\frac{D_{ijk}}{P_{ijk}}\right) = \mu + \alpha_i + \beta_j + \gamma_k + \varepsilon_{ijk} \quad (1)$$

Where M_{ijk} denotes the mortality rate of female BC in the age group i, the time period j, and the birth period k, which is calculated as the ratio of the number of deaths from BC in women (D_{ijk}) to the total number of women exposed to BC risk (P_{ijk}). μ denotes the intercept; α_i denotes the coefficient of age group i (i = 20-24, ... , 80-84); β_j denotes the coefficient of time period j (j = 1994, ... , 2019); γ_k denotes the coefficient of birth cohort k (k = 1910-1914, ... , 1995-1999); ε_{ijk} denotes random sampling error and obeys standard normal distribution.

Equation (1) can be viewed as a multiple regression model, where the three regression coefficients in the model are the net effect of each regression coefficient after controlling for the other two regression coefficients. Equation (1) is subject to only one constraint (21):

$$\sum \alpha_i = \sum \beta_j = \sum \gamma_k = 0 \quad (2)$$

APC analysis is performed by using the apc_ie package in STATA (version 15.0).

Nordpred project

Nordpred project can use the Poisson Age-Period-Cohort (APC) models to calculate prediction of BC mortality. The predictions are relatively reliable due to its correlation with age structure and population scale. The prediction process can refer to the description of the data processing section, and it is carried out in the open-source software R (version4.1.1).

Results

Dynamic statistics of breast cancer mortality in urban and rural women in China from 1994 to 2019

Figure 1 shows the annual mortality of BC in urban and rural women in China from 1994 to 2019. In general, the change trends of the two areas are similar. The mortality rates in 2002, 2005, 2010, and 2012 all formed a "v"-shaped structure with their respective adjacent years. However, there are obvious differences, the urban mortality rate is always higher than that of the rural areas, but the range of change in urban areas is lower than that of the rural areas. It is worth noting that although these mortality rates reflect time trends over the past 30 years, the depicted trends may be biased by women's chronological age and birth year.

Figure 2 can just prove this point, that is, there is a significant difference in BC mortality rates from the perspective of women's age and birth year, indicating the existence of effect from age and birth year on the risk of BC death in Chinese

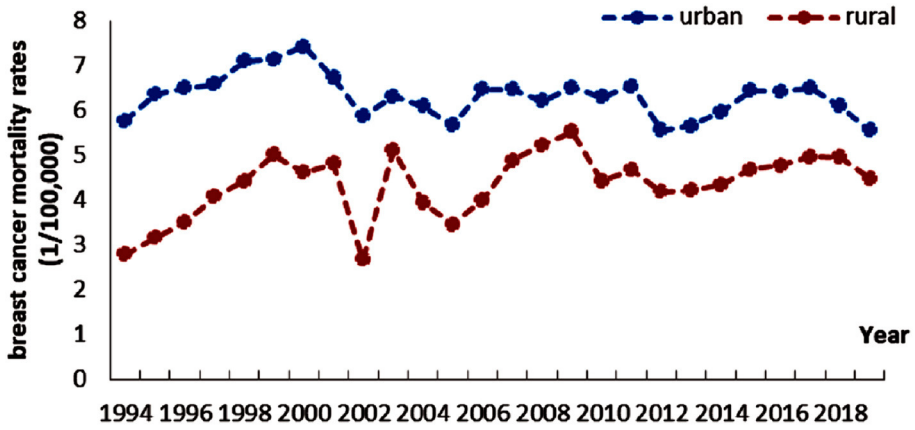

FIGURE 1
Breast cancer mortality rate for women aged 20–84 years old, 1994–2019, urban and rural China.

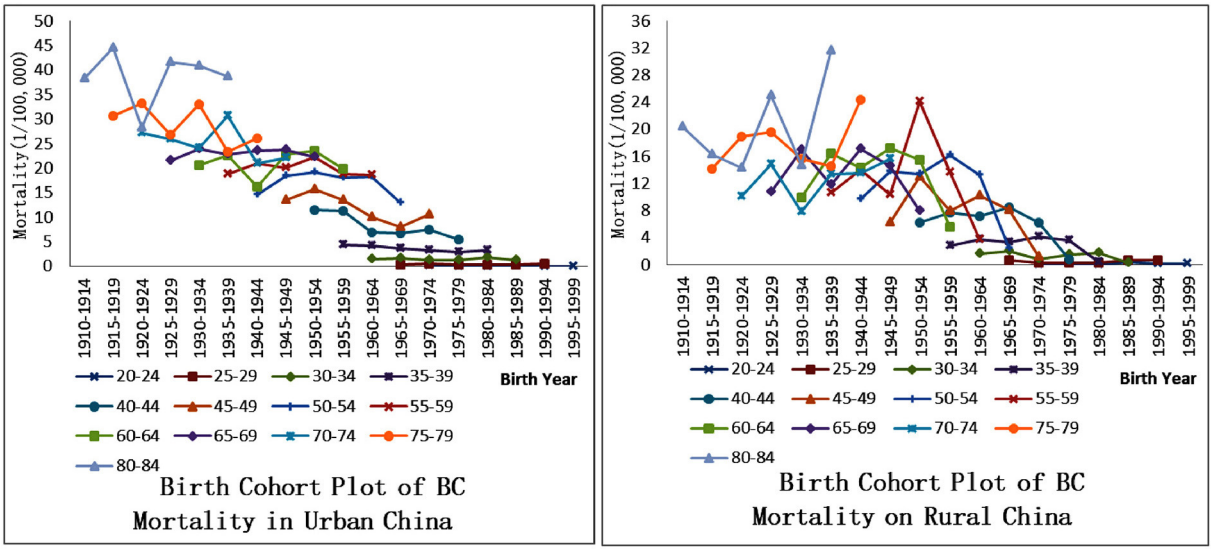

FIGURE 2
Birth cohort plot of breast cancer mortality among urban and rural women, China.

women. In urban areas, the mortality rate for women aged 80–84 who were born in 1910–1914 is the highest (except in 1920–1924), and the rates are the lowest for women aged 20–24 who were born in 1995–1999. In short, it generally follows the pattern of "when the birth period is earlier, the mortality rate will increase with the increase of age." But this pattern is not obvious in rural areas. The BC mortality rate of women over 40 years old in rural areas fluctuates greatly under the change of birth year. The APC model can extract age and birth cohort effects from the overall temporal trend, allowing a more precise assessment of temporal trends in BC mortality.

Age-Period-Cohort modeling results in urban and rural areas

Table 2 summarizes age, period, and cohort effect estimates for urban and rural China, respectively. The estimated effects provide a measure of adjusted risks of BC mortality by age/year. We plot the contents of the table as a graph and get Figure 3.

The age effect of breast cancer mortality

The age effect of BC mortality in both urban and rural women in China shows an inverted "J" shape with age, which

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TABLE 2 APC model analysis results of BC mortality rates for women in urban and rural China.

Age	Urban	Rural	Period	Urban	Rural	Cohort	Urban	Rural
20–24	−3.622	−2.682	1994	−0.239	−0.251	1910–1914	0.949 (0.338)	0.666
	(1.281)	(0.964)		(0.116)	(0.129)			(0.300)
25–29	−2.152	−1.693	1999	−0.050	0.116 (0.097)	1915–1919	0.911 (0.303)	0.213
	(0.594)	(0.553)		(0.085)				(0.247)
30–34	−1.013	−0.761	2004	−0.133	−0.104	1920–1924	0.716 (0.288)	0.308
	(0.390)	(0.379)		(0.071)	(0.090)			(0.213)
35–39	−0.268	−0.177	2009	0.120	0.265 (0.081)	1925–1929	0.640 (0.278)	0.476
	(0.304)	(0.300)		(0.068)				(0.183)
40–44	0.399	0.272	2014	0.111	0.092 (0.100)	1930–1934	0.606 (0.275)	0.200
	(0.247)	(0.243)		(0.088)				(0.180)
45–49	0.598	0.318	2019	0.191	−0.118	1935–1939	0.483 (0.278)	0.519
	(0.212)	(0.212)		(0.111)	(0.124)			(0.169)
50–54	0.846	0.562				1940–1944	0.279 (0.292)	0.559
	(0.178)	(0.177)						(0.185)
55–59	0.868	0.554				1945–1949	0.296 (0.307)	0.471
	(0.151)	(0.154)						(0.209)
60–64	0.800	0.563				1950–1954	0.296 (0.325)	0.540
	(0.133)	(0.138)						(0.229)
65–69	0.808	0.544				1955–1959	0.112 (0.349)	0.221
	(0.122)	(0.133)						(0.265)
70–74	0.828	0.517				1960–1964	−0.090	0.078
	(0.123)	(0.140)					(0.376)	(0.295)
75–79	0.863	0.933				1965–1969	−0.415	−0.155
	(0.135)	(0.144)					(0.411)	(0.333)
80–84	1.045	1.050				1970–1974	−0.377	−0.500
	(0.157)	(0.170)					(0.442)	(0.389)
						1975–1979	−0.730	−0.762
							(0.507)	(0.468)
						1980–1984	−0.618	−1.098
							(0.581)	(0.644)
						1985–1989	−0.728	−0.863
							(0.767)	(0.787)
						1990–1994	−0.651	−0.345
							(0.216)	(1.025)
						1995–1999	−1.679	−0.528
							(4.854)	(2.460)
cons	1.891	1.555						
	(0.293)	(0.165)						
AIC	4.8649	4.9453						
BIC	−184.034	−146.032						

The values in this table are the regression coefficients of the three effects, and the standard errors are in parentheses.

indicates that the risk of BC death in women gradually increases with age, and it also shows that the rate of change in mortality with age is slow in the old, comparing the faster rate of change in the young. What's more, starting from the age of 40, the age effect of BC mortality in both urban and rural women increases to a positive value, which means that for women over 40 years old, age is a risk factor to BC mortality. In addition, there are also differences in the age effect of BC mortality between urban and rural areas. In the age group below 40 years old (negative effect stage), the absolute value of the urban age effect coefficient is always larger than that in rural areas (showing that the urban curve is below the rural curve), and also in the age group above

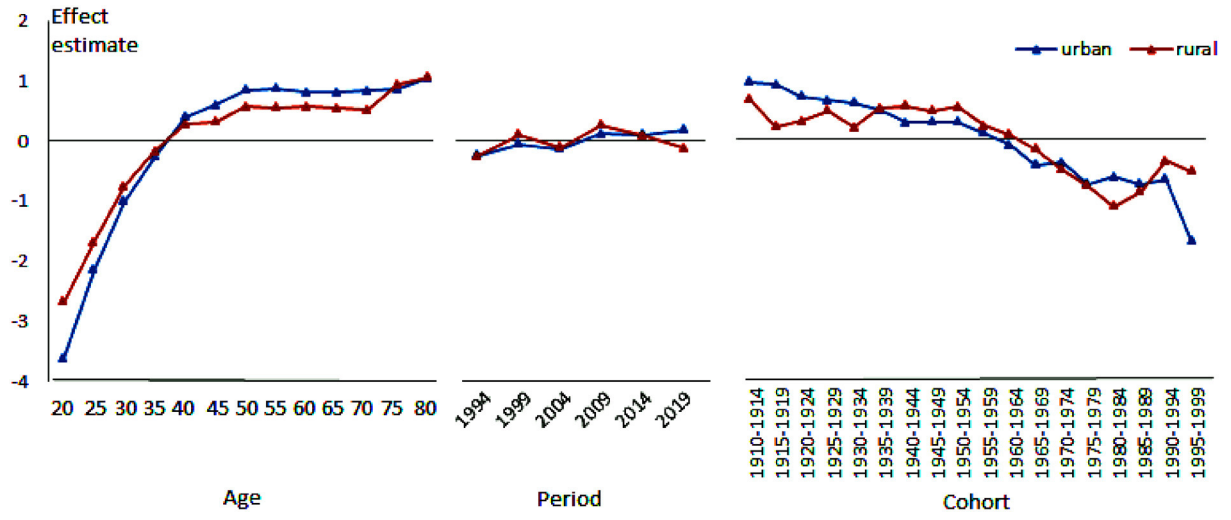

FIGURE 3
Age, period and cohort effect on breast cancer mortality in urban and rural China.

40 years old (positive effect stage) as does (showing that the urban curve is above the rural curve). On the one hand, it shows that the age effect of BC mortality in urban women increases significantly faster than in rural areas. On the other hand, it also shows that when age becomes a risk factor of BC mortality, urban women are at higher risk.

The period effect of breast cancer mortality

The period effect of BC mortality in Chinese urban and rural women generally shows an "M" shape with time, that is, it shows two repeated fluctuations of "up-down." Moreover, the period effect difference in BC mortality among urban and rural women is relatively tiny. The most significant difference appears in 2019. The urban period effect is larger than that of the previous period (2014), while the rural areas keep a continuous downward trend or even drop to a negative value on the basis of the previous period (2014).

The birth cohort effect of breast cancer mortality

The birth cohort effect of BC mortality in both urban and rural areas in China generally shows a downward trend with birth year, and change from positive value to negative value during 1960–1969, that is, for women who were born before this period, their birth year is a risk factor to BC mortality. In addition, when the birth year acts as a risk factor, the cohort effect in urban areas changes from strong to weak, and the cohort effect in rural areas is just the opposite; When birth year is the protective factor, the cohort effect in urban areas changes more rapidly than in rural areas, showing that the inhibitory effect is stronger in urban areas for most of the periods.

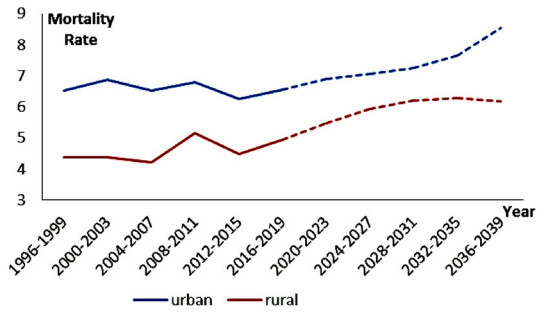

FIGURE 4
Prediction of breast cancer mortality in Chinese women (age standardization).

Prediction of breast cancer mortality in urban and rural women in China from 2020 to 2039

Figure 4 shows the age-standardized BC mortality rates prediction results for Chinese urban and rural women by using the Nordpred project. Whether in the past or the future, the BC mortality rate for urban women has always been higher than that in rural areas, and future projections for both areas are on upward trends. Over the forecast period of the next 20 years, the gap in BC mortality between the two areas shows a trend

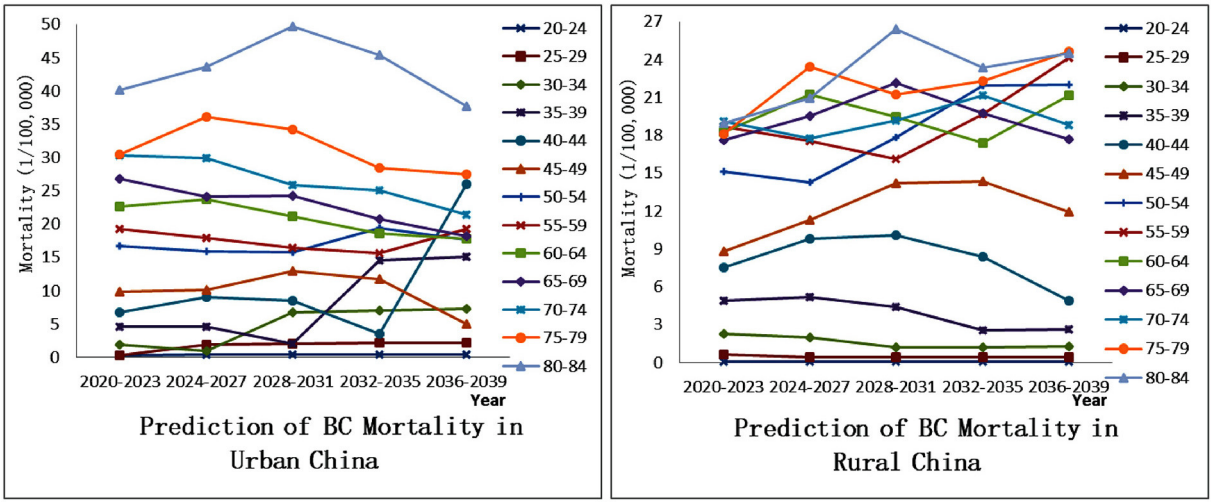

FIGURE 5
Prediction of breast cancer mortality in Chinese women (different age groups).

of gradually narrowing and then rapidly widening. (1) 2020–2031: the gap is gradually narrowing. During this period, the rising rate of urban mortality has slowed significantly, while the rising rate of rural mortality has just accelerated. (2) 2032–2039: the gap is rapidly widening. At this time, the rate of mortality growth in urban areas accelerates significantly, but in rural areas, it becomes slow and even has a slow downward trend after reaching the highest value in 2032–2035.

To more accurately judge the difference between the overall trend and the trend of female BC mortality in different age groups, we also plot the predictions of BC mortality in Chinese urban and rural women by age group, as shown in Figure 5. From the perspective of urban areas, there is a pattern that "the mortality rate of BC increases with age." However, it is obvious that relatively young women (25–29, 30–34, 35–39, 40–44, etc.), rather than older women (the trend is just the opposite), are in line with the trend in total mortality from 2020 to 2039 (Figure 4). From the perspective of rural areas, the female mortality rate in the 20–54 age group shows the same pattern as the urban one, but the situation in the 55+ age group does not conform to this pattern. Moreover, similarly, the BC mortality rate of younger women (25–29, 30–34, 35–39, 40–44, 45–49,etc.) and the total mortality rate are closer to the trend of change from 2020 to 2039, indicating that the BC mortality rate in the future is more inclined to young people.

Discussion

This paper collects BC mortality data for women aged 20–84 years in urban and rural China from 1994 to 2019 and uses the APC model to extract the net effects of age, period, and birth cohort. At the same time, the Nordpred project is used to predict the trend of BC mortality in urban and rural areas in the next 20 years. Moreover, a multi-dimensional analysis is made for the exploration of BC determinants. Our study has great significance. First, under the background of China's urban-rural dual structure, the unequal allocation of various resources and the difference in the change of BC mortality between the two areas are typical representations. At the same time, China is continuously narrowing the urban-rural gap through programs such as "rural revitalization" and "common prosperity," which can provide a reference for other BC high-incidence regions in the world with uneven development. Second, through the APC model and the prediction results, we construct a long temporal system that includes the past, present and future for the first time, taking history as a guide to continuously improve health and allow more and more women to escape the shadow of BC. This is something that previous research has not covered. Third, under the framework of the theory of social determinants of health, we divide a clear structural level from the micro-individual to the macro-environment, making up for the lack of theoretical framework of previous research, and reflecting the importance of joint efforts by different subjects such as individuals, communities, and governments to change the current situation of high morbidity and high mortality of BC.

The complete temporal system: Past, present and future

The birth cohort effect extracted by the APC model can be traced back to a relatively early period, and it can show the changing trend of BC mortality during 1910–1999 under the data frame of this paper. We find that the birth cohort effect weakened with birth period and it shows the characteristics of

alternating strong and weak in urban and rural areas. This is actually a reflection of the changes in ideology, the inheritance of traditional culture, the reform of the medical system and the development of health technology that accompany the transformation of China's social and economic structure. The founding of the Republic of China in 1912 opened a new chapter of women's liberation (39). The rapid development of agriculture before 1949 gradually improved women's diets, especially in rural areas where "natural advantages" (21), In the early days of the founding of the People's Republic of China, the government-led medical security system began to play a role (40), and the cooperative medical system, which was rapidly promoted nationwide in the 1960's (41), became one of the driving forces for the transformation of the positive and negative attributes of the birth cohort effect. Since the reform and opening up in 1978, the medical system reform has been on the right track, and the medical technology has been also becoming more advanced, urban areas with relatively mature and complete facilities gained the upper hand at this time. However, the loss of the "collective economy" made it more difficult for the rural areas where the development of health organizations has been slow (42). Simultaneously, the development of science and technology in China has made rapid progress. The combination of it and the medical field (43) has also ushered in the dawn of BC screening and treatment. All these changes have found a breakthrough in the prevention or treatment of BC. However, the elderly who were born at a relatively early period happened to be the ones who experienced this series of "earth-shaking" changes, the traditional ideas and concepts have been deeply ingrained, and their ability and willingness to accept new things are relatively low, so these changes actually have a very limited impact on the elderly.

The period effect extracted by the APC model can be viewed as the present change in BC mortality. Overall, the period effect of BC mortality in urban and rural areas has only a small fluctuation. This largely depends on which of the BC protective factors and risk factors prevail over time. BC mortality has a downward trend when protective factors such as improvements in medical technology and people's lives play leading roles. However, BC mortality has an upward trend when risk factors such as environmental pollution, bad living habits, and job competition pressure play leading roles. Partially, the biggest difference between urban and rural period effects occurred in 2019. The rural revitalization plan (44) in recent years has made great contributions to narrow the gap between urban and rural areas, which has improved the situation in all aspects of the countryside and achieved remarkable results in curbing the high mortality rate of diseases.

Prediction of BC mortality over the next 20 years has great significance. (1) The stage in which the urban-rural mortality gap is gradually narrowing. This may be the result of the accumulation of rural risk factors over time. Since the 1980's, farmers have chosen to work in cities to increase their income. On the one hand, due to their low level of education and lack of special skills, they had to engage in high-risk jobs such as construction and textile industry; On the other hand, these farmers are not official residents of cities, and most of them are excluded from the city's medical and social security benefits. Coupled with the restriction of the household registration policy, if there are BC patients among these people, they should be registered in the rural areas rather than the city where they live (13). (2) The stage in which the urban-rural mortality gap is rapidly widening. With the reform of the household registration system (45), a large number of farmers can flock to cities and even settle down to enjoy the city's medical benefits. The population base of cities becomes larger, and the morbidity and mortality of BC will increase. In addition, the role of some "big city diseases" should not be ignored. (3) BC mortality rates in both urban and rural areas will be more skewed toward younger groups in the future. This may be related to the higher morbidity caused by the more westernized lifestyle of young people in the future (19), and the extremely high morbidity causes extremely high mortality. Figure 6 shows influencing factors of BC in urban and rural areas in the course of social development in China.

In such a long temporal system, we deeply understand that although the worsening result of BC ultimately manifests as the death of an individual, it is the product of different environmental backgrounds constructed at various stages of social development. The societal change affects the activities of micro-individuals, making BC different between individuals, and individuals in turn affect their living environment in order to adapt or change this state. To discuss the influence of micro-individual and macro-environment more clearly, we rely on the theory of social determinants of health to analyze various carcinogenic factors according to the level.

The theory of social determinants of health: From the micro-individual to the macro-environment

The theory of social determinants of health divides the influencing factors of disease into the six parts.

(1) Age and genetic factors. The age effect extracted by the APC model is one of the most basic features in the analysis of population heterogeneity, and it is also the innermost ring factor in the hierarchical model of health social influencing factors established by Dahlgren and Whitehead in 1991. Our results show that BC mortality increases with age in urban and rural China, which is consistent with the accumulation of time exposure to risk factors and the decline of bodily functions (especially immunity) in the elderly. At the same time, the age group of 40–44 is the key point that age changes from a

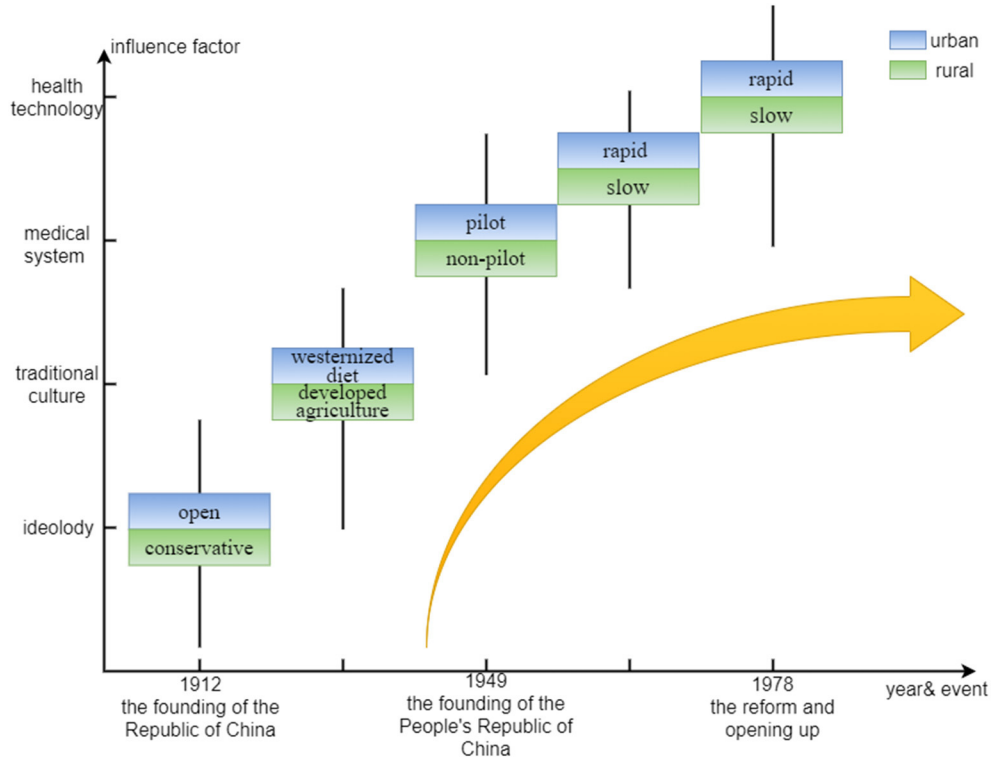

FIGURE 6
Influencing factors of breast cancer in urban and rural areas in the course of social development in China.

protective factor to a risk factor. On the one hand, women in this age group are under the dual pressure of family and work. On the other hand, they are on the verge of menopause, when the human body is relatively sensitive to changes in hormones (46), making it easier to induce BC. In addition, Monticciolo et al. did research on genetics-based increased BC risk and calculated the lifetime risk of 20% or more (5).

Additionally, from the perspective of histological and molecular classification of BC, there are obvious age-clustering characteristics of special types of BC. According to Renan et al. medullary carcinoma usually affects patients aged 30–40 years, while women aged 50–60 years are more affected by cribriform carcinoma and tubular carcinoma. Mucinous carcinoma, neuroendocrine carcinoma, and invasive lobular carcinoma are more common in the elderly. Also, postmenopausal women are more affected by metaplastic carcinoma and apocrine carcinoma (47). Based on comprehensive gene expression profile studies, the four molecular subtypes of BC include Luminal A, Luminal B, enriched HER2 (HER2+), and Triple Negative (48–50). At the same time, they also show differences in age structure. Anna et al. found that women aged 20–39 years more often had HER2+ and Triple Negative tumors, while women aged 70–89 years more often had luminal A-like tumors (51). Different histological and molecular classifications of BC have different prognosis and treatment response, and the mortality rate is also quite different. Therefore, every link in BC diagnosis, prognosis, drug target, and treatment response prediction is crucial.

(2) Personal lifestyle. Many obvious bad behaviors in urban areas can greatly increase BC risk, resulting in higher BC mortality rates in urban areas than in rural areas. For example, the average age of marriage postponed from 23.4 in the 1990's to 27.1 in the first decade of the 21st century, the breastfeeding rate fell from 67% in 1998 to 28% in 2014 (21), increased beef and pork intake and decreased vegetable intake (52), and the more serious psychological stress and depression (53), etc. In addition, there is evidence of quantitative analysis, including "a 10 g increase in daily alcohol consumption is associated with a 7.1% increase in BC risk" (54), and "the sedentary behavior is significantly positively associated with BC risk" (55). The late marriage age, reduced breastfeeding (56), high fat intake (57), huge psychological pressure, high drinking rate, and lack of physical activity are all more obvious manifestations of urban areas than rural areas with relatively conservative ideas.

(3) Social support network. With the development of the economy, China's health service supply has also achieved a

double leap in quality and quantity, and the popularization of medical insurance has provided a guarantee for the prevention and treatment of BC. However, it cannot be denied that the development of medical and health technology needs a long time, and the medical support currently in the period of progress cannot exert its maximum function. As a priority area for the promotion of various medical and health policies, urban areas have advantages over rural areas. In addition, the publicity of BC-related knowledge is insufficient, and people's access to scientific information is very limited, especially in rural areas. Liu et al. conducted a questionnaire on BC self-screening awareness and found that women's awareness of BC is very low (58), which would increase women's unconscious exposure to more carcinogenic factors.

(4) Socioeconomic status. In general, urban women have higher levels of income and education. When people's income is higher, their prevention and treatment of diseases have a money basis, and higher education levels can make them more likely to accept the relevant prevention knowledge and disease treatment process (13).

(5) The nature and environment of work. Research has shown that when young women work long-term night shifts, their BC risk increases by 2.15 times (12). Working at night can cause a disturbance in the biological clock and abnormal estrogen levels in the body. Moreover, changes in light at night may affect the normal circulation of melatonin (8), which increases the BC risk. In addition, some specific occupations have a higher incidence of BC, such as medical staff, teachers, company employees, etc. (59, 60). These people are often stressed and have many night shifts.

(6) Macro-social and economic development and environmental status. In many cases, individual efforts alone cannot escape the risk factors in the macro-environment. In urban areas, rapid economic development can be projected onto advances in the medical field, such as the upgrading of medical equipment, the improvement of medical technology, and the cultivation of medical talents, which has an advantage over rural areas in slowing or halting the upward trend in BC mortality. However, the environmental pollution problems brought about by urban development have weakened its advantages. For example, PM2.5 contains endocrine-disrupting pollutants, which can potentially affect breast density by interfering with the growth of breast cells and increasing the relative number of fibrous tissue (61), promoting the occurrence of diseases.

In conclusion, the theory of social determinants of health profoundly reveals that the occurrence of BC is affected by multi-level factors, and high-level factors will play a role by affecting low-level factors. It also points out that reducing BC risk requires a concerted effort by many parties. Figure 7 shows the construction process of the temporal system and the theory of social determinants of health.

Limitation

This paper also has some limitations. First, limitations of the APC model approach: the estimates of the two birth cohort effects are unreliable. For example, the mortality rate for women aged 80–84 in 1994 is the only data source for estimating the cohort effect for 1910–1914; the mortality rate for women aged 20–24 in 2019 is the only data source for estimating the cohort effect for 1995–1999. Second, limitations of data availability: this paper selects annual data. Although there is a time span of nearly 30 years, there are only two types of study areas (urban and rural areas). It is unavoidable that the quantitative analysis bias is too large due to the small sample size. Therefore, we only conduct qualitative analysis. Despite its limitations, this paper provides useful ideas and policy recommendations for BC prevention and treatment.

Conclusion

Using the APC model and the Nordpred project, our study first collates the BC mortality changes in urban and rural Chinese women in a long temporal system. BC risk is the result of mapping changes in China's socioeconomic structure to individuals and is also the result of catalysis or mitigation of individual different activities. Therefore, with the basis of the theoretical framework of social determinants of health, we have clarified the difference between the innate genetics and acquired habits of micro-individuals, the role of communities, institutions, and families at the middle level, and the impacts of macro-environment. The inequality between urban and rural areas in these aspects has become an important reason for the difference in BC risk. To this end, we make the following recommendations.

First, the inequality between urban and rural areas needs to be addressed urgently. Most of the urban high mortality is due to its high morbidity, so urban areas should focus on BC prevention. The rapidly increasing mortality rate in rural areas is more caused by inadequate screening in the early stage, lack of understanding of relevant information, and untimely treatment in the later stage, so rural areas should focus on BC screening and treatment. In addition, with the advancement of programs such as "rural revitalization" and "common prosperity," the resolution of urban-rural inequality in China is just around the corner. Advances in health care can help prevent and treat BC, despite the increased risk factors that come with development. Therefore, giving all women equal access to high technology for prevention and treatment would be an effective way to break the positive relationship between development and BC risk (62). Second, attention should be paid to the issue including mortality rates rising and skewing toward younger people in the forecast. Appropriate inclination

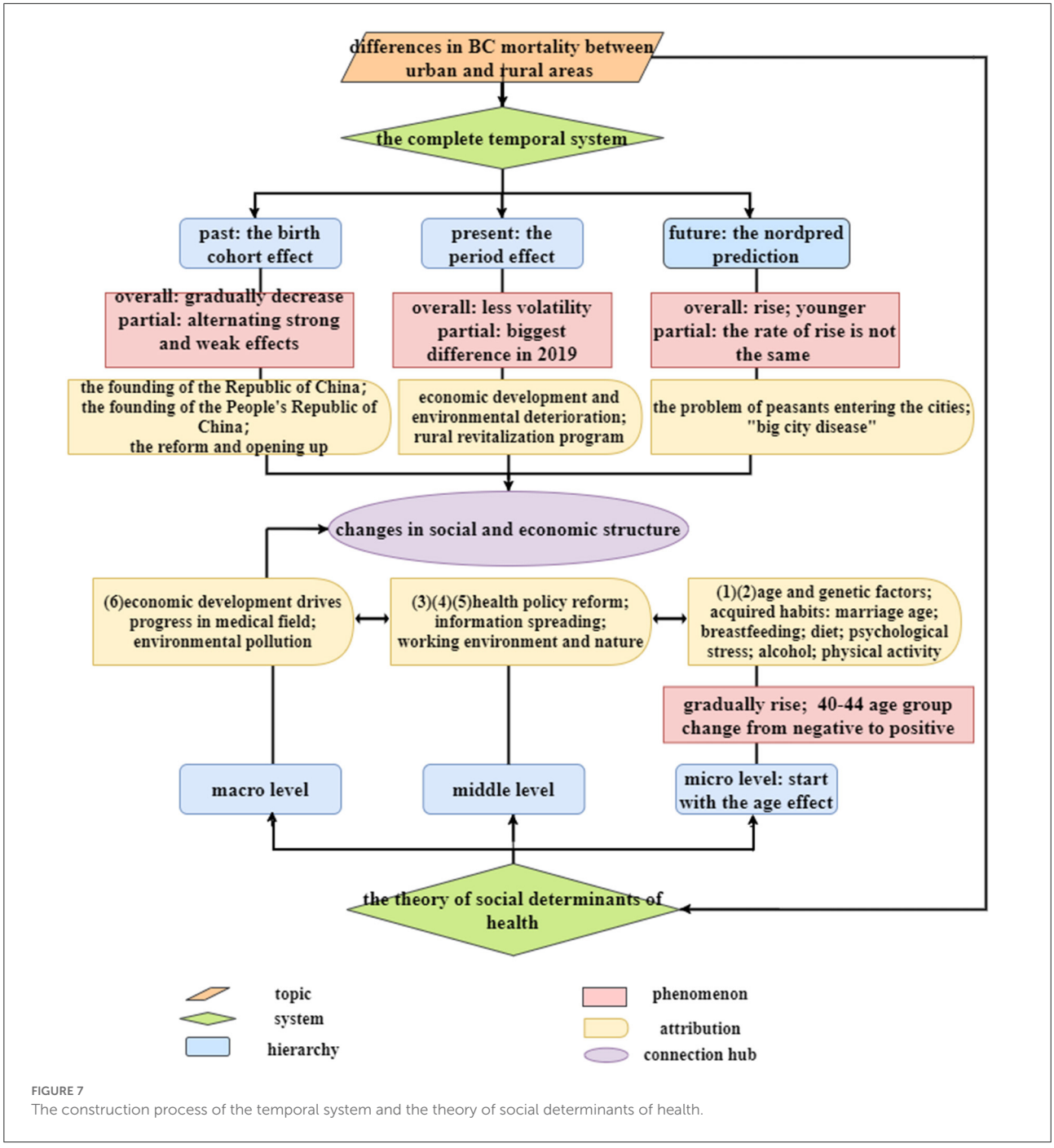

FIGURE 7
The construction process of the temporal system and the theory of social determinants of health.

of medical resources to rural areas is a direct means to intervene in the rapid increase in the mortality rate of rural BC in the next 10 years. At the same time, in order to avoid the sudden increase of urban BC mortality due to the accumulation of early risk factors, solving the problem of farmers entering the city and "big city disease" should be put on the agenda. Last, reducing BC risk requires a concerted effort. Everyone should try their best to maintain a healthy lifestyle and a positive attitude; Families and communities should create a harmonious and warm atmosphere, provide more emotional support and do a good job of publicity about BC prevention; Governments should make overall plans in terms of education level improvement, special occupational attention, medical welfare security, and sustainable economic and environmental development. Only in this way can the goal of human health be achieved.

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 authors.

Author contributions

XB is responsible for framework design and writing-original draft. XZ is responsible for data analysis. WX is responsible for visualization. YW, YC, GG, BW, and YLai are responsible for data collection and literature retrieval. BS and YLi are responsible for supervision and writing—review and editing. All authors contributed to the article and approved the submitted version.

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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.

Publisher's note

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Medical use and costs for native fathers and children from transnational marriage families in Taiwan from 2004 to 2017

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Objectives: This is the first study to examine health care utilization in terms of medical use and costs in native fathers and children from transnational families.

Methods: Taiwan National Health Insurance Research Database was used to compare the annual medical use and inflation-adjusted medical cost for ambulatory care from 2004 to 2017 between native fathers and children from transnational and native families.

Results: Native fathers from transnational families had lower annual medical use (−0.23 visits) but higher total medical costs (New Taiwan dollars, NT$, 966), especially in dialysis and psychiatry, compared with those from native families. Unlike fathers from transnational families, their children were observed to consistently have lower medical use (−1.35 visits) and costs (NT$ −636), compared with those from native families.

Conclusions: There was different medical use and costs in transnational marriage families, possibly as a result of features in transnational marriage families. These findings provide insight for future health care policies to address the different health care utilization by exploring the unmet needs and barriers relating to children and fathers from transnational families.

KEYWORDS

medical cost, medical use, transnational marriage, immigrant family, minority, healthcare utilization

Highlights

- Although some studies reported a lower health care utilization rate in terms of medical expenditures or health care consumption for specific diseases in immigrants, none focused on fathers and children from immigrant marriage families.
- This is the first study to examine medical use and costs in fathers and children from transnational families, and it demonstrated different medical use and costs between native fathers and children from transnational families and native families.
- Further studies are warranted to exploring whether there are unmet needs or barriers relating to the different health care utilization in children and fathers from transnational families.

Introduction

Although the World Health Organization set up health equality as the primary target in 2000 (1), different health care utilization was observed in different socioeconomic and ethnic minorities, such as individuals with low socioeconomic status, ethnic minority status and immigrants (2–4). However, transnational marriage families, a special societal minority, has not received comprehensive population-wide analysis of medical use and costs so far. Transnational marriage brokerage (also called the mail-order bride phenomenon) is a commercialized marriage through international marriage brokering agencies; most often women from less developed countries marry men in more developed countries. Although this phenomenon occurs worldwide, it seems more common in East and Southeast Asia (5–7). In Taiwan, international marriages contributed to 15.3 to 23.8% of annual marriages from 2004 to 2017 (8), and newborns of international marriages accounted for 13.2 to 6.1% of all newborns in Taiwan from 2004 to 2018 (8). After the emergence of transnational marriages, several studies have examined the health equality for these East or Southeast Asian female marriage immigrants (9, 10); however, thus far, this attention has mainly been paid to female marriage immigrants, and their Taiwanese family members (husbands and children) have received much less attention. To the best of my knowledge, studies examining the profiles of native men with female marriage immigrants have been conducted using informant methods (i.e., information gathered by their female marriage immigrants, not self-report by their native-born husbands) (11–13), and no study has directly examined their health status and medical use and costs. There may be different health care utilization for these male spouses and children because men who cannot get married to local women need international marriage brokering agencies to get married instead, which may be the result of their socioeconomic vulnerabilities and interpersonal or health problems (5). Furthermore, owing to the lack of firm relationships in commercialized marriages and the differences in culture and language between couples in commercial marriage, fathers and children from such families may have more health problems than those from native families (13, 14).

Taiwan has a statutory health insurance system with obligatory national insurance, which makes it a privilege to explore medical use and costs in this special minority group. Taiwan launched a single-payer mandatory enrollment National Health Insurance Program in 1995, which is a single-payer system is publicly funded primarily through payroll-based premiums with copayment. The regular premiums are calculated based on the insured's salary, and are shared by the insured, the employer, and the government. Furthermore, the insurance premium and copayment will be subsidized or reduced for the disadvantaged groups (15). Taiwan's National Health Research Institutes established and continued to maintain the Taiwan National Health Insurance Research Database (TNHIRD) for public research purposes. The TNHIRD has almost full coverage (99.99%) of citizens and hospitals contracted in Taiwan, and the health care information in the TNHIRD includes primary care, hospital care, pharmaceutical care, home care, and dental care and linkable health-related databases, such as birth, death, and maternal and welfare datasets (16). The complete data on annual insured health care costs make it possible to identify medical use and costs across differing socioeconomic and ethnic minorities.

This study explored and compared the medical use and costs between native fathers and children from transnational families and fathers and children from native families. I did not compare marriage immigrant mothers and native mothers because marriage immigrant mothers did not have information on medical use and costs in the health insurance system before their international marriages. Furthermore, lower medical use is expected in immigrant mothers after they were enrolled in the National Health Insurance program because of the difficulties of access to health care services such as unfamiliarity, transportation and differences in language and culture (17).

Methods

Study sample

All datasets used in this study were from TNHIRD database. This study sample consisted entirely of liveborn children with complete information on the nationality of both parents from the Taiwan Birth Certificate Registration from 2004 to 2016 to ascertain native Taiwanese fathers from transnational families and native families. I restricted transnational marriage families to those in East or Southeast Asian countries, which were defined as China, Vietnam, Indonesia, Thailand, the Philippines, Malaysia, Myanmar and Cambodia. I did not include South Korea and Japan in East or Southeast Asian countries because the development index in these countries was close to or higher than that in Taiwan. Because the Taiwan Birth Certificate Registration dataset only contained the identity of mothers, a linkage to the Taiwan Maternal and Child Health Database with key variables of mother's id and the sex and birth year of was made to obtain complete identity on children and their fathers. The Taiwan Birth Certificate Registration database includes data on 99.78% of all births nationwide in Taiwan from 2004 to 2016 (18).

Covariates

In this study, I used age (by the end of the study) and low-income family status as controlling covariates. Low-income family status was determined using the Low-Income and

Middle-Low-Income Households dataset. Low-income family defined by the Taiwan government is that individuals whose family incomes evenly distributed to the number of family members is under the minimum living expense and household assets, which is adjusted once every 4 years based on the growth rate of consumer price index (19). In 2022, household assets is average movable property under 75,000 New Taiwan dollar (NT$) and an overall real estate value under 3.76 million NT$ for low-income family, and with average movable property under 112,500 NT$ and an overall real estate value under 5.64 million NT$ for middle-low-income family, respectively (20).

Medical use and cost

I used a national health facility database, the Taiwan National Health Insurance Research Database, to examine participants' medical use and cost. Medical use was measured by the frequency and cost of care associated with ambulatory visits (including treatment with Western medicine, emergency care, community care, and home care). Although the Taiwan's National Health Insurance has covered the traditional Chinese medicine, I focused only on Western Medicine instead of traditional Chinese Medicine because traditional Chinese Medicine was limited to a certain area. All medical costs, comprising consultation fees, diagnostic fee, laboratory examination fee, medicine service fee, and medicine fee, were recorded in points and under the global budget floating and average value system, in which 1 point equaled 0.8347 to 1.0573 NT$. Because of the global budget payment system, the medical payments is settled by the end of every season in different bureaus of National Health Insurance Administration, thus the costs varied in different seasons by year and geographic regions from 2004 to 2017. On December 1, 2021, the exchange rate of NT$ against the US and Euro dollar was approximately 28 to 1 and 32 to 1, respectively (21). To address economic inflation, I used the latest consumer price index released by Directorate-General of Budget, Accounting and Statistics, Executive Yuan, Taiwan, with the reference year of 2020 as 1 to obtain inflation-adjusted medical cost.

I used the individual's average annual medical use and cost, which was medical use, and costs were further adjusted by the individual's follow-up time. Fathers were followed from January 1, 2004, until death or the end of study (December 31, 2017), whereas children were followed from their birth date until death or the end of the study.

Statistical analysis

All statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA). I compared demographic and low-income status between native fathers and children from transnational families and fathers and children from native families by using chi-square tests for categorical variables and independent *t*-tests for continuous variables.

To estimate the difference in average annual medical use, average inflation-adjusted medical cost per visit, and average annual inflation-adjusted medical cost in total and in the top leading medical specialties between native fathers and children from transnational families and fathers and children from native families, Wilcoxon rank-sum test and general linear models (GLMs) were used. For Wilcoxon rank-sum test, the median of medical use indexes was compared without adjustment for any covariates. For the GLM, the mean difference of medical use indexes was compared with adjustment for demographic and low-income status, and adjusted regression coefficients and 95% confidence intervals (CIs) were reported. If the 95% CI of adjusted regression coefficients contains the null value of 0, no difference was observed between groups. Finally, I used treemaps and arrow diagrams to depict the proportions and ranking of average annual inflation-adjusted medical cost in different medical specialties between native fathers and children from transnational families and fathers and children from native families.

Results

Difference of medical use and costs

This sample included 1,300,684 fathers and 1,763,330 children, 6.9% of whom were fathers and 6.3% of whom were children whose spouses and mothers were from East or Southeast Asia. Table 1 presents the difference in sociodegraphics and medical use and costs between native fathers from transnational families and fathers from native families. Native fathers from transnational families were older and more likely to have low-income status than fathers from native families. Generally, the average annual ambulatory medical use was approximately six to seven visits. Although I first observed that native fathers from transnational families had higher medical use than fathers from native families, after controlling for their age and low income, the opposite finding was observed; native fathers from transnational families had −0.23 (95% CI: −0.33 to −0.14) lower average annual ambulatory medical use than fathers from native families. In terms of average annual inflation-adjusted medical cost, native fathers from transnational families were significantly associated with $966 (95% CI: $791 to $1141) higher ambulatory medical care costs in total than fathers from native families. Given fewer average annual outpatient visit and higher average annual inflation-adjusted medical cost in native fathers from transnational families, they had higher average medical cost per visit than fathers from native families. Specifically, such higher medical costs were observed in most common medical

TABLE 1 Demographics, medical use and costs between fathers from transnational and native families.

Variable	Fathers from native families $N = 1,211,001$		Native fathers from transnational families $N = 89,683$		Statistics	
Age (year), mean (SD)	40.42 (6.04)		45.75 (7.40)		$P < 0.001$	
Low–income, *n* (%)	43,538 (3.60)		8,906 (9.93)		$P < 0.001$	
Cumulative person–year, sum	16,912,801		1,242,825		–	
	Median (IQR)	**Mean (SD)**	**Median (IQR)**	**Mean (SD)**	**Unadjusted median difference[a]**	**Adjusted mean Difference[b] B (95% CI)**
No. of average annual outpatient visit	5 (3, 8)	6.63 (14.20)	5 (2, 9)	7.04 (7.09)	$P < 0.001$	−0.23 (−0.14, −0.33)
Total annual average medical care costs (NT$)	3065 (1537, 5304)	5028 (24473)	3155 (1513, 6954)	7166 (32459)	$P < 0.001$	966 (791, 1141)
Average cost per visit (NT$)	596 (463, 741)	759 (1135)	632 (485, 890)	1018 (1562)	$P < 0.001$	103.4 (94.6, 112.2)
Medical care in top 10 medical specialties (NT$)						
Family medicine	217 (78, 507)	461 (910)	228 (67,634)	643 (1448)	$P < 0.001$	100 (93, 106)
General medicine	168 (51, 431)	442 (7875)	158 (37, 497)	598 (7294)	$P < 0.001$	65 (11, 120)
Dialysis	0 (0, 0)	131 (6630)	0 (0, 0)	553 (14177)	$P < 0.001$	273 (221, 324)
Surgery	80 (0, 279)	251 (2036)	90 (0, 323)	327 (2805)	$P < 0.001$	61 (46, 76)
Orthopedics	86 (0, 272)	248 (522)	72 (0, 278)	279 (694)	$P < 0.001$	19 (16, 23)
Urology	0 (0, 67)	249 (1614)	0 (0, 92)	376 (2734)	$P < 0.001$	29 (17, 41)
Psychiatry	0 (0, 0)	115 (1139)	0 (0, 0)	375 (3213)	$P < 0.001$	213 (204, 223)
Emergency department	0 (134, 383)	321 (901)	125 (0, 437)	416 (1093)	$P < 0.001$	89 (83, 96)
Rehabilitation	0 (0, 0)	179 (983)	0 (0, 0)	241 (1985)	$P = 0.008$	2 (−4, 10)
Otorhinolaryngology	268 (83, 656)	522 (2857)	134 (28, 445)	407 (865)	$P < 0.001$	−150 (−131, −170)
Dermatology	87 (20, 263)	261 (1553)	43 (0, 173)	220 (1710)	$P < 0.001$	−41 (−30, −52)
Gastroenterology	12 (0, 183)	354 (1683)	0 (0, 185)	409 (2336)	$P < 0.001$	−60 (−48, −72)

[a]Aanaysis was conducted using Wilcoxon rank–sum test.
[b]Adjusted for age and low–come status.
SD, Standard deviation; IQR, Interquartile range.
Fathers from native families serve as the reference group.
New Taiwan dollars (NT$).
On December 1, 2021, the exchange rate of NT$ against the US and Euro dollar was approximately 28 to 1 and 32 to 1, respectively, based on the Bank of Taiwan (https://rate.bot.com.tw/xrt/all/2021-12-01?Lang=en-US).

specialties, including family medicine, general medicine, dialysis, surgery, orthopedics, urology, and psychiatry; however, lower medical costs were found in otorhinolaryngology, dermatology, and gastroenterology.

A similar analysis was conducted to determine the difference in medical use and costs between children from transnational families and children from native families (Table 2). Compared to children from native families, children from transnational families were more likely to be boys, older, and from low-income families. Generally, the average annual ambulatory medical use and the average annual inflation-adjusted medical cost were 20.84 visits and 12021 NT$ for children from native families and 16.98 visits and 9,842 NT$ for children from transnational families. Unlike their fathers, children from transnational families were consistently more likely to have lower medical use (adjusted regression coefficient: −3.16 and 95% CI: −2.04 to −4.28) and medical costs in total (adjusted regression coefficient: −2166 NT$ and 95% CI:−1714 to −2618) and in most medical specialties, except for family medicine, but no difference was observed in average medical cost per visit.

Proportion and ranking of medical costs in different medical specialties

The proportion of the average annual inflation-adjusted medical cost in different medical specialties with regard to the total medical cost between groups is summarized in Figure 1. Generally, the top leading medical cost of specialties was for general medicine, gastroenterology, emergency care,

TABLE 2 Demographics, medical use and costs between children from transnational and native families.

Variable	Children from native families $N = 1,652,141$		Children from transnational families $N = 111,189$		Statistics	
Age (year), mean (SD)	6.33 (3.50)		6.66 (3.52)		$P < 0.001$	
Sex (boy), *n* %	854,713 (51.73)		57,868 (52.04)		$P < 0.001$	
Low–income, *n* (%)	62,993 (3.81)		11,045 (9.93)		$P < 0.001$	
Cumulative person–year, sum	10,446,715		739,436		–	
	Median (IQR)	**Mean (SD)**	**Median (IQR)**	**Mean (SD)**	**Unadjusted median difference[a]**	**Adjusted mean Difference[b] B (95% CI)**
No. of average annual outpatient visit	18 (12, 22)	20.84 (43.13)	16 (9, 20)	16.98 (18.32)	$P < 0.001$	−3.16 (−2.04, −4.28)
Total annual average medical care costs (NT$)	8729 (5712,11023)	12021 (73236)	6950 (4568, 8936)	9842 (45326)	$P < 0.001$	−2166 (−1714, −2618)
Average cost per visit (NT$)	474 (426, 543)	537 (731)	483 (427, 543)	540 (1201)	$P = 0.102$	−0.58 (−4.26, 3.1)
Medical care in top 10 medical specialties (NT$)						
Family medicine	307 (35, 1173)	1614 (20004)	365 (58, 1271)	1741 (23948)	$P < 0.001$	24 (18, 30)
General medicine	0 (0, 162)	199 (11558)	0 (0, 192)	294 (24393)	$P = 0.031$	60 (−15, 135)
Surgery	0 (0, 24)	68 (434)	0 (0, 35)	76 (429)	$P = 0.062$	−2 (−5, 1)
Pediatrics	4211 (2164, 7239)	3016 (28194)	2789 (1149, 5433)	2496 (27316)	$P < 0.001$	−673 (−500, −846,)
Otorhinolaryngology	579 (84, 1978)	916 (6233)	360 (0, 1448)	763 (1323)	$P < 0.001$	−221 (−184, −258)
Ophthalmology	155 (0, 396)	219 (521)	94 (0, 284)	176 (355)	$P < 0.001$	−60 (−57, −63)
Dermatology	61 (0, 229)	110 (411)	0 (0, 142)	81 (203)	$P < 0.001$	−36 (−35, −37)
Psychiatry	0 (0, 0)	58 (552)	0 (0, 0)	55 (541)	$P < 0.001$	−10 (−7, −13)
Rehabilitation	0 (0, 0)	706 (5417)	0 (0, 0)	713 (5417)	$P < 0.001$	−75 (−43, −107)
Emergency Department	343 (0, 1029)	411 (814)	282 (0, 975)	442 (810)	$P = 0.044$	−2 (−6, 2)
Pediatric Surgery	307 (35, 1173)	68 (628)	0 (0, 0)	57 (415)	$P < 0.001$	−13 (−8, −18)

[a]Aanaysis was conducted using Wilcoxon rank–sum test.
[b]Adjusted for sex. age and low–come status.
SD, Standard deviation; IQR, Interquartile range.
Children from native families serve as the reference group.
New Taiwan dollars (NT$).
On December 1, 2021, the exchange rate of NT$ against the US and Euro dollar was approximately 28 to 1 and 32 to 1, respectively, based on the Bank of Taiwan (https://rate.bot.com.tw/xrt/all/2021-12-01?Lang=en-US).

otorhinolaryngology, dermatology, surgery and orthopedics for these fathers. However, specifically compared to fathers from native families, native fathers from transnational families reported higher proportions of medical use in dialysis (7.45 vs. 2.58%) and psychiatry (5.27% vs. 2.30%) but lower proportions in otorhinolaryngology (5.78 vs. 10.41%) and dermatology (3.14 vs. 5.24%). In contrast, unlike their fathers, the proportion and ranking of medical cost in different medical specialties was similar between children from transnational families and children from native families. The leading medical specialties were pediatrics, otorhinolaryngology, rehabilitation, family medicine, emergency care, ophthalmology, and general medicine. These patterns were also reflected in the ranking of medical cost in different top leading medical specialties in Figure 2.

Discussion

This study demonstrated clear different patterns of health care utilization and different health conditions between native fathers and children from transnational families and fathers and children from native families with full-population data from Taiwan. Different patterns of medical use and costs were observed between fathers and children from transnational families. Specifically, native fathers from transnational families were associated with overall lower medical use but higher medical costs, especially for medical specialties of dialysis and psychiatry, while their children were associated with overall lower medical use and costs. To the best of my knowledge, this is the first study to examine medical use and costs in fathers and children from transnational families.

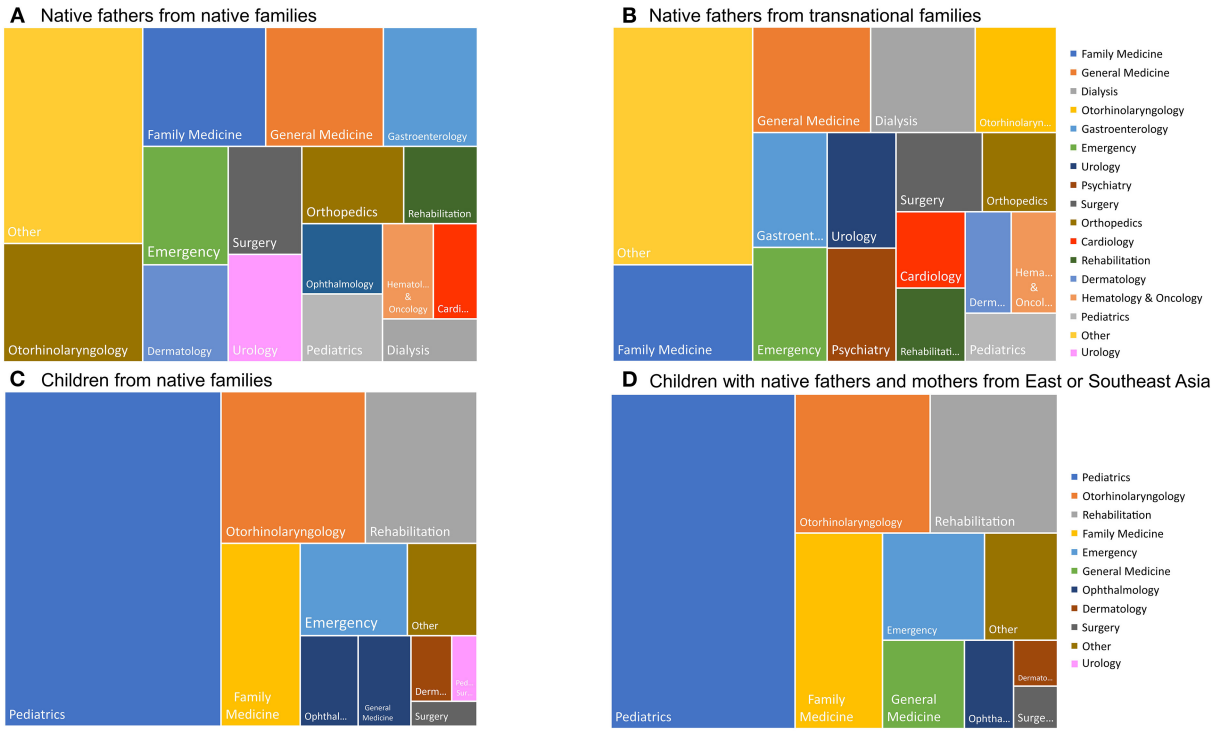

FIGURE 1
The proportion of total inflation-adjusted medical cost in 2004 to 2017 for top leading medical specialties for fathers from native families **(A)**, native fathers from transnational families **(B)**, children from native families **(C)**, and children from transnational families **(D)**. Medical specialties were included if their explained proportions of the total cost reached at least 2.5%.

These results provided essential information regarding the medical use and costs in this special subpopulation and public policy implications.

Compared with fathers from native families, lower medical use but higher medical costs and different relative rankings of medical specialties in native fathers from transnational families suggested different patterns of health care utilization and different health conditions between them. Two possible explanations for the inconsistent health utilization (i.e., lower medical use but high medical costs) of native fathers from transnational families. First, it may be the combination of more difficulties in accessing healthcare in native fathers from transnational families and the payment system in the Taiwan National Health Insurance. Although there is high accessibility of healthcare in Taiwan with short waiting times for medical care; individuals can normally reach for consultations on the day that they make an appointment (22), native fathers from transnational families might still have relatively high difficulties in accessing healthcare because they have been reported being more likely to live in rural areas (23) with less medical resources, resulting in lower medical use. This has been supported by a study that the probability of health care utilization were 0.48 to 0.78 times for Taiwanese who resided in rural areas than for those living in areas with the highest urbanization level (24). Furthermore, the Diagnosis-Related Group payments system in Taiwan under the Taiwan National Health Insurance has given additional bonus payments to healthcare providers in rural areas in order to eliminate the rural-urban gap in healthcare infrastructure. Under these circumstances, individuals with similar or lower health care utilization may had higher medical cost.

Second, the other explanation for the inconsistent health utilization is that native fathers from transnational families had more severe disease conditions that required more medical resources in their physician office visits. In addition, higher medical costs for native fathers from transnational families indicated overall poorer health, which is similar to that observed in low socioeconomic status (25) and ethnic minority (26). I observed that different medical uses and costs was related to specific medical specialties, especially chronic health conditions (i.e., dialysis) and mental health, which are consistent with the limited current literature (10–12). Based on female marriage immigrants' reports on their Taiwanese male spouses, the prevalence of disability of their Taiwanese male spouses was 5.6% (11) to 7.7% (12, 14), all of which was higher than the national statistics of 4.5% in Taiwan (27). Because of disability and care needs among native fathers from transnational families,

A **Fathers**

Native fathers from native families

Leading specialty	Percentage of medical cost
1. Otorhinolaryngology	10.41
2. Family Medicine	9.22
3. General Medicine	8.84
4. Gastrogenterology	7.06
5. Emergency	6.38
6. Dermatology	5.24
7. Surgery	5.01
8. Urology	4.99
9. Orthopedics	4.96
10. Rehabilitation	3.59
16. Dialysis	2.58
17. Psychiatry	2.30

Native fathers from transnatioanl families

Leading specialty	Percentage of medical cost
1. Family Medicine	9.13
2. General Medicine	8.38
3. Dialysis	7.45
4. Otorhinolaryngology	5.78
5. Gastrogenterology	5.75
6. Emergency	5.72
7. Urology	5.36
8. Psychiatry	5.27
9. Surgery	4.61
10. Orthopedics	3.96
12. Rehabilitation	3.43
13. Dermatology	3.14

B **Children**

Children from native families

Leading specialty	Percentage of medical cost
1. Pediatrics	45.81
2. Otorhinolaryngology	13.84
3. Rehabilitation	10.73
4. Family Medicine	9.15
5. Emergency	6.23
6. Ophthalmology	3.32
7. General Medicine	3.02
8. Dermatology	1.69
9. Pediatric Surgery	1.06
10. Surgery	1.04

Children from transnatioanl families

Leading specialty	Percentage of medical cost
1. Pediatrics	41.25
2. Otorhinolaryngology	12.56
3. Rehabilitation	11.84
4. Family Medicine	11.45
5. Emergency	7.32
6. General Medicine	4.86
7. Ophthalmology	2.91
8. Dermatology	1.35
9. Surgery	1.25
10. Pediatric Surgery	0.97

FIGURE 2
Ten leading medical specialties by total inflation-adjusted medical cost from 2004 to 2017 and percentage difference for fathers from native families and native fathers from transnational families **(A)** and children from native families and children from transnational families **(B)**.

it has been reported that the transnational marriage with female marriage immigrants is a health care workforce strategy of the male spouse's family members, including male spouses and their parent (28); these female marriage immigrants have to take care of the family members' needs, which has been observed in South Korea (29).

Psychiatry is another medical specialty with a relatively higher ranking in native fathers from transnational families than in those from native families, indicating a higher prevalence of mental disorders and more needs for health care in native fathers from transnational families.

Interestingly, I observed that three medical specialties, otorhinolaryngology, dermatology and gastroenterology, were associated with lower medical use and costs in native fathers from transnational families than fathers from native families. There were two possible explanations. First, it may be a reflection of their attitudes toward the medical illness of otorhinolaryngology, dermatology and gastrointestinal problems as minor ailments. They may not be concerned about these minor ailments, resulting in fewer medical help-seeking behaviors. In contrast, they may be more concerned with major medical illnesses from other common medical specialties, such as family medicine, general medicine, and surgery, which have a large portion of health care expenditure. This is partially supported by a study reporting that Taiwanese husbands of female marriage immigrants had poorer health attitudes and health-promoting lifestyles and behaviors (10). Second, the medical costs might have switched from otorhinolaryngology, dermatology and gastroenterology to family medicine and general medicine. In Taiwan, there is

no gatekeeper system in primary care, and people who want to seek formal medical care can normally see a specialist on the day that they make an appointment (22). People who have sufficient medical knowledge of their medical conditions can efficiently seek a medical specialist to solve their illness without extra referrals. However, it has been reported that Taiwanese husbands with transnational marriages were more likely to be less educated (11, 30, 31) and have inadequate health literacy (10). As a result, when they had medical illnesses of otorhinolaryngology, dermatology and gastrointestinal problems, they may see family physicians or general physicians instead of otorhinolaryngologists, dermatologists, or gastroenterologists.

Unlike fathers from transnational families, children from transnational families were observed to have lower medical use and costs, with a similar pattern of ranking in leading medical specialties compared with children from native families. A possible explanation is that there may be barriers and unmet needs for receiving medical care in children from transnational families. Because children usually have access to health care services accompanied by their primary caregivers rather than by themselves alone, such barriers may come from the difficulties in accessing health care services among children's primary caregivers. Compared to natives, immigrants had more difficulties accessing health care services, such as unfamiliarity, transportation and differences in language and culture (17), resulting in a lower health care utilization rate (32–35). These results are not only compatible with the current literature but also indicate the possible barriers of access to health care services for children from immigrant families. Another possible explanation is that parents from transnational families might have more conservative attitude of health care utilization; they may only take their children for healthcare visits under serious health conditions. This is partially supported by the data of Organization for Economic Cooperation and Development and World Health Organization, that the number of healthcare visits was lower in the East or Southeast Asian countries of transnational families than that in Taiwan (36). Finally, it is a priority to address the different medical use and costs in transnational marriage families, which can be accomplished by exploring possible barriers to access health care utilization and increasing health literacy to reduce these barriers.

Limitations

There were some limitations in this study. First, there was a diversity of transnational marriages in Taiwan; although a large proportion of transnational marriages were based on marriage brokerage, some of them were love marriages. It has been suggested that marriages based on a strong bond between couples have positive impacts on physical and mental health (37). However, I identified transnational marriage families based on nationality information from a national birth registered dataset, which is not able to distinguish the different bases of transnational marriages. Some important demographic characteristics (such as type of living, education and other social determinants) which may explain or confound the study findings was not included in the Taiwan National Health Insurance Research Database. In addition, some medical costs cannot be captured in the Taiwan National Health Insurance Research Database. For example, transportation costs and medical unnecessary health care intervention (e.g., cosmetic surgery) are not covered by the Taiwan National Health Insurance (38). Finally, the generalizability of these medical uses and costs to age ranges and other countries is limited. In terms of age ranges, because I used the national birth registered datasets, which were established from 2004 to 2016 and followed to 2017, the age of children enrolled in this study was not $>$ 13 years old, medical use and costs may not cover the common diseases in late adolescence. Similarly, for fathers, age ranges at childbirth are usually between 20 and 40. Because this study only has a 13-year follow-up period, the majority of the fathers would not be older than 55 years, and medical use and costs may not cover the common diseases in late adulthood. In addition, because Taiwan implemented a national health insurance system, individuals' medical use may differ from that in countries where private health insurance is prevalent, such as the United States.

Conclusions

The first national cohort study is conducted to understand medical use and costs for native fathers and children from transnational families in Taiwan. Native fathers from transnational families were associated with overall lower medical use but higher medical costs, especially for medical specialties of dialysis and psychiatry, while their children were associated with overall lower medical use and costs. These results indicate that different medical use and costs in immigrant families and provide insight to address different health care utilization by exploring the barriers and unmet needs relating to health care utilization in children and fathers from transnational families.

Data availability statement

The datasets presented in this article are not readily available because the data that support the findings of this study are available from Ministry of Health and Welfare, Taiwan, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of

Ministry of Health and Welfare, Taiwan. Requests to access the datasets should be directed to Ministry of Health and Welfare, Taiwan.

Ethics statement

The studies involving human participants were reviewed and approved by China Medical University Hospital. 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

The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

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Conflict of interest

The author declares 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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Organizational commitment of health professionals and associated factors in primary healthcare facilities of Addis Ababa, Ethiopia: A multi-center cross-sectional study

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Background: Organizational commitment has a positive impact on an organization's ability to provide professional services. Committed human power pushes an organization to achieve its goals, but non-commitment can lead to increased medical errors, prolonged inpatient admissions, and repeated hospitalizations leading to low quality of healthcare provision. However, to the best knowledge of researchers, there are no studies examining organizational commitment in the healthcare setting of Addis Ababa, Ethiopia.

Objective: The aim of this study was to assess the level of organizational commitment and associated factors among health professionals working in the primary health facility of Addis Ababa, Ethiopia.

Methods: A facility-based cross-sectional study was conducted among 459 healthcare professionals selected by simple random sampling from 12 health centers. Data were collected by three data collectors and one supervisor using a pretested questionnaire. Data were checked for completeness, cleaned, and entered into Epi-Data version 3.1.and exported into SPSS version 25 for analysis. In binary logistic regression statistical analysis, variables with $p < 0.2$ were entered in multivariate binary logistic regression analyses; then, the regression result was presented using COR, AOR with 95% CI, and a p-value <0.05 as a level of significance.

Result: The respondent's percent mean score of organizational commitment was 48.4%. Age group above 30 years (AOR = 1.52, 95% CI, 1.01, 2.30), those who were satisfied with their job (AOR 2.02, 95% CI 1.30, 3.13), and those who perceive good transformational leadership behavior (AOR: 1.85, 95% C.I, 1.18, 2.90) were significant factors of organizational commitment among health professionals.

Conclusion and recommendation: Organizational commitment was lower in magnitude in the study setting. Age, job satisfaction, and transformational leadership behavior were significant predictors of organizational commitment.

KEYWORDS

organizational commitment, work commitment, health professionals, primary health facilities, Addis Ababa

Background

In the 21st century, human resources and their performance are rendered as one of the most important factors for organizational success in achieving a set of organizational goals (1). Sustaining and improving the organization's ability to use human capital effectively and efficiently is a major challenge (2). Employee organizational commitment is one of the many obstacles that today's organizations face in terms of human resources (3). An accountable organization will also strive to have a positive work environment and ensure that the organizational framework and structure provide resources for employees' organizational commitment (4). The three dimensions that continue to limit the success of the development of universal health coverage by 2030 are availability, distribution, and performance of health workers (5). Ethiopia is one of the countries with a minimal health workforce with a density of 0.96 per 1,000 population. This is far below the African density of health workers (2.2/1,000 population and five times less than the minimum threshold of 4.45 per 1,000 population set by the World Health Organization (WHO) to meet the Sustainable Development Goal (SDG) health targets) (6). It is difficult to have an efficient and effective health system without a sufficient number of skilled, motivated, and supported health professionals. The involvement of highly skilled and committed health workforce is a critical component of the health system's performance (7).

The level of health professionals' organizational commitment was variable around the world. Studies from Urmia, Iran, Saudi Arabia, and the Philippines showed 67.3, 52.1, 3.13, and 63.9% of organizational commitment, respectively (8–11). Organizational commitment and job satisfaction in Zimbabwe, South Africa, and Namibia indicated that the mean score of organizational commitment was 4.76, 2.83, and 3.93, respectively (12). In Ethiopia, organizational commitment level varies from 32.9 to 74.6% (13–15).

Organizational commitment has both positive and negative consequences for organizations, especially in the case of the health sector. Health professionals with high commitment have characteristics of a strong desire to strive for achieving organizational goals, better job satisfaction, desire to stay in the organization, low absenteeism, low turnover intention, good mental spirit, increased effort and motivation, and retention in the organization by their sense of belongingness, affiliation, and attachment to organizations that leads to better organizational performance, their better manifestation of personal and organizational goals (16).

Contrary to the above points, employees with low organizational commitment have characteristics of low productivity and individual performance, feeling of discrimination in the workplace, ignorant of the needs of others, low participation in organizational matters, high absenteeism rate, low punctuality to the workplace, reduced interest to stay in the organization, high turnover, burnout, lack of trust, and motivation leading to work termination (17). Hence, all these preclude the organization from achieving its goals. In a healthcare setting, these lead to increased medical errors and increased and/or repeated hospitalizations. It also results in reduced patient satisfaction toward health services provided and elevated medical costs, cumulatively leading to interruptions of normal function. These ultimately result in a loss of organizational effectiveness and efficiency. In an organization where all these are common healthcare problems, it, finally, leads to low quality of healthcare (17–20).

In Ethiopia, to the extent of knowledge of the researcher so far, four published research works were found on the organizational commitment of health professionals. These were a study done in a Gurage zone (14), Bench Sheko zone (21), Jimma zone (15), and Jimma university teaching and specialized hospital (JUSTH) (13). Even though these studies showed important findings, they had certain limitations. The studies in Jimma and JUSTH focused on one profession: health professionals providing institutional delivery services and nurses, respectively. On the contrary, the study done in the Gurage zone had not assessed the effect of perceived leadership style on the organizational commitment of health professionals. A study done in the Bench Sheko zone included the effect of employee empowerment on the organizational commitment of health professionals, but all of them were not included the relationship between turnover intention and organizational commitment. It is also glanced that all the above four studies were conducted in the countryside and no

Abbreviations: AOR, adjusted odds ratio; CDC, communicable disease control; EPI INFO, epidemiology information; HAI, healthcare-associated infection; IP, infection prevention; PPE, personal protective equipment; SPSS, software package of social science; SSI, surgical site infection; USA, United States of America; WHO, World Health Organization.

sufficient studies are found in Addis Ababa, the capital city of Ethiopia.

Generally, even though a few studies are available in Ethiopia, majority are focusing on a single profession like the nurse profession or only localized to a single sphere, and still, there is a gap in showing organizational commitment and its predicting factors among healthcare professionals that are working in the primary healthcare setting, especially in the current study area. Furthermore, in the presence of a high prevalence of medical error (57.6%), high admission rate (74.7%), high turnover intention (77.5%), and so many problems that affect the quality of healthcare in Addis Ababa, still, no study shows the level of organizational commitment in this area (22–24). Therefore, the current study aimed to assess the level and factors affecting organizational commitment among health professionals working at primary health facilities in Addis Ababa, Ethiopia. The finding of this study will serve as an input in the development of successful change in management policies to improve job performance. It will also help as input for health policymakers to plan staff development activities, such as training, and decide remuneration scales to increase the level of commitment among health professionals.

Methods

Study design, setting, and period

An institution-based cross-sectional study was conducted among health facilities in Addis Ababa, Ethiopia. The proposed study was confined to Addis Ababa, the capital city of Ethiopia. There were eleven sub-cities of Addis Ababa city administration with a total population of 5,006,000. The study was conducted in primary public healthcare facilities of the Addis Ababa city administration. The city covers an estimated area of 527 Km^2 with an estimated density of 5,165.1 people per square kilometer. The city has 11 sub-cities and 120 woredas. There are seven hospitals owned by the Addis Ababa health bureau, five hospitals owned by the Federal Ministry of Health, one hospital by Addis Ababa University, three hospitals by non-governmental organizations, three hospitals by the defense force, and 34 hospitals by private owners. There were 100 functional public health centers. There were a total of 7,486 health professionals working in primary public health facilities (25). This study tried to include professionals working in a health center. The study was conducted from 31 March to 15 April 2021.

Population and eligibility criteria

The source populations were all health professionals working at primary public healthcare facilities (health centers) in Addis Ababa. Study populations were all sampled health professionals in a selected primary health facility that fulfilled inclusion criteria. The study unit was of randomly selected health professionals working at a randomly selected health center. Health professionals who were contract staff and those who were not available during data collection time due to annual leave, maternal leave, and sick leave were not involved in the study.

Sample size determination, sampling technique, and sampling procedure

The sample size was determined using the single population proportion formula by considering the study done in Bench Sheko zone, SNNP region of Ethiopia using the following parameters; organizational commitment as 74.6% (21), 95% C.I, 5% margin of error, 5% non-response rate, and 1.5 design effect since the sampling technique was multistage. Based on all the assumptions, the final sample size was 459.

Sampling procedure

A multistage sampling technique was used to select 459 study participants as follows. Out of eleven sub-city found in Addis Ababa city, 30% (4) sub-cities namely Gullele, Addis Ketema, Kolfe, and Kirkos sub-cities were selected by lottery method. Again, from each selected sub-cities, 30% of health centers were selected using a simple random sampling method. Proportional allocation of sample size was used for each randomly selected health center to select a sufficient amount of study subjects considering the total number of clinical staff in each health facility. Finally, the study subjects were selected by lottery method.

Data collection tools and procedures

Data were collected using self-administered, structured, and pretested questionnaires. Validated tools were adapted from previously published pieces of literature (13–15, 21) which were checked for internal consistency of each question for a composite variable after the pretest. The questionnaire was divided into seven parts. Each part focus on socio-demographic variables, organizational commitment questions, job satisfaction, perceived organizational support questions, transformational leadership behaviors, perceived psychological empowerment, and turnover intention. Organizational commitment scale, perceived organizational support, transformational leadership behavior, and perceived psychological empowerment scale were addressed on a five-point Likert scale with response options ranging from 1 (very Disagree) to 5 (very Agree). A tool related to the job

satisfaction scale was also addressed by a five-point Likert scale ranging from 1 (very dissatisfied) to 5 (very satisfied), while the turnover intention was addressed by agree (yes) and disagree (no) questions. The mean score for the level of organizational commitment was reported as the percentage of the score for a mean (%SM) after the calculation of the standardized mean value. It was calculated using the formula %SM = (Actual score –Potential minimum score/Potential maximum–Minimum)*100 (14).

Variables and measurements

The dependent variable was an organizational commitment with a score ranging from 24 to 120. The mean overall organizational commitment scores were classified as low if it was below the means score and high if it was above the mean score. Job satisfaction score ranges from a minimum of 31 to a maximum of 155. It has sub-component scales like autonomy, professional opportunities, scheduling, pay and benefit, relation, and interaction. The higher the sum of the scores shows the higher (above the means core) and more satisfied with their job (15). Transformational leadership behavior measures individuals' opinions about how their immediate leaders were motivating and inspiring to them and how they were involved in setting good relationships. The score ranges from a minimum of 16–80. The higher the sum of the scores shows the higher (above the means core) the more good transformational leadership behavior. Perceived organizational support denotes the extent to which employees see that organizations recognize their contribution and care about their wellbeing. The score ranges from a minimum of 8–40. The higher the sum of the scores shows the higher (above the means core) had more good perceived organizational support. Perceived psychological empowerment denotes the extent to which organizations give authority and freedom to their employees to do formal tasks. The score ranges from a minimum of 6–30. The higher the sum of the scores shows the higher (above the means core) had more good perceived psychological empowerment. Turnover intention is an intention when a health professional in a healthcare facility is actively searching for a job during the data collection time or who is seriously thought about looking for a job in the last few months or who intends to leave the organization soon.

Data quality assurance

The quality of data was maintained through different mechanisms. Tools were adapted from previously published and validated works. Two days of training were given to Diploma/BSc nurses on the overall purpose and procedure of the study.

A pretest was done on 5% ($n = 23$) of the sample of health professionals working in Saris and Abinet Health centers (HC that were not considered for the actual data collection process). The supervisor was checking the completeness, consistency, and appropriateness of the collected data daily. The questionnaire was adjusted accordingly, and data were cleaned before entering into Epi-data software version 3.1 (The EpiData Association Odense, Denmark). Variable coding, cleaning, and recording were made through SPSS software (IBM Corporation, 2015).

Data management and analysis

The data were coded and entered, and double-verified using EPI-DATA 3.1 software. Then, entered data were exported to SPSS version 25 for analysis. Descriptive statistics were used to summarize the data, and the results were presented using frequency tables, percentages, and graphs. Factors associated with the dependent variable were assessed using binary logistic regression. During bivariate analysis, variables with a p-value ≤ 0.25 were considered a candidate for multivariate logistic regression. Adjusted odds ratio (AOR) with 95% CI and P-value ≤ 0.05 were used to declare the presence of an association between explanatory variables and the level of organizational commitment of respondents. The Hosmer-Lemeshow goodness-of-fit test was applied to check model fitness.

Operational definition

Organizational commitment: The score ranges from 24 to 120. The mean overall organizational commitment scores were classified as low if it is below the means score and high if above the mean score.

Job satisfaction means a positive or pleasurable emotional state resulting from the appraisal of one's job or job experience. It has subscales like autonomy, professional opportunities, scheduling, pay, and benefits. The score ranges from 31 to 155. The higher the sum of the scores shows the higher (above the means core) and more satisfied with their job (15, 21). Internal consistency of the variables was checked after pretest giving Cronbach's alpha (α) of 0.85.

Transformational leadership behavior measures individuals' opinions about how their immediate leaders were motivating and inspiring them and how they were involved in setting good relationships. The score ranges from 16 to 80. The higher the sum of the scores shows the higher (above the means core) better transformational leadership behavior having internal consistencies of 0.82.

Perceived organizational support indicates the extent to which employees see that organizations recognize their contribution and care about their wellbeing. The score ranges from 8 to 40. The higher the sum of the scores shows the higher (above the means core) had more good perceived organizational support having internal consistency of 0.87.

Perceived psychological empowerment indicates the extent to which organizations give authority and freedom to their employees to do formal tasks. The score ranges from 6 to 30. The higher the sum of the scores shows the higher (above the means core) had better perceived psychological empowerment (13, 21) having internal consistency of 0.79.

Ethical consideration

Ethics approval was secured from Addis Ababa public health Research and Emergency management directorate with a reference number ኦ/ኦ/ጦ/10507/227; then, a support letter was submitted to the selected sub-city Administration office and respective selected health center. The data were collected after the purpose or objective of the study was explained to each participant, and written informed consent was obtained by keeping COVID-19 mitigation protocols. Any personal identifying variables of each participant were kept confidential. To assure confidentiality, coding number was assigned to the study participants without mentioning their names.

Result

Socio-demographic characteristics of the participants

Among 459 questionnaires distributed, 453 were collected from the respondents (two questionnaires were unfilled, three questionnaires were not returned, and one questionnaire was incomplete) giving the response rate of the study to be 98.7%.

The participant's ages ranged from 21 to 58 years with a mean (±SD) score of 29.16 (±4.75) years, 60.9% were women, and more than half (57%) were married. Regarding their profession, 45.5% of them were nurses and 64.5% of participants were Bachelor's degree (BSc) holders. They had work experience ranging from 1 to 33 years with a mean (±SD) of 5.32 ± 3.55years. Their monthly salary ranges from 3,333 to 11,330 EBR with a mean of 6,711.34 (±1,692.36) EBR (Table 1).

TABLE 1 Socio-demographic characteristics of health professionals working in primary health facilities of Addis Ababa, Ethiopia, 2021.

Variables	Categories	Frequency	Percentage
Sex	Male	177	39.1
	Female	276	60.9
Marital status	Never married	195	43
	Married	258	57
Age	20–29	283	62.5
	≥30	170	37.5
Level of education	Diploma	141	31.1
	Bachelor degree	292	64.5
	Master's degree and above	20	4.4
Profession	Nurse	206	45.5
	Health officer	102	22.5
	Pharmacist	48	10.6
	Midwife	50	11
	Laboratory technician	28	6.2
	Others**	19	4.2
Work experience(years)	0–2	84	18.5
	3–5	182	40.2
	6–8	120	26.5
	≥9	67	14
Number of children	0	302	66.6
	≥1	151	33.4

Others**: medical doctors (GP), environmental health, and health extension.

TABLE 2 Job satisfaction items with respective mean and percentage scores of health professionals working in public primary health facilities of Addis Ababa, Ethiopia, 2021.

Job satisfaction factors	Mean row score and SD	%SM
Autonomy	13.28 ± 3.43	58.0
Professional opportunity	12.49 ± 3.89	53.1
Scheduling	16.97 ± 4.22	59.9
Support	22.04 ± 6.50	53.7
Pay and benefit	18.34 ± 7.10	40.5
Relationship and interaction	14.41 ± 3.76	65.0

Level of organizational commitment

Organizational commitment percentage means the score of health professionals who participated in this study was 48.4%. On the contrary, the mean (±SD) raw score of this scale was 70.47 ± 13.77 ranging from 26 to 118. From the given organizational commitment items, 237 (52.3%) of the respondents scored a low level of organizational commitment and 216 (47.7%) of the health professionals scored a high level of organizational commitment.

Level of job satisfaction

For the job satisfaction part, the total mean score was 53.7%. From the given job satisfaction items, 51.7% of the respondents were dissatisfied and 48.3% of the health professionals were satisfied with individual components of satisfaction percentage means to score and raw mean score are shown in Table 2 below.

Level of transformational leadership behavior

The overall level of transformational leadership behavior (percentage means score) of health professionals who participated in this study was 53.1% (SM %) with a mean (±SD) raw score of 49.95 ± 13.15. From the given transformational items, 45% of the respondents had a poor perception of transformational leadership behavior while 55% of the health professionals had a good perception of transformational leadership.

Level of perceived organizational support

The perceived organizational support percentage mean score was 52.6%, and the total mean (±SD) raw score was 24.82 ± 6.48. Almost half of the respondents (50.3%) had a good perception of organizational support, whereas 49.7% had a poor perception of organizational support.

Level of psychological empowerment and turnover intention

Regarding perceived psychological empowerment, the total mean score was 65.4% with a total mean (±SD) raw score of 21.69 ± 5.20, while turnover intention total mean score was 66.5%. Of the total participant, 69.3% had an intention to leave their current organization.

Predictors of organizational commitment

In a binary logistics regression model, age above 30, type of profession, number of children, job satisfaction, transformational leadership style, perceived organizational support, and turnover intention were assessed and became a candidate for multivariable logistic regression at p-value < 0.25.

Independent predictors of organizational commitment

Those variables, which showed significant association with an organizational commitment of health professionals in bivariate binary logistic regression, were entered into the multivariable logistic regression and checked for multi-collinearity (by VIF and tolerance), normality (by histogram), and to what extent the model is good fitted (Hosmer-Lemeshow goodness of fit) and for those factors with $p \leq 0.05$ considered as statistically significant as shown in Table 3 below.

Age (above 30) AOR (1.521, 95% C.I 1.008–2.295, p-value = 0.047), job satisfaction AOR 2.015 (95% C.I: 1.299–3.125, P-value = 0.002), and transformational leadership AOR (1.845, 1.175, 2.897) were statistically significant associated factors for good organizational commitment.

Discussion

The major goal of healthcare organizations is to improve healthcare quality. To improve healthcare quality, it is highly detrimental to identify the level of organizational commitment, as well as contributing factors. As a result, this study was conducted to assess the level of organizational commitment and associated factors of health professionals working in a primary public healthcare facility in Addis Ababa, Ethiopia.

According to the current study, health professionals' organizational commitment was 48.4% (%SM). Overall, low commitment among healthcare professionals in Addis Ababa is a cause for concern, given that organizational commitment has implications for the efficiency, effectiveness, and sustainability of the health system.

The percentage mean score (%SM) of the current study was 48.4% which is in line with the study conducted in Saudi Arabia (47.88%) (8), but higher than a study done in Lahore (2.25) (26), Zimbabwe (2.83) (12), and Jima University Specialized Teaching Hospital where the raw means core was 70.45 ± 8.22 with only 72 (32.9%) of the nurses score high level of organizational commitment (13). In the case of Lahore (Turkey), the discrepancy might be due to their inclusion criteria difference (being large and research hospitals) and also they had used convenience sampling methods. In such large research hospitals, the workload might be high. Regarding the study done in Zimbabwe, the majority of employees were not permanent employees and were not unionized (27). As a result, they might deny telling real commitment level. The discrepancy observed from JUSTH was more likely explained by methodological differences employed in the sample size (n = 242), and the study participants were only nurses. In addition, the discrepancy might be attributed to the difference in study setting in that study that was conducted in a referral hospital tied to high workload which can greatly affect employee's commitment to the organization's interest.

Organizational commitment of the current study was lower than studies conducted in Iran (72.80 ± 4.95) (11), Portugal (3.97) (28), Gurage (64.81%) (14), Jimma (72.71%) (15), and Bench Sheko zone (74.6%) (21). The discrepancy might be justified by the fact that the study conducted in Iran used a small sample size, it focused only on emergency medical technicians, and the tool used to assess satisfaction was different from the one used in the current study. The

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TABLE 3 Predictors of organizational commitment with respective *p*-value, AOR, and confidence interval in multivariable regression of health professionals working in primary health facilities of Addis Ababa, Ethiopia, 2021.

Variable	Categories	Organizational commitment		COR (95% C.I)	AOR	95% CI	P-V
		Not committed	Committed				
Age	20–29 (Ref)	159	124				
	≥30	78	92	1.5 (1.03, 2.22)	1.52	(1.01,2.30)	0.047*
Profession	Nurse (Ref)	111	95				
	Health officers	47	55	1.37 (0.85–2.20)	1.35	(0.81, 2.25)	0.251
	Pharmacist	20	28	1.66 (0.87–3.09)	1.73	(0.88, 3.41)	0.113
	Midwife	34	16	0.55 (0.29–1.06)	0.62	(0.31, 1.23)	0.171
	Laboratory technician	14	14	1.17 (0.53–2.57)	1.08	(0.47, 2.48)	0.862
	Others	11	8	0.85 (0.33–2.2)	1.15	(0.43, 3.12)	0.780
Turn over intention	No(Ref)	85	54				
	YES	152	162	1.68 (1.12–2.52)	1.44	(0.93, 2.23)	0.098
number of children	0 (Ref)	165	137				
	≥1	72	79	1.32 (0.89–1.96)	1.06	(0.67, 1.66)	0.810
Job satisfaction	Unsatisfied (ref)	148	86				
	Satisfied	89	30	2.51 (1.72–3.67)	2.02	(1.3, 3.13)	0.002***
Transformational leadership	Poor (ref)	131	73				
	Good	106	143	2.42 (1.65–3.54)	1.85	(1.16,2.90)	0.008**
Perceive organizational support	Poor (ref)	133	92				
	Good	104	124	1.72 (1.19–2.50)	1.190	(0.768, 1.84)	
Perceive psychological empowerment	Poor (ref)	104	89				
	Good	133	127	1.12 (0.77–1.62)	0.77	(0.51, 1.18)	

study conducted in Portugal focused only on the affective component of organizational commitment, and it also included only nursing profession. In regards to the study conducted in a Gurage zone (14), the discrepancy could be due to the difference in the number of items and level of the Likert scale used to measure organizational commitment. In the current study, the organizational commitment was measured with 24 items on a five-point Likert scale, whereas a study conducted in the Gurage zone used nine items on a seven-point Likert scale. In terms of the study setting, the latter focused on both hospitals and health centers. However, since this study only emphasized health centers, the disparity may be attributed to the comparatively high incentive and different opportunities available in hospitals vs. health centers. The findings of the current study also differ from a study that was done at Jimma zone among health professionals that provide institutional delivery (15), and the discrepancy might be due to study participant difference which means only one profession was included. Regarding the latest study done in the Bench Sheko zone, organizational commitment in this study setting was higher than a finding of the current study, and the reason behind this might be the study area and socioeconomic status. When we see the study area of this finding, there were a lot of burdens other than a professional job. The payment might be not enough due to a lot of expenditures. The monthly income used for house rent, daily transportation, high cost of child education payment, etc. results in dissatisfaction and, in turn, results in a low commitment to their organization.

Among socio-demographic characteristics, the age of respondents had a significant association with organizational commitment. The age groups (30–39) were found to be significantly associated. This age commitment might be due to the age at family responsibility more rendered it but the low age group might be not such responsible. In contrast, older age groups who have worked for many years might be decreased their commitment due to burnout and they might be busy by having different responsibilities. This study finding was consistent with the study done in Iran with age group (31–40) but inconsistent with the finding in Gurage zone, JUSTH, and study done in Bench Sheko zone. The reason behind this might be due to the difference in the number of a participant in the age group. In this study, the number of participants in the age group of 30–39 was higher than in a study done in Gurage, JUSTH, and Bench Sheko zone (13, 14, 21).

This study also found a significant and positive association between job satisfaction and the organizational commitment of health professionals. The odds of having good organizational commitment were almost 2.02 times higher among those with job satisfaction than those without job satisfaction (AOR 2.02, 95% CI 1.30 and 3.13). This was the most important finding from this study which has support from theories. Accordingly, Frederick Herzberg's Two-Factor Motivation Theory is based on job satisfaction in the workplace. There are intrinsic factors that are related to job satisfaction, and extrinsic factors are associated with dissatisfaction. Meeting employees' lower-level needs (hygiene factors) by improving pay, benefits, and safety prevent employees from becoming dissatisfied but will not motivate them for better performance. To motivate workers, focus on changing the intrinsic nature and content of jobs themselves by enriching them to increase employees' autonomy and their opportunities to take on additional responsibility, gain recognition, and develop their skills and careers (29). Furthermore, Abraham Maslow's Hierarchy of Needs Theory strengthens this stating that satisfied employees will have a higher commitment to their organization (30).

This study also showed a significant association between organizational commitment and job satisfaction. The odds of organizational commitment were two times higher among those who were satisfied with their job than those who were less satisfied AOR 2.02 (95% C.I: 1.3–3.13). This was congruent with previous studies (Saudi Arabia, Iran, Philippines, Nigeria, Gurage zone, Jimma zone, and Bench Sheko zone) when job satisfaction of health professionals increases, their organizational commitment level also increases. From the job satisfaction component, pay and benefit and autonomy had a significant association with organizational commitment.

The other predictor that had a significant association with organizational commitment in this study was perceived transformational leadership behavior. The odds of having good organizational commitment were nearly two times higher among those with perceived transformational leadership style than those without perceived transformational leadership style (AOR: 1.85, 95% C.I: 1.18 and 2.90). This was in agreement with a study from Gurage (14), Jimma (15), and Bench Sheko zone (21) where the perceived transformational leadership style of health professionals was found to be a significant and strong predictor of organizational commitment. This could be due to the ability of transformational leaders to work with their followers or employees. Following this, a transformational leader is well-known for developing a futuristic plan, inspiring followers to achieve results beyond normally expected of them, and surpassing their interests for the goals of the organization (31). If health professionals are believed that they are not treated well by their immediate leader, they may believe they are not part of the organization and do not devote their time to the organization. Those health professionals who have positive perceived transformational leadership behavior of managers have an increased level of organizational commitment than those who have negative perceptions.

Perceived organizational support had a significant association in a study done in the Gurage zone, JUSTH, and Bench Sheko zone, but in this study, it had no significant association. This might be due to the difference in the number of managers and supervisors. In Addis Ababa, there are organized hierarchical management systems but in those areas mentioned above in most cases few managers and supervisors. The other factor might be socioeconomic and environmental conditions. In the case of the Gurage and Bench Sheko zone, the study setting had poor infrastructure such as transportation, and the supervisor might be not supported based on the standard, but in the case of JUSTH, the participant was a nurse and the profession by itself needs strict support from a supervisor.

Limitation of the study

The finding of this study was limited to health centers. Therefore, the finding may not be generalized to health professionals working at hospitals. Since the study relied on the experience and exposure of health professionals, it might have recall bias and social desirability bias.

Conclusion and recommendations

From this finding, it was concluded that the level of organizational commitment of health professionals working in primary health facilities of Addis Ababa was lower than what was reported in many other studies. Age of group of the participant, job satisfaction, and transformational leadership behavior were factors significantly associated with the organizational commitment of health professionals. Based on the study findings, the following recommendations to all concerned bodies.

For policymakers

- Addis Ababa city administration, FMOH, Addis Ababa Health Bureau, each sub-city, and woreda health offices recommended maximizing the job satisfaction of their employees.
- For health, managers found Addis Ababa's primary health facility.

    - Health managers at all health department levels and health facilities are expected to adopt a transformational leadership style that is more attentive to health professionals' perceptions accordingly and also should have a special focus on the commitment of the under thirty age group.

- For researchers: since commitment level is a composite variable, further research is needed by including other antecedent factors which determine the organizational commitment of health professionals.

Transparency statement

The leading author (DD) affirmed that the manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained.

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.

Ethics statement

The studies involving human participants were reviewed and approved by Ethical approval was secured from Addis Ababa Public Health Research and Emergency management directorate with a reference number አ/አ/ጤ/10507/227 then a support letter was submitted to the selected sub-city Administration office and respective selected health center. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SA and AD: conceptualization. SA and DD: data curation and formal analysis. SA, AD, and DD: methodology. DD and AD: supervision and validation. SA: original draft preparation. DD: writing, reviewing, and editing the manuscript. All authors contributed to the article and approved the submitted version.

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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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A global review of racial, ethnic and socio-economic disparities in multisystem inflammatory syndrome in children related to COVID-19

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With over 500 million confirmed cases and 6.2 million deaths worldwide, the novel coronavirus has highlighted the underlying disparities in healthcare, unpreparedness to deal with a new disease and the need for monitoring and surveillance for a post-infectious syndrome as well as complicated diseases. Initially, children were thought to be spared but reports of a new phenomenon manifesting as Kawasaki-like disease, toxic shock syndrome, and multi-system inflammatory syndrome, which developed after a few weeks of severe COVID-19 infection, emerged in the pediatric population. As the pandemic progressed, increased prevalence of multi-system inflammatory syndrome in children (MIS-C) related to COVID-19 was seen in non-Hispanic blacks, Asians, and Latinos as compared to the white population drawing attention to a possible role of ethnicity and socio-economic disparities. The CDC currently reports that 31% of MIS-C cases were seen in Black Non-Hispanics and 26% in Latinos, who were historically more affected in previous pandemics. Furthermore, MIS-C cases in developing countries showed higher mortality as compared to high-income countries, which points toward the role of social determinants of health and limitations in a low-resource set up in increasing the disease burden of MIS-C, which should be treated as a public health emergency. Our review highlights the role of ethnicity, socio-economic factors, comorbidities, and differences in populations affected by MIS-C in high-income vs. low- and middle-income countries.

KEYWORDS

multi-system inflammatory syndrome, COVID-19, SARS CoV-2, children, infant, pediatric multi-system inflammatory syndrome, Kawasaki disease, health disparities

Introduction

What started as a mere flu in December 2020, the Coronavirus (COVID-19) pandemic caused by the SARS-CoV-2 virus resulted in over 6.2 million deaths from nearly 500 million confirmed cases (1). Early reports showed that children were mostly spared from severe forms of illnesses associated with COVID-19, with only 2% of cases diagnosed in the pediatric population up till February 2020 (2). Epidemiological studies further suggested that compared with adult patients' the clinical manifestations of COVID-19 in children were mostly mild and showed minimum mortality (3). However, this judgment was revised in April 2020 when several countries in Europe and North America reported cases of young patients with "Multi-System Inflammatory Syndrome in Children (MIS-C)" associated with SARS-CoV-2 also known as Kawasaki-like syndrome and toxic shock syndrome (4). Reports of clusters of children and adolescents affected by MIS-C admitted to ICU or requiring mechanical ventilation emerged from the UK, Italy, and New York, followed by other parts of the US (5, 6). It was further found that Black and Hispanic children formed an overwhelming majority (66%) of those who developed the life-threatening MIS-C (7).

Although rare, this condition needs extensive surveillance in areas with a high burden of COVID-19, which have shown consistent patterns of racial/ethnic differences (8, 9). The exact role of race and ethnicity on clinical outcomes of COVID-19 is unknown, but given the general consensus, there is a greater need to examine the factors behind disproportionate levels of adverse clinical outcomes (10). Particularly in pediatric populations where reports of severe disease have been limited owing to incomplete public health data worldwide (11). The current studies lack data on race and ethnicity-specific presentations of the syndrome, the mechanism of genetic predisposition to MIS-C, and further research into its' worldwide distribution, given that it should be treated as a public health emergency that requires intensive care and surveillance. Literature regarding disparities in COVID-19 has largely addressed the adult population while the extent of racial and ethnic disparities in children is relatively unknown. While MIS-C initially emerged in the US and Europe, soon after cases were reported in the developing countries which was a source of immediate concern and attention for communities worldwide. It is also imperative to understand the variation in clinical features and severity of this disease in affected countries and to assess the potential role played by social determinants of health. Given the scarcity of data in the current literature, in this review we compare the distribution of MIS-C in High-Income Countries (HICs) and Low-Income Countries (LMICs) and explore the role of social and living conditions, comorbidities, and ethnicity in the development of MIS-C as well as the extent of severe forms of the disease in certain populations.

Case definition

Variously termed as Kawasaki-like disease, pediatric multi system inflammatory syndrome temporally associated with COVIRD-19 (PIMS-TS) or MIS-C, case definitions have been produced by the World Health Organization, US Centers for Disease Control and Prevention and the UK Royal College of pediatrics (Table 1).

Difference between Kawasaki like disease and MIS-C (STING PATHWAY)

In a retrospective observational study from Japan Kawasaki-disease Shock Syndrome (KDSS) and MIS-C were seen to overlap in clinical symptoms however are 2 separate entities. Kawasaki disease is a medium-sized vessel vasculitis usually in children under 5 years of age preceded by fever for at least 5 days and generalized inflammation that involves lymph nodes and particularly the skin and mucous membranes (12). KD progresses to Kawasaki disease shock syndrome (KDSS) when there is a 20% decrease in systolic blood pressure (13). COVID-19 can also develop severe course characterized by acute respiratory distress syndrome (ARDS) with a hyperinflammatory response (14). Multi-system inflammatory response in COVID-19 is characterized by systemic inflammation involving multiple organs such as cardiac, renal and gastrointestinal. Entry of a foreign antigen in the body causes activation of simulator of interferon genes (STING) which leads to release of inflammatory cytokines, predominantly type 1 IFN. The STING pathway is shown to be activated in KD brining about an inflammatory response that consists of neutrophils, macrophages and cytotoxic T cells which are seen on the histology of coronary arteries affected in KD (12). It has been reported that type 1 IFNs drive the immune response in SARS-CoV-2 (15). It was when Domizio et al. (16) identified a H-151 STING inhibitor that served as a therapeutic agent in reducing severe inflammation in SARS-CoV-2 an important role of STING pathway in COVID-19 was found. CT angiogram can also play an important role in young patients with symptoms of KD overlapping with COVID-19 to identify coronary aneurysms in a timely manner so that the fatal risk of thromboses and lumen narrowing can be diagnosed initially.

Methods

In this narrative review, a thorough literature search of all peer-reviewed articles published between 31st

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TABLE 1 Case definitions by WHO, US-CDC and Royal College of Pediatrics, UK.

World Health Organization (WHO) (15th May 2020) Multi-system inflammatory syndrome in children and adolescents temporally related to COVID-19	US-Center of Disease Control (CDC) (14th May 2020) Multi-system inflammatory syndrome in children (MIS-C)	Royal College of Pediatrics and Child Health (RCPCH) (1st May 2020) Pediatric multisystem inflammatory syndrome temporally associated with COVID-19
Fever >3 days AND elevated markers of inflammation (ESR, CRP or procalcitonin)	Fever ≥38.0°C for ≥24 hours or report of subjective fever lasting ≥ 24 h	Fever >38.5
0–19 years	<21 years	Child
At least 2 of the following: 1. Rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands or feet) 2. Hypotension or shock 3. Features of myocardial dysfunction, pericarditis, valvulitis or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP) 4. Evidence of coagulopathy (by PT, PTT, and elevated d-Dimers) 5. Acute GI problems (diarrhea, vomiting or abdominal pain)	Evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal respiratory, hematologic, gastrointestinal, dermatologic or neurological)	Persistent fever, inflammation (Neutrophilia, elevated CRP and lymphopenia) and evidence of single or multi-organ dysfunction (Shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features. This may include children fulfilling full or partial criteria for Kawasaki disease.
No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal/streptococcal shock syndromes	No alternative plausible diagnoses	Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice).
Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19	Positive for current or recent SARS-CoV2 infection by RT PCR, serology or antigen test or COVID-19 exposure within the 4 weeks prior to onset of symptoms	SARS-CoV-2 PCR testing may be positive or negative

December' 2019 to 1st April' 2022 was undertaken using keywords "multi-system inflammatory syndrome", "COVID-19", "SARS COV-2", "coronavirus", "children", "infant", "Kawasaki/Kawasaki-like disease", "pediatrics", "pediatric multi-system inflammatory syndrome" and any other relevant keywords and supplementary concepts were identified. Reference lists of the identified studies were also screened to look for similar studies. Multiple electronic databases were searched, which included PubMed, Google Scholar, Elsevier, Wiley Online Library, ScienceDirect, and WHO COVID-19 database. To increase the scope of our search, pre-prints from Medxriv were also included. An inclusion and exclusion criteria were pre-decided to guide our search, which is as follows:

Inclusion Criteria:	Exclusion Criteria:
• Case reports, case series, cohort papers and case-control studies • Mean age ≤ 18 years • Addressing MIS-C as a complication or Kawasaki-like disease as a potential complication of SARS-CoV-2 • The country or region mentioned • Data on race and/or ethnicity mentioned • Addressing the socio-economic backgrounds of patients with MIS-C • Articles published in the English language	• Opinions, letters, editorials, review articles • Mean age > 18 years • Studies that only discuss COVID-19 in the pediatric population but not MIS-C • Country or region not mentioned • Race and/or ethnicity are not mentioned • Articles not published in the English language

MIS-C and ethnicities

Previous studies published on COVID-19 in adults have highlighted racial/ethnic and socio-economic disparities and race discrimination continued in the provision of vaccines and treatments (17). A policy statement by American Academy of Pediatrics highlighted that the impact of racism starts from birth disparities which give rise to mental health problems and chronic stress conditions such as cortisol that predisposes children and adolescents to chronic disease (18). A study that enrolled 640 COVID-19 patients in the UK concluded that compared to white members, black individuals were at a 4 times higher risk of COVID-19, and it was twice higher in Asian and other non-white persons (19). However, there is limited data relevant to the pediatric population and if a certain ethnic group is at a higher risk of developing COVID-19, particularly MIS-C. Currently, the CDC website reports 7,880 MIS-C cases, 31% of which are Black Non-Hispanic and 26% are Hispanic/Latino, who are also disproportionately affected by COVID-19 (20). As seen in Kawasaki disease, which has shown a predominance in genetically susceptible children, similar patterns have been seen in MIS-C, in which higher prevalence was reported in Black, Hispanic, and South Asian populations (4, 21, 22). Dufort et al. reported a case series of 99 pediatric patients with confirmed and suspected MIS-C who belonged to New York. 31 out of 78 (40%) patients were black, and 31 out of 85 (36%) were Hispanic, compared to 29 out of 78 (37%) white patients (23). Adult deaths in New York showed a similar pattern. Compared to 22% African Americans and 29% Hispanic-Latinos in the overall population, the two groups accounted for 28 and 34% of deaths, respectively (24). Another study from New York reported that 45 and 39% of MIS-C patients were Hispanic/Latino and Black, respectively, compared to 9% White, 3% Asian, and 3% other ethnicities (25). In another cohort from NYC, among 223 patients meeting the MIS-C criteria, race/ethnicity data was available for 184 patients. 34.4% (75 patients) were Black, given the overall population of Black children 22.2 and 19.9% of patients under 20 years hospitalized due to COVID (26). From April to June 2020 the incidence of MIS-C in various states of America was 9.26, 8.92, and 2.94 times higher in Black, Hispanic or Latino, and Asians compared to white patients (27). Black and Hispanic populations also have the lowest rates of vaccination, and parents to date show hesitancy to vaccinate their children against COVID-19. Only 21% of children between 12 and 15 years were vaccinated, and 32% of those between 16 and 17 years of age among the racial/ethnic groups (28).

The racial disparities were not only confined to the United States of America (USA). Toubiana et al. reported 21 confirmed cases of Kawasaki Disease—like/MISC in the Paris region in France, where children of color were overrepresented, similar to what we saw in the USA. Twelve (57%) children had at least one parent from a sub-Saharan African or Caribbean Island, and 3 (14%) children were of Asian (Srilanka/China) descent (29). A study from the UK reported 15 cases of PIMS-TS (Pediatric Inflammatory Multisystem Syndrome-temporally associated with SARS-CoV-2) associated with COVID-19, and all children belonged to African/Afro-Caribbean, South Asian, mixed, or minority ethnic groups, which is relatively large given that only 3.3% of children are Black and 10% percent are Asian. In addition, these children showed severe cardiac symptoms, and 67% were admitted to the ICU (30). Another cluster of 8 children from the UK was reported with hyperinflammatory shock syndrome; all patients were Afro-Caribbean, Asian, and Middle Eastern, and all of them were admitted to the ICU and required mechanical ventilation, one child died, and the rest were discharged on surveillance (31). In Latin America, MISC was more widely reported compared to other developing countries, perhaps due to differing political opinions regarding the to approach the pandemic and lockdown policies making children more exposed to the infection during daily activities, which further support the point of view that children of Hispanic-Latino ethnicity are at a higher risk of developing MIS-C (32–34).

Table 2 summarizes the race and ethnicity findings of MIS-C.

MIS-C and comorbidities

The most common underlying condition in children with MIS-C was obesity (21, 23, 25, 26, 32, 35–38). The second most common comorbid highlighted in these cohorts was

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TABLE 2 MIS-C according to Race and Ethnicity in different countries.

Authors	*N*	Country/ Region	Race and ethnicities
Jonat et al.	54	USA	Hispanic: 29.6% White: 35% African America: 19%
Abrams et al.	1,080	USA	Hispanic: 41% Non-Hispanic Black: 36% Non-Hispanic White: 14%
Shust et al.	8		Black and Hispanic affected disproportionately
Toubiana et al.	21	France	57% African ancestry and 14% Asian
Shelly Riphagen et al.	8	UK	6 Afro-Caribbean 1 Asian 1 Middle-Eastern
Kathleen Chiotos et al.	6	UK	2 Blacks 2 Whites 2 unknowns No Hispanic or Latino descent
Ramcharan et al.	15	UK	All patients were from: African/Afro-Caribbean South Asian Mixed Other minority ethnic groups
Masih et al.	1	UK	White Caucasian
Swann et al.	651	UK	Ethnicity was recorded in 88% (576/651) of cases: White: 57% (330/576) South Asian: 12% (67/576) Black: 10% (56/576) Children who met MISC criteria: White: 16 Black: 9 South Asian: 4 Other: 16 Missing: 7
Marisa Dolhnikoff et al.	1		African
Patrick Davies et al.	78	UK	Afro-Caribbean: 37 Asian: 22 White: 17 Other: 2
Sussana Felsentein et al.	29	UK	Caucasian: 12 (41.4%) South East Asian: 6 (20.7%) East Asian: 2 (6.9%) African/Caribbean: 4 (13.8%) Unknown or multi-ethnic: 5 (17.2%)

(Continued)

TABLE 2 (Continued)

Authors	*N*	Country/ Region	Race and ethnicities
Nele Alders et al.	57	UK	PIMS-TS patients were mostly of non-Caucasian ethnicity ($n = 26$ [84%] vs. $n = 5$ [50%])
Feldstein et al.	186	USA	35/186 (19%): White non-Hispanic 46/186 (25%): Black non-Hispanic 9/186 (5%): Another race and non-Hispanic 57/186 (31%): Hispanic or Latino 41/186 (22%): Unknown race
Dufort et al.	99	USA	Of 78 patients with data on race, 29 (37%) were white, 31 (40%) were black, 4 (5%) were Asian, and 14 (18%) were of other races; of 85 patients with data on ethnic group, 31 (36%) were Hispanic.
Kaushik et al.	33	USA	45%: Hispanic/Latino 39%: Black 9%: White 3%: Asian 3%: Others
Bandi et al.	474	USA	25.1%: non-Hispanic white 43.2%: African American 24.7%: Hispanic 1.5%: Asian Remaining were identified as other races
Cheung et al.	17	USA	6 Jewish 2 non-Hispanic 4 Hispanic 4 black 1 Asian
Mariawy Riollano-Cruz	15	USA	10/15 patients (66%): Hispanic or Latino 5/15 (34%): Other races
Shanana Godfred et al.	570	USA	40.5% Hispanic/Latino (Hispanic) 33.1% non-Hispanic black (black) 13.2% non-Hispanic white (white)
Rivera-Figueroa et al.	1	USA	African American
Daniel et al.	1	USA	Multiracial (Caucasian and Hispanic)
Arnaldo Prata Barbosa et al.	79	Brazil	58% White
Kate Webb et al.	23	South Africa	Blacks (18) South African colored (5) No whites
Torres et al.	27	Chile	Latin American
Al-Aamria et al.	1	KSA	Arab

asthma (4, 22, 39–43). Hypothyroidism, non-alcoholic fatty liver disease, respiratory illness preceding 4 weeks of hospitalization, and glucose-6-phosphate-dehydrogenase deficiency were also seen in some cases (43, 44). Other comorbidities seen in severe COVID-19 cases were neurological problems, immunocompromised, premature births, and hematological problems, but only obesity was associated with MIS-C (40). Similar findings were seen in adult patients, where Black patients had higher prevalence of obesity, diabetes, hypertension, and chronic kidney disease compared to white patients (45). Black ethnicity was shown to be associated with comorbidities in a cohort where African American patients with 3 or more comorbidities formed a higher proportion of overall patients with severe COVID-19 (46). Particularly in the US, obesity was associated with factors such as age, race, Hispanic origin, and education of the household head which are directly related to ethnicity and one's socio-economic status (47). Furthermore, studies suggest that asthma is related to socio-economic factors, which are directly linked with ethnicity as well, such as environmental exposures, access to healthcare, stress, and psychological/cultural factors that have been associated with increased asthma morbidity (48).

MIS-C in the developing world

Compared to High-Income Countries (HIC's), studies from the developing world have reported higher rates of hospitalization and deaths from MIS-C (49). The first case to be reported in South Asia was from Pakistan, where a cluster of 8 children reported confirmed MISC at a university hospital in the city of Lahore, all of whom showed cardiovascular involvement, and one died due to myocardial infarction and subsequent organ failure (50). Involvement of coronary artery disease and the overall infectivity rate in Pakistan in children younger than 20 years was higher (>10%) compared to the rest of the world (50, 51). In India, neonates and infants were affected by MIS-C with various manifestations ranging from in-utero exposure to SARS-CoV-2 in a premature infant (52), fatal respiratory distress syndrome with hypotensive shock and meningoencephalitis (53), cavitary lung lesions (54), persistent neutropenia (55) to dermatological involvement (56). In Iran, a retrospective study that covered 3 hospitals in regions most severely hit by the pandemic reported 45 confirmed cases of MISC and a mortality of 11% ($n = 5$) (57). Another case report from Iran showed a 5-year-old girl with Kawasaki disease like inflammatory syndrome with severe symptoms consistent with MISC that improved with standard treatment consisting of IVIG and anti-biotics (58).

At the time of writing this review, studies from Low- and Middle-Income Countries (LMIC's) showed a lesser number of MISC patients compared to HICs but a higher proportion of deaths (49). This is alarming due to a number of factors. Firstly, many physicians working on the front lines were stretched to not allocate enough time for clinical research and data collection. Secondly, lack of testing capacity overwhelmed in-patient facilities, and limited pediatric ICU and ventilator resources can cause many patients to return undiagnosed. Thirdly, children make up a large part of the population in LMICs compared to HICs and have more exposure to risk factors of lower respiratory diseases such as air pollution, incomplete immunization, malnutrition, greater prevalence of infectious diseases like TB and HIV, and overcrowded conditions with water and sanitation problems (59). Therefore, the number of cases of MISC can be largely underestimated.

It is essential to consider practical prevention strategies according to the limitations of populations in low-income countries. In communities with widespread transmission mass awareness and advocacy campaigns regarding the spread of the disease can be carried out with focus on limiting healthy children from visiting healthcare facilities, regular well-child visits for newborns and infants for preventive care and timely vaccinations, local availability of telephone triage system, immediate closure of schools and public places or at least restricting entrance for children as well as nutritional education for parents as diet plays a huge role in the development of immune system (60).

Table 3 summarizes findings from High-Income and Low- and Middle-Income countries based on the recent World Bank Classification (61).

MIS-C and socio-economic factors

Given the ethnically diverse nature of the aforementioned HICs, the high number of cases suggests a relationship between socio-economic factors and MIS-C. Higher COVID-19 infection rates have been associated with lack of insurance, overcrowded neighborhoods where social distancing is ineffective, and high exposure jobs within the service industry, transport, and healthcare sectors which are dominated by people of color (62). Especially Hispanic families who mostly live in metropolitan areas in apartment buildings, bigger families, and mainly use public transport (63). This can lead to adults exposing more children to coronavirus at home and serve as a possible explanation for the increased number of COVID-19 cases progressing to MIS-C. Discrimination within the healthcare system, limited healthcare access because of lack of transportation to take their children to the hospital on time, cultural and linguistic barriers, inability to take time off work, possible distrust in the system due to inherent biases and fears of deportation for symptomatic adults also play a role in acquiring timely access to healthcare (64, 65). A retrospective case-control study in Massachusetts conducted on 44 patients with MIS-C (Hispanic = 44%, Black = 26%) concluded that a higher social vulnerability index (SVI), lower socio-economic status (SES), Hispanic ethnicity, and Black

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TABLE 3 MISC in high income countries.

Authors	*N*	Country/ Region	Clinical features	ICU admissions	Limitations
Jonat et al.	54	USA	Mucocutaneous, GIT and neurologic symptom Male—57%, Comorbid—Obesity	57% with no deaths	
Caro-Patón et al.	12	Spain	Cardiogenic shock, myocardial injury and ventricular dysfunction	100% with no death	Single center study
Elizabeth et al.	58	England	Vomiting (84%), abdominal pain (54%), diarrhea (52%), rash (52%), conjunctival injection (45%), female—57%	79% needed mechanical ventilation	
Lucio Verdoni et al.	Group 1: $n =$ 19 Group 2: $n =$ 10	Italy	Children showing immune response to SARS-CoV-2 after the epidemic—older, higher rate of cardiac involvement, had features of Macrophage activation syndrome and associated with a 30 times higher incidence of a severe form of Kawasaki disease.		Small case series. Kawasaki like disease—rare condtion (0.001 children affected by SARS-CoV-2)
Antona et al.	156	France	Kawasaki-like disease (61%), myocarditis (70%), macrophage activation syndrome (23%), seritis (22%)	67% with one death vasopressors—73%	
Zahra Belhadjer et al.	35	France and Switzerland	Comorbid—asthma and overweight Complication—Acute cardiac decompensation. Left ventricular systolic function recovered with immunoglobulin.	64% with no death 29%—Invasive mechanical ventilatory support	
Marie Pouletty et al.	16	France	Hemodynamic failure, Orchitis, Aseptic meningitis, Raynaud syndrome and Anosmia Respiratory features observed in adult COVID patients were not seen.	44% with all in remission.	Direct link between the Kawasaki Disease and SARS-CoV-2 not demonstrated.
Maria Paz Deza Leon et al.	1	Europe	Female, 6 years old Underlying group A Streptococcus infection Treatment—IVIG, aspirin, ECMO COVID-19 milder in children—a genetic predisposition for cardiac complications or a previously unrecognized inflammatory response to COVID-19.	Admitted in PICU	Case report
Astrid Elisabeth Rojahn et al.	1	Norway	Comorbid—Food allergies. Increase in incidence of the disease after 3–4 weeks of COVID-19 peak suggests a delayed immune response.	Transferred to PICU with cardiogenic shock, Incipient multiorgan failure, hypotension, oliguria, altered sensorium, and tachypnea.	Case report

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TABLE 3 (Continued)

Authors	*N*	Country/ Region	Clinical features	ICU admissions	Limitations
Antonio Torrelo et al.	4	Spain	Target and targetoid skin lesions, confluent macules, papules and plaques, with different sizes, some with hemorrhage or a small central crust.		Case series
Kim et al.	768	Korea	The incidence of Kawasaki Disease in Korea is 217.2 per 100,000 children <5 years old, 10–30-fold higher than that of KD in North America and Europe.		Editorial
Toubiana et al.	21	France	Myocarditis, Kawasaki like shock syndrome, coronary artery dilatations, GIT symptoms. High proportion of the affected children and adolescents were of African ancestry	81% with no deaths	Small sample size
Shelly Riphagen et al.	8	UK	Males dominant Warm, vasoplegic shock, refractory to volume resuscitation—treated with noradrenaline and milrinone. Adenovirus and enterovirus were isolated.	100% with 7/8 requiring mechanical ventilation. Discharged after 4–6 days. 1 death.	Small sample size
Kathleen Chiotos et al.	6	UK	Females dominant. Myocardial dysfunction, troponin leak, severe enteropathy and relative thrombocytopenia. 67%—neurological symptoms Patient 4—aseptic meningitis consistent with Kawasaki disease.	100% with 3/6 intubated and 2/6 non-invasive mechanical ventilation. 1/6 stayed in PICU, others discharged after 8–17 days.	Small sample size
Ramcharan et al.	15	UK	Male dominan Treatment—Norepinephrine and vasopressin, Epinephrine. Impaired left ventricular function, valve regurgitation and/or coronary artery involvement, systemic hypotension.	100% with deaths. Discharged on aspirin.	Small case series, unable to establish management—treatment guidelines and some patients not referred.
Mike Masih et al.	1	UK	Male, 9-year-old History of asthma. PMIS-TS is a post infective, delayed antibody-mediated dysregulated immune response, with an onset between 2 and 4 weeks after initial infection.		Case report

(Continued)

TABLE 3 (Continued)

Authors	*N*	Country/ Region	Clinical features	ICU admissions	Limitations
Michele et al.	1	UK	Male, 11 years old Comorbid—Pneumonia High-grade conduction system disease is a potential complication of MIS-C.	Admitted in PICU, requiring high-flow nasal cannula support (15 liters per minute, 50% FiO2)	Case Report
Swann et al.	651	UK	Male dominant Asthma, neurological problems, immunocompromised, premature births, hematological and oncological co-morbids, obesity. Children who met the WHO preliminary definition for MIS-C were significantly older, of non-white ethnicity and five times more likely to be admitted to critical care and receive mechanical ventilation.	18% with 9% requiring mechanical ventilation	Case record form as data collection. Initially, diagnostic serology was not available. Loss of follow up.
Patrick Davies et al.	78	UK	Males' dominant High proportion of Asian and Afro-Caribbean children	100% Mechanical ventilation—36, ECMO—3	
Dolinger et al.	1	USA	Male, 14-year-old Comborbids—Crohn's disease Treated with infliximab for TNF-α blockade.	Admitted	Case report
Andrea et al.	1	USA	Female Treated with enoxaparin injections MIS-C affects children beyond infancy	Admitted	Case report
Nele Alders et al.	57	UK	Comorbids—Overweight/Obese	63% with 37% mechanically ventilated.	Incomplete data due to referral nature of the center. Small, localized sample size.
Feldstein et al.	186	USA	The 4 patients who died were 10–16 years of age; 2 of the patients had diagnoses of underlying conditions.	80% with 20% mechanically ventilated. 3/186 received ECMO support. 4 deaths.	Results are not generalizable. No comparison group. Retrospective chart.
Dufort et al.	99	USA	Males' dominant Comorbid—Obesity	80% with 2 deaths Mechanical ventilation—10%	Initially, limited availability of testing.
Kaushik et al.	33	USA	Males' dominant. Comorbids—overweight/obese	67% with 1 death. Mechanical ventilation—5	
Bandi et al.	474	USA	Male dominant Asthma	12%, 1 intubated	Small sample size Type 2 error in assessing risk of COVID-19 in asthmatic patients

(Continued)

TABLE 3 (Continued)

Authors	*N*	Country/ Region	Clinical features	ICU admissions	Limitations
			No ED or hospital admissions for children with asthma—asthma not a risk factor for COVID-19 in children nor a severe disease.		
Cheung et al.	17	USA	Females' dominant	88% with 59% on vasoactive support.	Small sample size Short follow up period Inability to establish causality
Chiu et al.	1	USA	Male, 10-year-old Stable vital signs and a normal ambulatory saturation. Severely diminished left ventricular systolic function with trace pericardial effusion.		Case report
Maria et al.	1	USA	Female, 6 years old Syncope on day 3 of illness. Maculopapular rash on all extremities. Prominent cardiac silhouette and mildly decreased left ventricular function.	Admitted to PICU, ECMO started	Case report
Einat Blumfield et al.	16	USA	Males dominan Comorbids—Obesity, asthma, sickle cell disease, ventricular septal defect and UTI. In children with MIS-C associated with COVID-19, the most common thoracic imaging abnormalities were cardiomegaly, congestive heart failure or pulmonary edema, and pleural effusions.	69% with 1 on mechanical ventilation	Small sample size
Heidemann et. al	3	USA	Presented with vasculitis and cardiac manifestations who responded to intravenous immunoglobulin and aspirin.	1 admitted, 2 intubated.	Small sample size
Mariawy Riollano-Cruz et al.	15	USA	Males' dominant Comorbids—Asthma, Hypothyroidism, non-alcoholic fatty liver disease, respiratory illness Treated with broad spectrum antibiotics and prophylactic anticoagulation with Enoxaparin The disproportionate burden of disease among Hispanic/Latino and black/African–American ancestry	93% with 53% mechanically ventilated 1 death—required ECMO during the 9 days of admission. One patient required an intra-aortic balloon pump to treat cardiogenic shock.	
DeBiasi et. al	177	USA	Male dominan Comorbid—Asthma, Neurologic, Diabetes, Obesity, Cardiac, Hematologic and Oncologic		Retrospective design.

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TABLE 3 (Continued)

Authors	*N*	Country/ Region	Clinical features	ICU admissions	Limitations
Shanana Godfred et al.	570	USA	Male dominant Comorbid—Obesity Long-standing inequities in housing, economic instability, insurance status, and work circumstances of patients and their family members have systematically placed social, racial, and ethnic minority populations at higher risk for COVID-19 and MIS-C.	63.9% with 10 deaths. Intubated—13%	Possibility of reporting bias. Inconsistency in completion of case report forms.
Shema Hameed et al.	35	USA	Males dominant	68.5% with one death due to extensive right cerebral infarct whilst on ECMO. Mechanical ventilation—20%	Small sample size
Rivera-Figueroa et al.	1	USA	Male, 5 years old	Admitted with high flow nasal cannula. Discharged after 6 days.	Case Report
Elaine et al.	1	Brazil	Male, 10 years old Discharged at 14th day of hospitalization		
Omar Yassef et, al	409	Latin America	Male dominant Pre-existing medical condition, known immunodeficiency, respiratory tract infection, gastrointestinal symptoms and low socio-economic conditions were associated with PICU admission		Some cases misdiagnosed as no confirmatory test and that the CDC case definition is broad.
Al-Aamria et al.	1	KSA	Female, 10–15 years old FST for G6PD screening was positive	Admitted, intubated and ventilated Died at day 33 due to multiple organ dysfunction syndrome.	Case report
Daniel et al.	1	USA	Male, 14 years old Comorbid—constipation and eczem Family history for ulcerative colitis	Admitted, intubated and mechanical ventilation Discharged at 12-day on low dose aspirin and penicillin G prophylaxis.	Case report
MISC in upper-middle and low-and middle-income countries (1)					
Hançerli Törün et al.	570	Turkey	Comorbid—obesity and Chronic Lung Disease Cardiovascular involvement—most common clinical characteristic (493)	63.9%	
Ozsurekci et al.	52	Turkey	Comorbid—neurometabolic/genetic disorders, hematologic/oncologic and chronic pulmonary disease		Retrospective study with a small sample size

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TABLE 3 (Continued)

Authors	*N*	Country/ Region	Clinical features	ICU admissions	Limitations
			No deaths in MIS-C group		
Haslak et al.	76	Turkey	Kawasaki disease, cardiac murmur, hepatomegaly and musculoskeletal findings	27 (35.5%)	
Shafique et al.	8	Pakistan	Fever (for more than 3 days), stomachache, vomiting, diarrhea, red eyes, rashes on the trunk and shock.		Lack of awareness among clinicians Restricted of access to healthcare Poor referral system
Bahrami et al.	1	Iran	History of upper respiratory symptoms over the past 3 weeks. At the time of discharge—evidence of desquamation in fingers was observed. Prescribed low dose aspirin (3 mg/kg daily) and repeat echocardiogram after 1 week.		Case report
Arnaldo Prata Barbosa et al.	79 (13% had MIS-C)	Brazil	Males' dominant Comorbid—Non-progressive encephalopathy, chronic respiratory disease, onco-hematological disease, congenital heart disease, under nutrition. ARDS—71%. No deaths in MIS-C group.	Mechanical ventilation—14, Discharged—90%	Results are not generalizable. Some lacking details about treatment and investigations.
Satareh Mamishi et al.	45	Iran	Mortality—11% Comorbids—acute lymphocytic leukemia, chronic kidney disease, cerebral palsy and Budd– Chiari syndrome Clinical presentation predominantly consisted of sepsis-like disease and toxic-shock like disease		
Kate Webb et. al	23	South Africa	Males' dominant. Comorbids—Pre-natal HIV exposure, Obesity, AML, Epilepsy	52% due to cardiac abnormalities. No deaths.	Patients were not tested for COVID-19
Balasubramanian et al.	1	India	Male, 8-year-old MISC shares common features with KD, Staphylococcal/streptococcal toxic shock, bacterial sepsis and macrophage activation syndrome. High CRP levels—mediated by IL-6.	Admitted, recovered in 2 weeks.	
Torres et al.	27	Chile	Comorbid—overweight, asthma, primary immunodeficiency, GATA 3 deficiency, prematurity and gestational age of 33 weeks	59% with duration of stay of 5 days. O2 support—13/27 Mechanical ventilation—12/27	Small sample size Lack of definitive outcome. Loss of follow up. Chances of underreporting.

race were independently associated with developing MIS-C (66). Mitigating social determinants of health is important as future winter waves of SARS-CoV-2 are anticipated. Improved housing decreases in overcrowding, and improved nutrition has for years proven to be effective interventions for controlling respiratory infections such as tuberculosis (67). Factors such as reducing smoke exposure, financial support to low-income households, improving access to healthcare, free and accessible testing, and provision of shelter to those in need have great potential to improve future pandemic morbidity and mortality (68).

Conclusion

This review highlights the need for high-quality data on ethnicities and socio-economic positions of patients affected by MISC, especially in regions severely impacted by COVID-19. Social determinants of health should be routinely considered in clinical assessments the same way as age and sex, as they can play an important role by aiding in the creation of tailor-made policies for risk mitigation. It is important to note the equitable distribution of resources, such as critical care and hospital beds for pediatric patients with MISC, is essential for reducing mortality because most of the resources were allocated to adult COVID-19 patients. In LMICs, where lockdown policies put vulnerable populations such as the elderly and children at a higher risk of exposure as most people live in overcrowded conditions, there should be strict surveillance. Good standard healthcare is not free in most LMICs, hospitals funded by the government are found to be stretched, and the cost associated with prolonged hospital admissions and critical care can be a factor that holds back families from seeking hospital care until an emergency arises. In addition to social determinants of health, comorbidities were another driving factor leading to the overrepresentation of ethnic minorities getting affected by MISC. Further genetic studies are also needed to warrant the role of genetic susceptibility to MISC in children. This review can form the basis of larger cohort studies investigating the role of ethnicity and social determinants of health in developing MISC that pose a serious public health concern. Our review also elucidates the importance of cross-cultural prospective cohorts to correctly assess the wide clinical variability of this syndrome and help us solidify common socio-economic and racial/ethnic factors driving the severity of MIS-C. Including data from LMICs helped in gaining a new perspective for the occurrence of this syndrome as we saw how delays in attaining appropriate treatment, unavailability of critical care and a lack of timely diagnosis led to severe forms of disease. In conclusion our review identified similar patterns of racial findings, socio-economic strata and limitations of health set ups across different countries of the same economic classification which can aid policy makers in making effective strategies to mitigate the development of MIS-C therefore further studies in the same area should be focused on.

Author contributions

ZA conceived the idea, developed the methodology for the study, and wrote the first draft. ZA, KS, FB, OS, and MS were equally involved in literature review, synthesizing results from the literature, and writing and editing of the manuscript. AW contributed to editing. IU and AN contributed in the overall structure and editing of the manuscript. All authors read, critically analyzed, edited, and approved the final manuscript.

Conflict of interest

Author AN is employed by Hamad Medical Corporation.

The remaining 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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Antidepressant use pattern and disparities among cancer patients in the United States

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Many cancer patients also suffer from depression, however, pharmacotherapy of depression and related disparities in US cancer survivors have not been examined in a nationally representative sample. In the present study, 2,590 adult cancer survivors participating in the National Health and Nutrition Examination Survey 2011–2020 were included and antidepressant use pattern was investigated. To examine disparities by social-demographic characteristics and access to healthcare, multivariate logistic regression analysis was conducted in 422 cancer patients who were using antidepressants and 230 cancer patients who were not using antidepressants but were diagnosed with depression. Results suggested that 21% of adult cancer survivors were using antidepressants and selective serotonin reuptake inhibitors were the most common type of antidepressants used. Antidepressant users were more likely to be female, non-Hispanic white, those who were married or living with partner. In addition, those without a routine place to go for healthcare were less likely to use antidepressants. Disparities were not found by age, family income levels, education, or health insurance coverage. The findings highlight disparities in antidepressant use in cancer patients in the US. Policy makers need to better allocate healthcare resources and facilitate availabilities of affordable care to every patient in need.

KEYWORDS

antidepressant, cancer, depression, epidemiology, health disparities

Introduction

Depression in cancer patients is a common mental health condition. It was reported that 16.5% of cancer patients in palliative care settings were diagnosed with depression (1). While prevalence of depression varies by the type and stage of cancer, it negatively affects cancer patients' quality of life (2) and long-term survival outcome (3, 4). It also increases healthcare cost and utilization (5). For example, it was estimated US Medicare beneficiaries with cancer who had newly diagnosed depression had about 47% higher monthly medical cost than cancer patients without depression (6).

Antidepressants have been prescribed for treatment of depression in cancer patients. Despite the need in disparity research for depression in cancer patients (7), very few nationally representative studies have examined disparities in antidepressant use in this population. A previous study indicated that 18.3% of adult cancer survivors used antidepressants in 1999–2012 in the US, however the study did not report whether the use rate varied by social-demographic characteristics of cancer patients (8). Another national study found that US adult cancer patients were more likely to report medication use for depression in 2010–2013, compared to adults with no history of cancer; also, there was a disparity such that female patients, non-Hispanic white, and those widowed or divorced were more likely to use antidepressants (9). Because the comparison was made to the general public without cancer diagnosis, it is not known whether the observed disparity in antidepressant use was true or was a reflection of differences in prevalence of depression in cancer patients, as certain groups of cancer patients were more likely to have depressive symptoms (10) and this may have accounted for a higher likelihood of antidepressant use in these groups.

The objective of the study was to examine antidepressant use patterns among adult cancer survivors using recent US nationally representative data with a focus on potential disparities due to social-demographic characteristics or access to healthcare. Information on this topic will fill the gap in the literature and inform healthcare policy and facilitate optimal allocation of medical resources that may help eliminate inequality in healthcare at the national level.

Methods

Data source

The National Health and Nutrition Examination Survey (NHANES) is a research program conducted by the US National Center for Health Statistics (NCHS) to assess health and nutrition status of US residents (11). The continuous NHANES program involves a complex multi-stage sample design, and the research team conducts a household interview and a medical examination at a mobile examination center in about 5,000 participants each year, as a nationally representative sample, with data released in 2-year cycles since 1999, and the data are publicly available (11). For the 2019-2020 survey cycle, data collection was suspended in March 2020 because of the COVID-19 pandemic; in order to keep the nationally representative nature of the data, the NCHS combined the NHANES 2019-March 2020 data with NHANES 2017-2018 data, readjusted the sample weight and released them as the NHANES 2017-March 2020 Pre-pandemic data (12). To provide accurate estimate on a subgroup that may not be very common in the US general population, it was recommended to combine NHANES data from adjacent survey cycles in order to increase sample size (13). In the present study, data from NHANES 2011–2012, 2013–2014, 2015–2016, 2017-March 2020 were pooled (for 9.2 years of data, referred as NHANES 2011–2020 thereafter). The NCHS Ethics Review Board approved the NHANES protocol and each adult participant provided their consent to participate in the study.

Antidepressant use

The NHANES team collected information on prescription medication taken in the past 30 days as reported by participants during the household interview, and whenever possible, the interviewer examined the medication containers of products used. Each medication was classified using a 3-level nested therapeutic classification system using Lexicon Plus, a database containing information of all prescription drug products in the US (14). Antidepressants were identified by the second level code of 249 (8). Classification of antidepressants were based on the third level codes. A full list of antidepressants and their classifications can be found in Supplementary Table 1.

Social-demographic characteristics

Age, gender, race/ethnicity, education, marital status, and ratio of family income to poverty were obtained from the NHANES demographic data, and recoded as categorical variables as needed. For example, the ratio of family income to poverty were classified as low income ($\leq$1.85), middle income (1.86–3.49), and high income ($\geq$3.50), based on income-eligibility for federal food assistance programs, accounting for the number of individuals in the household (15).

Access to healthcare

Whether a participant is covered by a health insurance plan was inquired during the household interview. In addition, information about whether there is a place they usually go when they are sick or need advice about health was collected during the household interview. Both responses were coded as Yes or No according to answers to the interview questions.

Depression assessment

Participants completed the PHQ-9 questionnaire, a validated instrument for depression diagnosis and severity measure (16, 17) at the mobile examination center. The survey consisted nine questions related to frequency of depression symptoms in the past 2 weeks. PHQ-9 has been validated for use in cancer

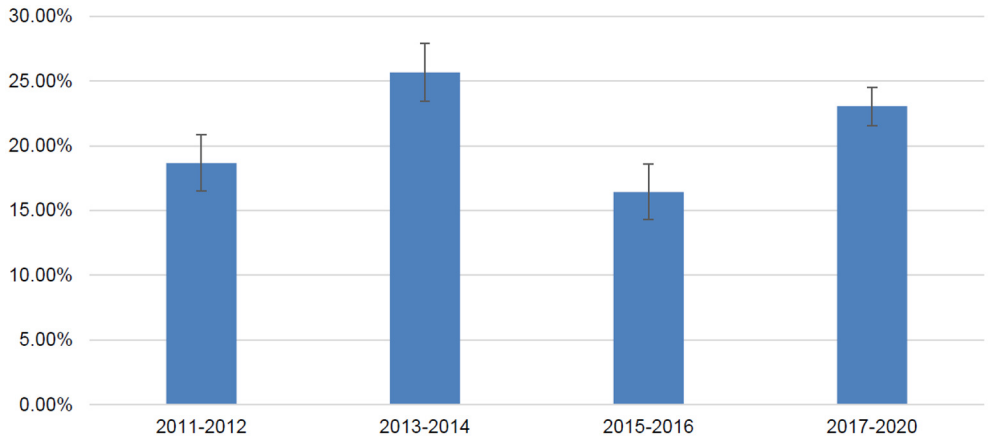

FIGURE 1
Prevalence of antidepressant use in adult cancer survivors in United States by NHANES data cycles.

patients; a cut-off score of 8 points could provide a sensitivity of 93% and a specificity of 81% to identify major depressive disorders in cancer patients (18). Participants who skipped one of the nine questions were included with the missing score of the question replaced by the average score of the other eight questions (19). A patient was considered to be depressed if the total score of PHQ-9 is eight points or higher.

Study population

To examine antidepressant use pattern, the study population included 2,590 adults aged 20 years or older who completed the NHANES interview and responded "yes" to the question "have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?"

To examine disparities in antidepressant use, the study included 422 cancer survivors who reported antidepressant use and completed a depression assessment at the mobile examination center, and the study then compared these patients with 230 cancer survivors who did not use antidepressants but were diagnosed with depression from the PHQ-9 questionnaire.

Statistical analysis

SAS 9.4 (SAS Institute, Cary, NC, USA) was used for statistical analysis. 9.2 years of sample weight was applied with SAS Survey procedures being used to account for the complex multi-stage NHANES study design (13). Prevalence of antidepressant use in cancer survivors was estimated by NHANES data cycles, followed by a descriptive analysis by the class of antidepressants. To assess potential disparity in antidepressant use due to social-demographic characteristics or access to healthcare, analysis was restricted to a group of participants who also completed the depression assessment, with a comparison between antidepressant users and those who did not use antidepressants but were diagnosed with depression, using multivariate logistic regression for survey data with all variables related to social-demographic characteristics and access to healthcare included in the model. Frequency data were presented as n (weighted n, weighted percentage). Results from logistic regression were presented as adjusted odds ratio (aOR) with their 99% confidence intervals (CI) to account for possible multiplicity issues in the model.

Results

Antidepressant use pattern

Among 2,590 adult cancer survivors from NHANES 2011-2020, 491 patients reported antidepressant use; the weighted number of adult cancer survivors was 25594234 and the weighted number of antidepressant users were 5460460. The overall prevalence of antidepressant use among adult cancer survivors was 21.33% (standard error 0.98%). Prevalence of antidepressant use in difference NHANES data cycles is presented in Figure 1. The prevalence varied between 16.43% (from NHANES 2015–2016) and 25.67% (from NHANES 2013–2014) without a significant linear trend over the time period examined in the study. When data were pooled together, selective serotonin reuptake inhibitors were the most common type of antidepressants used in this population, followed by serotonin and norepinephrine reupdate inhibitors, phenylpiperazine, tricyclic antidepressants, tetracyclic antidepressants, and monoamine oxidase inhibitors (Table 1).

TABLE 1 The type of antidepressant medications used by adult cancer survivors, NHANES 2011–2020.

Antidepressant drug class	Number of users	Weighted number of users	Percent in antidepressant users (standard error)
Selective serotonin reuptake inhibitors	283	30,74,202	56.30% (2.78%)
Serotonin and norepinephrine reupdate inhibitors	88	11,34,279	20.77% (2.74%)
Phenylpiperazines	67	7,87,278	14.42% (1.83%)
Tricyclic antidepressants	63	6,07,845	11.13% (1.69%)
Tetracyclic antidepressants	24	2,44,579	4.48% (1.00%)
Monoamine oxidase inhibitors	2	19,027	0.35% (0.31%)
Miscellaneous	46	6,20,054	11.35% (2.25%)

Social-demographic characteristics and access to healthcare by antidepressant use

Among adult cancer survivors who completed a depression assessment; 422 (weighted sample size 5212240) used antidepressants and 230 (weighted sample size 1819723) had depression but did not use any antidepressants. Comparison of social-demographic characteristics and access to healthcare between these two groups is presented in Table 2. Age, gender, race/ethnicity, marital status, education, and having a routine place to go for healthcare are significantly associated with antidepressant use in cancer survivors (all $P < 0.05$). Specifically, younger patients, male patients, racial minority groups, those widowed or divorced or separated, those with high school diploma or lower education, and those without a routine place to go for healthcare are less likely to use antidepressants even though they were diagnosed with depression.

Disparities in antidepressant use

Table 3 presents results from multivariate logistic regression analysis for associations between use of antidepressants and social-demographic characteristics and access to healthcare. Results revealed that social-demographic characteristics such as gender, race/ethnicity, and marital status were significantly associated with antidepressant use. For example, female patients were more likely to use antidepressants than male patients (aOR = 3.45, 99% CI = [1.43, 8.32]). Compared to non-Hispanic white patients, various other race/ethnic groups, including non-Hispanic black, Hispanics, and Asian, were 76–96% less likely to use antidepressants. Also, patients who were widowed or divorced or separated were less likely to use antidepressants than patients who were married or living with partner (aOR = 0.39, 99% CI = [0.17, 0.91]). For access to healthcare, those without a routine place to go for healthcare were less likely to use antidepressants despite being depressed (aOR = 0.13, 99% CI = [0.03, 0.50]), respectively. No significant association was found for age, income level, education, or health insurance coverage in the multivariate logistic regression analysis.

Discussion

Results from the present study indicated that ∼1 in every 5 cancer patients were using antidepressants in 2011–2020. Disparities in antidepressant use by social-demographic characteristics and access to healthcare were found; for example, among these with depression, racial minority cancer patients were less likely to use antidepressants than non-Hispanic white patients; those without a routine place to go for healthcare were also less likely to use antidepressants.

The prevalence of antidepressant use in US cancer patients was slightly increased in the past decade, compared to 18.3% in 1999–2012 as reported previously (8). The prevalence is also higher than that in the general US population (20, 21), which is likely due to a higher rate of depression in cancer patients. About 8% of US adults reported depressive symptoms (22) whereas depression could be much more common in cancer patients. For example, a review on prevalence of depression in cancer patients reported a median prevalence ranging from 15 to 29% (23). The prevalence of depression defined by PHQ-9 in this pooled study population was found to be 14.2%. When examined by NHANES data cycles, the prevalence varied from 10.7% (from NHANES 2015–2016) to 16.1% (from NHANES 2013–2014) in the past decade (Supplementary Figure 1). This indicates the prevalence of depression in cancer patients in the present study was at the lower end of the spectrum when compared to data from the published review (23). This is likely because PHQ-9 only accessed depressive symptoms over the past 2 weeks, leading to an underestimate of the prevalence.

While most previous studies on disparities of antidepressant use in cancer patients did not report the type of antidepressants used, the present study also found selective serotonin reuptake

TABLE 2 Social-demographic characteristics and access to healthcare by antidepressant use in adult cancer survivors in the United States.

	Those who used antidepressants ($N = 422$) Weighted $N = 52,12,240$	Those with depression diagnosis but without antidepressant use ($N = 230$) Weighted $N = 18,19,723$	Chi-square test P-value
Age (years)			0.031
20–40	22 (2,35,170, 4.5%)	18 (2,14,337, 11.8%)	
40–65	170 (25,45,749, 48.8%)	101 (8,46,278, 46.5%)	
65–79	153 (17,54,435, 33.7%)	80 (5,57,990, 30.7%)	
≥80	77 (6,76,886, 13.0%)	31 (2,01,118, 11.1%)	
Gender			0.038
Male	132 (15,46,934, 29.7%)	92 (7,39,787, 40.7%)	
Female	290 (36,65,306, 70.3%)	138 (10,79,936, 59.3%)	
Race/Ethnicity			<0.001
Non-hispanic white	311 (46,32,167, 88.9%)	104 (12,64,167, 69.5%)	
Non-hispanic black	42 (1,56,989, 3.0%)	60 (2,12,783, 11.7%)	
Hispanics	42 (1,55,023, 3.0%)	40 (1,66,536, 9.2%)	
Asian	6 (24,490, 0.5%)	15 (65,185, 3.6%)	
Other, including multi-racial	21 (2,43,571, 4.7%)	11 (1,11,052, 6.1%)	
Ratio of family income to poverty			0.100
≤1.85	170 (14,40,468, 30.4%)	124 (7,11,798, 42.4%)	
1.86–3.49	107 (14,12,380, 29.8%)	46 (4,80,294, 28.6%)	
≥3.50	104 (18,887,56, 39.8%)	40 (4,88,654, 29.1%)	
Marital status			0.034
Married/living with partner	219 (32,03,316, 61.5%)	100 (8,25,122, 45.6%)	
Widowed/divorced/separated	166 (15,97,973, 30.7%)	100 (7,99,414, 44.2%)	
Never married	37 (4,10,951, 7.9%)	29 (1,86,115, 10.3%)	
Highest education			0.021
High school diploma or lower	158 (16,38,422, 31.4%)	119 (8,36,949, 46.1%)	
Associate degree	165 (19,50,088, 37.4%)	71 (5,82,490, 32.1%)	
College degree or higher	99 (16,23,729, 31.2%)	39 (3,97,892, 21.9%)	
Covered by health insurance			0.059
Yes	408 (49,74,857, 95.4%)	205 (16,00,731, 89.0%)	
No	14 (23,73,83, 4.6%)	23 (1,97,093, 11.0%)	
Routine place to go for healthcare			<0.001
Yes	411 (50,54,483, 97.0%)	206 (15,08,722, 82.9%)	
No	11 (1,57,757, 3.0%)	24 (3,11,001, 17.1%)	

Data were presented as sample size (weighted sample size, weighted percentage). Counts for certain variables may not add to total number due to missing values.

inhibitors are the most common type of antidepressants used by cancer patients, which is similar to findings from a previous systematic review on prescribing patterns for cancer patients globally (24) as well as results from patients with depressive disorders in the US (25). With regards to efficacy of antidepressant use in cancer patients, a previous review summarized preliminary evidence from a limited number of randomized controlled trials and suggests they may be able to alleviate depression symptoms (26), however, a recent systematic review concluded a very low certainty evidence on benefits due to the lack of high-quality clinical trials (27). Future studies addressing this urgent need are warranted.

Race/ethnicity was found to be a major predictor among demographic characteristics for antidepressant use in US cancer patients. This is similar to results from previous studies with local or non-nationally representative samples. For example, Parikh et al. found African American patients with prostate cancer who developed depression after cancer diagnosis were less likely to receive antidepressant prescription than White

TABLE 3 Multivariate logistic regression of antidepressant use (yes vs. no but with depression diagnosis) in adult cancer survivors in the United States.

	Adjusted odds ratio with 99% confidence interval
Age (years)	
20–40	Reference
40–65	2.45 (0.72, 8.32)
65–79	2.14 (0.61, 7.47)
≥80	2.47 (0.52, 11.72)
Gender	
Male	Reference
Female	3.45 (1.43, 8.32)
Race/Ethnicity	
Non-Hispanic White	Reference
Non-Hispanic Black	0.19 (0.09, 0.43)
Hispanics	0.24 (0.09, 0.60)
Asian	0.04 (0.01, 0.21)
Other, including multi-racial	0.68 (0.21, 2.15)
Ratio of family income to poverty	
≤1.85	Reference
1.86–3.49	0.99 (0.42, 2.34)
≥3.50	1.23 (0.52, 2.87)
Marital status	
Married/living with partner	Reference
Widowed/divorced/separated	0.39 (0.17, 0.91)
Never married	0.76 (0.23, 2.53)
Highest education	
High school diploma or lower	Reference
Associate degree	1.64 (0.94, 2.87)
College degree or higher	1.65 (0.64, 4.24)
Covered by health insurance	
Yes	Reference
No	0.36 (0.07, 1.77)
Routine place to go for healthcare	
Yes	Reference
No	0.13 (0.03, 0.50)

All of these variables were included in the multivariate logistic regression model.

patients (4); similarly, elderly African American patients (28), or other minorities in race (29) were less likely to be prescribed with antidepressants than elderly white patients. This phenomenon of lower antidepressant use in these racial minority groups requires attentions from medical practitioners and healthcare policy makers because studies have shown a higher prevalence of depression following cancer diagnosis in these racial minority groups (4, 30).

Consistent with results in the general adult population (21), female patients were more likely to use antidepressants in the present study. It was also found those who were widowed or divorced were less likely to use antidepressants, similar to a previous study that compared cancer patients with general adult population (9). Nonetheless, income levels were not associated with antidepressant use from adjusted logistic regression analysis. Previous studies have shown a higher prevalence of depression in cancer patients from lower income families (31, 32); the lack of significant association with income may be partly explained by availabilities of federal insurance coverage such as Medicaid to assist with healthcare cost for families with lower income, or due to unmeasured confounding factors. Analysis of antidepressant cost in the US in 2014–2015 revealed that majority of antidepressants were available in a generic form in the US market with an average cost per generic prescription of $57 (33), which was relatively affordable with insurance coverage. Nonetheless, due to lack of information, it was not known whether there was a significant association between antidepressant use with the type of insurance; although comparison between cancer patients and adults without cancer diagnosis in a previous study revealed those with public insurance were more likely to take antidepressants than those with private insurance (9). Lacking a routine place to go for healthcare is associated with less likelihood of antidepressant use in the study. Despite governmental effort for increased health insurance coverage in the United States, the study revealed that 17% of patients who had depression but not treated with antidepressants did not have a routine place to go for healthcare. This highlights the need for better implementation of healthcare policy to eliminate the disparities in access to healthcare at the national level. While the impact on antidepressant use rate or the prevalence of depression is yet to be examined when such policies are implemented, effort should also be made to address known barriers such as uncertainty about treatment and cost (34) for increased adoption of treatment strategies in managing mental health problems in cancer patients.

There are several limitations in the study. First, PHQ-9 was used to define depression in the study population. While it is a valid screening tool for depression in cancer patients, it only measured self-reported symptoms over the past 2 weeks, and there was no baseline diagnostic data prior to antidepressant prescription available in the NHANES data. There were patients who were using antidepressants but not depressed according to results from PHQ-9 at the time of the study. This is likely because these patients may have started the medication due to an earlier diagnosis and after taking the medication for a period of time, their depressive symptoms may have been alleviated, leading to a lower score in PHQ-9 at the time of NHANES data collection. Comparisons of characteristics of antidepressant users by PHQ-9 scores were presented in Supplementary Table 2; those with a PHQ-9 score <8 were more likely to be younger, from low-income families, widowed or divorced or separated, and less likely to have a college or higher degree or health insurance

coverage. Second, medication was self-reported in NHANES with medication container being verified by the interviewer when possible; the data was still subject to potential under-reporting. However, data on medication use for depression in NHANES has been validated and allows investigation of antidepressant use pattern at the national level (35). Third, not all patients with depression need to be treated with prescriptive antidepressants; information on over-the-counter medications and psychotherapy management for depression were not available. The prevalence of antidepressant use may be an underestimate for prevalence of treatment for depression in cancer patients. Fourth, as a cross-sectional survey, the NHANES does not conduct any follow up studies for health outcomes; as such, the effect of antidepressant use on quality of life or symptom alleviation in this population was unknown. Fifth, the NHANES 2019–2020 did not include any data during the COVID-19 pandemic; it would be worth investigating how the pandemic may have affected mental health conditions of cancer patients and their access to healthcare, and whether the observed disparities were increased as a result from the pandemic. Despite these limitations, the study was the first study to our knowledge that examined disparities in antidepressant use in US cancer survivors using a nationally representative survey data; its results could be very relevant and helpful from a public health perspective for resources allocation and healthcare policy reforms. The findings highlight the critical need to address existing disparities in managing mental health problems in cancer patients and to eliminate inequality on access to healthcare in the US, particularly in racial minority groups. The study also highlights the increasing need on awareness of mental health problems in cancer patients while providing insights for healthcare practitioners for screening of depression in cancer patients and discussion of treatment options with those suffered from both conditions.

In conclusion, social-demographic characteristics and access to healthcare are determinants for pharmacotherapy of depression in US cancer patients. Policy makers and healthcare practitioners should be aware of this disparity and related barriers, and work together to find a solution to eliminate preventable inequalities and improve the health of every patient.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://www.cdc.gov/nchs/nhanes/index.htm.

Ethics statement

The studies involving human participants were reviewed and approved by the NCHS Ethics Review Board for NHANES protocol. The present study used publicly available de-identified data from NHANES and was exempt from IRB review. The participants provided their written informed consent to participate in the NHANES.

Author contributions

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

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Conflict of interest

Author YZ was employed by the company Wayzek Science.

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1000000/full#supplementary-material

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Association between socioeconomic status and arteriosclerotic cardiovascular disease risk and cause-specific and all-cause mortality: Data from the 2005–2018 National Health and Nutrition Examination Survey

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Background: Morbidity and mortality of arteriosclerotic cardiovascular disease (ASCVD) varied according to socioeconomic status (SES), and evidence on the association between SES and ASCVD risk, and cause-specific and all-cause mortality was nevertheless lacking in large-scale or population-based studies.

Methods: A multicycle cross-sectional design and mortality linkage study was conducted using data from Continuous National Health and Nutrition Examination Survey (NHANES) in the United States, including public use linked mortality follow-up files through December 31, 2019. Poverty income ratio (PIR) served as a SES index. A series of weighted Logistic regressions and Cox proportional hazards regressions were used to investigate the association between the SES and the risk of ASCVD and mortality, respectively.

Results: The study sample was comprised of 30,040 participants aged 20–85 years old during the 2005–2018 period. Weighted Logistic regression models consistently indicated significant relationship between people experiencing poverty and increased risk of ASCVD, and linear trend tests were all statistically significant (all P for trend < 0.001). Additionally, weighted Cox regression analysis consistently demonstrated that the hazards of cause-specific and all-cause mortality increased, with the decrease of each additional income level, and trend analyses indicated similar results (all P for trend < 0.001).

Conclusions: Our study confirmed that the SES was strongly linked to living with ASCVD, and cause-specific and all-cause mortality, even after adjusting for other factors that could impact risk, such as the American Heart Association (AHA)'s Life's Simple 7 cardiovascular health score and variables of age, sex, marital status, education, and depression severity.

KEYWORDS

arteriosclerotic cardiovascular disease, socioeconomic, poverty income ratio, mortality, National Health and Nutrition Examination Survey (NHANES)

Introduction

At the global level, cardiovascular disease (CVD) was a significant public health issue, accounting for around 30% of the yearly global mortality rate (~17.6 million persons per year) and 10% of the global disease burden (1, 2). And at a country level, CVD morbidity and mortality have declined in several high-income nations, but they continued to rise significantly in low- and middle-income nations in recent years (3). CVD was the leading cause of death in the United States, accounting for almost one-third of all deaths (4). In 2009, it was estimated that the total direct and indirect expenses of CVD in the United States were $312.6 billion (5). At the individual level, behavioral, medicinal, and/or surgical treatments were frequently required in response to these symptoms associated with that condition, which can adversely affect one's quality of life.

Morbidity and mortality of CVD varied according to SES (6). Even though most nations and areas have experienced socioeconomic progress and greatly enhanced the people's material living standards over the past few decades, the bulk of the nation's massive wealth gap still exists (7). From 2010 to 2018, CVD mortality in the general U.S. population remained stable, while the total number of CVD deaths rose (8). The reason for this was likely to be the lack of improvement in health and nutrition among people experiencing poverty, who were more susceptible to ASCVD (9). As a consequence of this health inequality, there may be differences in individual characteristics such as behavior or genetics, and more contextual factors such as the social and political environment ("the causes of the causes") as well as the interaction between them (10). Even though ASCVD risk was associated with a higher burden of traditional risk factors among individuals with low SES. However, risk factor profiles may not fully account for the observed differences, suggesting that low SES itself and other upstream characteristics may be independent risk factors for ASCVD (11).

Therefore, large-scale and population-based study was conducted to assess the association between SES and ASCVD risk and cause-specific and all-cause mortality, utilizing data from the NHANES.

Materials and methods

Database

The National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) launched numerous cycles of the United States cross-sectional Continuous NHANES from 2005 to 2018, providing public use linked mortality follow-up files through December 31, 2019 (12). In addition, the National Center for Health Statistics (NCHS) has connected many demographic surveys to death certificate information from the National Death Index (NDI) (13).

The NHANES utilized a complex, stratified, multistage, probability cluster design to create a nationally representative survey of the health and nutritional status of the non-institutionalized civilian population in the United States, with detailed information available in the NHANES survey methods and analytic guidelines (14). Additionally, data on the nutritional health and condition of non-institutionalized civilians in the US population were acquired *via* a series of home interviews, examinations, and laboratory measurements.

The public-use versions of the linked mortality follow-up files provided the mortality data for adult participants, which consisted of mortality follow-up data from the date of survey participation through December 31, 2019, after the files have been processed to minimize the likelihood of participant identification (13).

Study design and population

This was a cross-sectional study. The Continuous NHANES was used to collect data from 2005 to 2018 in 2-year increments for the initial sample. Only participants with available demographic data, and who answered the self-reported question medical conditions questionnaire (MCQ)160C—"Ever told you had coronary heart disease (CHD)?," MCQ160D—Ever told you had angina/angina pectoris, MCQ160E—"Ever told you had heart attack," or MCQ160F—"Ever told you had a stroke?" on the medical conditions section were included. Responses

marked as "missing," "refused," or "do not know" were regarded as missing in the original NHANES surveys. Participants who lacked information for one of the study covariates specified below were disqualified from the statistical analysis of data.

Data collection and weight selection

Demographic data such as age, sex, marital status, educational level, and PIR were collected using the Sample Person and Family Demographics questionnaires. For adults 20 and older, questions about smoking status and certain comorbid conditions were asked, in the home, by trained interviewers using the Computer-Assisted Personal Interviewing (CAPI) system.

Trained health technicians and interviewers were arranged to deliver standardized body measurements [e.g., blood pressure, body mass index (BMI), et al.] and questionnaires [e.g., depression severity, et al.] to survey participants at the mobile examination center (MEC). Specifically, after resting quietly in a sitting position for 5 min and determining the maximum inflation level (MIL), three consecutive blood pressure readings are obtained. If a blood pressure measurement is interrupted or incomplete, a fourth attempt may be made. All blood pressure determinations (systolic and diastolic) are taken in the MEC. The body measures data were collected in the MEC, and BMI was calculated as weight in kilograms divided by height in meters squared, and then rounded to one decimal place. Depression was measured using the Patient Health Questionnaire (PHQ-9), a nine-item screening instrument that asks questions about the frequency of symptoms of depression over the past 2 weeks. A final follow-up question assesses the overall impairment of the depressive symptoms. Response categories "not at all," "several days," "more than half the days," and "nearly every day" were given a score ranging from 0 to 3. A total score was calculated ranging from 0 to 27.

The NHANES 2005–2018 MEC exam data weights were used in all analyses to take stratification and clustering into account because of the complex sample design.

Primary study variables

Assessment of ASCVD

"Has a doctor or other health professional ever told {you/SP} that {you/s/he}... had a coronary heart disease/angina, also called angina pectoris/heart attack (also called myocardial infarction)/stroke?" was a question on the medical conditions section of the household questionnaires *via* home interview, and those who answered "yes" were deemed to have a history of ASCVD.

Independent variable

Assessment of SES

PIR—an index for the ratio of family income to poverty served as a SES index in our study. The Department of Health and Human Services' (HHS) poverty guidelines were used as the poverty measure to calculate this index. These guidelines are issued each year, in the Federal Register, for determining financial eligibility for certain federal programs such as Head Start, Supplemental Nutrition Assistance Program (SNAP) (formerly Food Stamp Program), Special Supplemental Nutrition Program for Women, Infants, and Children (WIC), and the National School Lunch Program.

PIR was calculated by dividing family income by the poverty guidelines, specific to family size, as well as the appropriate year and state. The values were not computed if the income screener information [Income questionnaire (INQ) 220: <$20,000 or ≥$20,000] was the only family income information reported. If family income was reported as a range value, the midpoint of the range was used to compute the variable. The values of PIR at or above 5.00 were coded as 5.00 or more because of disclosure concerns. The values were not computed if the family income data was missing.

There were three distinct categories of *SES*: low income (PIR < 1.3), middle income (PIR $= 1.3$–3.5), and high income (PIR ≥ 3.5) (15, 16).

Covariates and confounders

It was necessary to account for a number of possible confounding factors. Age and Life's Simple 7 cardiovascular health score were included in the analysis as continuous variables. The "Life's Simple 7" criteria, devised by the AHA to describe ideal cardiovascular health, included not smoking, regular physical activity, healthy diet, keeping normal weight, and controlling cholesterol, blood pressure, and blood glucose levels. The Life's Simple 7 cardiovascular health score varied from 0 to 14 (0 was the worst score and 14 was the optimal score) and was calculated by adding the number of ideal health metrics achieved. The sex was categorized as male and female. The marital status category included married, living with a partner, separated, divorced, widowed, and never married. The educational background was specified as college graduate or above, some college or AA degree, high school graduate, 9–11th grade, <9th grade. The categories for smoking status were former, current, and never. BMI was classified as low (i.e., <18.5), normal (i.e., 18.5–25), overweight (i.e., ≥25) (17). The PHQ-9 was used to determine the severity of depression; scores of 5, 10, 15, and 20 were used as the thresholds for mild, moderate, moderately severe, and severe depression, respectively (18, 19).

Accumulating evidence has shown that there were several disparities in risk factors and ASCVD among the general populations, including discrepancy in age (20, 21), sex (22–24), marital status (25, 26), educational level (27), depression severity (28), and the American Heart Association's Life's Simple 7 cardiovascular health score (29, 30).

Comorbid conditions

Information on comorbidities was self-reported by participants. Regarding the question "Have you ever been told by a doctor or health professional that you have …?" persons who answered "yes" were perceived as having the following comorbidities: congestive heart failure (CHF) and arthritis.

Hypertension was diagnosed by: blood pressure/cholesterol (BPQ) 020: ever told you had high blood pressure; BPQ 030: told had high blood pressure−2+ times; BPQ 040a: taking prescription for hypertension; using anti-hypertension drug; judging hypertension on average blood pressure. And average blood pressure was calculated by the following protocol: 1. If only one blood pressure reading was obtained, that reading is the average. 2. If there is more than one blood pressure reading, the first reading is always excluded from the average. 3. If only two blood pressure readings were obtained, the second blood pressure reading is the average. 4. If all diastolic readings were zero, then the average would be zero.

Chronic obstructive pulmonary disease (COPD) was characterized by a reduction in expiratory air flow rates. This is defined in spirometry as a reduction in the ratio of the expiratory volume measured in the 1st second of a forceful exhalation (FEV_1) to the total volume of air exhaled in a complete forced expiration (FVC), the FVC being an estimate of the individual's effective lung volume. Eligible participants performed an initial or "baseline" 1st test spirometry examination. Then a selected subsample of participants whose Baseline 1st Test Spirometry results showed a FEV_1/FVC ratio below the lower limit of normal and/or below 70% were asked to repeat spirometry after inhaling a β_2-adrenergic bronchodilator medication to open up their airways. This helps differentiate asthma from COPD (31). Asthma patients usually show improvements in post-bronchodilator spirometry testing, while patients with COPD exhibit little, if any, response to the medication. Spirometric testing using β_2-adrenergic bronchodilator is routinely employed by clinicians to diagnose asthma in both children and adults, and current clinical practice guidelines (32) consider post-bronchodilator spirometry testing is essential for the initial diagnosis of asthma. Thus, COPD was diagnosed by: $FEV_1/FVC < 0.7$ post-bronchodilator; MCQ160p: ever told you had emphysema; using drug: selective phosphodiesterase-4 inhibitors, mast cell stabilizers, leukotriene modifiers, inhaled corticosteroids, age above 40, with smoke history, or chronic bronchitis.

Other than that, Parkinson's disease was diagnosed by taking anti-Parkinson agents; and the diagnostic criteria for diabetes are: doctor told you to have diabetes; glycohemoglobin HbA1c (%) > 6.5; random blood glucose (mmol/L) ≥11.1; 2-h oral glucose tolerance test (OGTT) blood glucose (mmol/L) ≥11.1; use of diabetes medication or insulin.

Follow-up and outcomes

The period of follow-up lasted from the date of the interview through the last follow-up time, December 31, 2019, or the date of death, whichever came first. Records from the NDI provided information on these included participants' causes of death. The endpoints for this study were all-cause mortality, which encompassed all known and unknown causes; cardiovascular mortality, which encompassed causes of diseases of heart and cerebrovascular diseases death.

Statistical analysis

For categorical data (i.e., Sex, Marital Status, Educational level, Smoking Status, Depression Severity, BMI, CHF, CHD, Hypertension, ASCVD, Angina, Heart Attack, Stroke, Arthritis, COPD, Diabetes, PD), we used weighted proportions and corresponding 95% confidence intervals (CIs), while for continuous data (i.e., Age, PIR, the American Heart Association's Life's Simple 7 cardiovascular health score), we used weighted means and associated standard deviations (SDs). Design-based χ^2-tests and Analysis of variance (ANOVA) were used to investigate whether categorical and continuous variables were associated with SES, respectively. The aforementioned χ^2-test and ANOVA were survey-weighted models.

The weighted Kaplan–Meier curves were used to present the rate of cause-specific and all-cause mortality. Survival rates by SES were compared using the Mantel-Cox Log-rank test. The survival probabilities were estimated as the time intervals from the date of interview to the last follow-up time, December 31, 2019, or the date of death.

In order to find the association between SES and ASCVD risk and cause-specific and all-cause mortality, we conducted a sensitivity analysis by gradually adjusting for potential confounders. Specific details are described below: a series of weighted Logistic regressions analyses were conducted to assess the association of ASCVD risk with SES in various models following adjusting for potential confounders. Gradually, covariates were placed into the multivariable model by a priori selection. Crude and adjusted odds ratios (OR) and their 95% CIs between ASCVD risk and SES were reported. Similarly, a series of weighted Cox regressions analyses were conducted to estimate the associations between SES and the probabilities of cause-specific and all-cause death, after controlling for possible

confounding factors in various models. The correlation between the SES and outcomes was provided as a crude and adjusted hazard ratio (HR) and its 95% CIs.

Our study defined the "high income," which corresponded with the PIR $\geq$ 3.5, as the reference group. Trend analyses were conducted by entering the SES as continuous variable and rerunning the corresponding regression models.

NHANES (2012) has reported the warning on the analysis combing data across 2005–2006 and 2007 later due to survey design changes (33). Thus, sensitivity analysis on the estimates was performed. For the 2005–2006 and 2007–2018 survey periods, weighted Logistic regressions analyses were conducted to assess the association of ASCVD risk with SES in full adjusted models, respectively.

For statistical analysis, R (version 4.1.2; https://www.R-project.org) was utilized. Sampling design elements include the primary sampling units (PSUs), strata, and weights. However, ignoring the design elements that are included can often lead to inaccurate point estimates and/or inaccurate standard errors. Thus, the complexity of the sampling design was taken into account in each analysis by specifying PSUs, strata, and weights using the R package "survey" (version 4.1-1). We used MEC exam weights for all sample estimations (34–36). A two-sided $P < 0.05$ was considered statistically significant for testing the hypotheses of the study.

Results

Participant characteristics

According to inclusion and exclusion criteria, the unweighted sample for the final analysis consisted of 30,040 participants aged 20–85 from 2005 to 2018, representing 185.16 million non-institutionalized United States residents. The number of participants in the low income (weighted prevalence = 20.60%, 95% CI = 19.44–21.76%), middle income (weighted prevalence = 35.72%, 95% CI = 33.79–37.66%), and high income (weighted prevalence = 43.68%, 95% CI = 40.70–46.66%) levels were 9,232, 11,419, 9,389, respectively. while 2,929 participants (weighted prevalence = 7.68%, 95% CI = 7.14–8.22%) had ASCVD. These corresponded to 38.14, 66.14, 80.88, and 14.22 million adults in the general population, respectively. Characteristics of the study participants according to SES were presented in Table 1. Statistically significant differences were found for SES regarding socio-demographic, the physical and mental health-related factors, and comorbid conditions. Of note, Participants with lower incomes were characterized by younger, female, lower Life's Simple 7 cardiovascular health scores, low BMI, and current smokers, as well as higher rates of mild to severe depressive symptoms.

The association of SES with ASCVD risk

Results of weighted Logistic regressions analyses of SES in relation to the risk of the ASCVD were displayed in Table 2. There were significant association between SES and increased risk of the ASCVD in model 1 (unadjusted model), model 2 [adjusted for age (continuous), sex (male or female), and marital status (Married, Living with partner, Separated, Divorced, Widowed, Never married), educational level (divided into <9th grade, 9–11th grade, high school graduate, some college or AA degree, college graduate or above), depression severity (None, Mild, Moderate, Moderately Severe, Severe)], and model 3 [further adjusted for the American Heart Association's Life's Simple 7 (continuous)]. For example, the result in model 3 showed that participants with the middle and low income, the risks of having ASCVD increased by 31% (OR = 1.31, 95% CI = 1.13–1.51), 80% (OR = 1.80, 95% CI = 1.55–2.10), respectively, compared with participants in the high-income level. And there was statistical significance in all of the trend analyses (all P for trend < 0.001).

Survival analysis

The leading causes of death in different SES were listed in Table 3. All-cause, cardiovascular, or malignant neoplasm mortality rates were 4.49, 1.20, and 1.36% for participants with high income levels, respectively; among middle-income leveled participants, mortality rates for all-causes, cardiovascular diseases, or malignant neoplasms were 9.34, 2.81, and 2.26%, respectively; and the prevalence of all-cause, cardiovascular, or malignant neoplasms mortality was 10.19, 2.85, and, 2.24% for low-income participants, respectively;

The Kaplan-Meier curves for all-cause, cardiovascular, and malignant neoplasms mortality were presented in Figures 1A–C, respectively. The median follow-up time from the date of interview to the last follow-up time, December 31, 2019, or the date of death was 89.00 months (ranged from 1 to 180 months). Moreover, the median age of participants at the date of interview was 49 years old (ranged from 20 to 85 years old), and the median age of participants at the last follow-up time, December 31, 2019, or the date of death was 57 years old (ranged from 21 to 99 years old). The upper red survival curve for high-income participants were all above the lower curve including blue survival curve for middle-income participants and green survival curve for low-income participants across the entire 180 months of follow-up (all log rank $P < 0.001$), visually indicating that survival probability of high incomes was greater than both middle- and low-income groups, suggesting a survival benefit.

The results from a series of weighted Cox regressions analyses in Table 4 consistently indicated that low-income participants were at a higher risk of all-cause death. For instance, A weighted multivariable Cox regression model 3 showed that

TABLE 1 Baseline characteristics of study participants[a].

Characteristic	Total	High income	Middle income	Low income	*P*-value
Age	47.37 ± 0.24	48.57 ± 0.30	47.97 ± 0.32	43.79 ± 0.46	<0.0001
Poverty income ratio	3.04 ± 0.03	4.69 ± 0.01	2.32 ± 0.01	0.79 ± 0.01	<0.0001
Life's simple 7	8.23 ± 0.03	8.61 ± 0.04	8.01 ± 0.04	7.80 ± 0.06	<0.0001
Sex (%)					<0.0001
Male	49.26 (47.10, 51.42)	51.44 (50.48, 52.39)	48.57 (47.58, 49.56)	45.83 (44.70, 46.96)	
Female	50.74 (48.47, 53.01)	48.56 (47.61, 49.52)	51.43 (50.44, 52.42)	54.17 (53.04, 55.30)	
Marital status (%)					<0.0001
Married	55.62 (52.35, 58.89)	68.36 (66.80, 69.92)	52.37 (50.54, 54.20)	34.23 (32.32, 36.15)	
Living with partner	8.16 (7.54, 8.79)	5.73 (5.00, 6.46)	8.33 (7.56, 9.10)	13.04 (11.84, 14.25)	
Separated	2.36 (2.13, 2.59)	1.10 (0.84, 1.36)	2.38 (2.02, 2.73)	5.02 (4.39, 5.65)	
Divorced	10.58 (9.90, 11.27)	8.14 (7.47, 8.81)	11.82 (10.97, 12.66)	13.62 (12.44, 14.80)	
Widowed	5.50 (5.10, 5.89)	2.99 (2.58, 3.39)	7.19 (6.58, 7.80)	7.88 (7.15, 8.60)	
Never married	17.78 (16.79, 18.77)	13.69 (12.56, 14.82)	17.92 (16.59, 19.25)	26.21 (23.67, 28.75)	
Educational level (%)					<0.0001
College graduate or above	30.02 (27.65, 32.40)	49.44 (47.07, 51.82)	18.51 (17.00, 20.03)	8.80 (7.58, 10.02)	
Some college or AA degree	31.82 (30.28, 33.36)	30.08 (28.49, 31.67)	35.66 (34.29, 37.03)	28.84 (26.75, 30.93)	
High school graduate	23.37 (21.86, 24.88)	16.01 (14.75, 17.27)	29.12 (27.66, 30.58)	29.00 (27.35, 30.65)	
9–11th grade	10.12 (9.25, 11.00)	3.77 (3.10, 4.44)	11.60 (10.59, 12.61)	21.05 (19.48, 22.62)	
<9th grade	4.67 (4.22, 5.11)	0.70 (0.54, 0.87)	5.10 (4.47, 5.73)	12.31 (11.16, 13.45)	
Smoking status (%)					<0.0001
Never	54.58 (52.20, 56.95)	60.12 (58.60, 61.63)	52.11 (50.47, 53.74)	47.12 (45.10, 49.15)	
Former	25.09 (23.43, 26.74)	27.16 (25.77, 28.56)	26.08 (24.79, 27.37)	18.96 (17.83, 20.09)	
Current	20.33 (19.14, 21.53)	12.72 (11.69, 13.75)	21.81 (20.57, 23.05)	33.92 (31.85, 35.98)	
Depression severity (%)					<0.0001
None	77.20 (73.63, 80.76)	84.53 (83.62, 85.44)	75.26 (74.13, 76.39)	65.02 (63.55, 66.49)	
Mild	15.17 (14.43, 15.91)	11.52 (10.70, 12.34)	17.01 (16.06, 17.96)	19.71 (18.65, 20.77)	
Moderate	4.85 (4.45, 5.24)	2.79 (2.39, 3.20)	4.87 (4.36, 5.38)	9.15 (8.42, 9.89)	
Moderately severe	2.00 (1.78, 2.23)	0.85 (0.64, 1.05)	2.05 (1.70, 2.41)	4.37 (3.79, 4.94)	
Severe	0.78 (0.68, 0.89)	0.31 (0.18, 0.44)	0.81 (0.61, 1.01)	1.75 (1.41, 2.09)	
Body mass index (%)					<0.0001
Normal	28.10 (26.59, 29.61)	29.49 (28.03, 30.95)	26.58 (25.25, 27.90)	27.81 (26.28, 29.35)	
Overweight	70.38 (67.13, 73.63)	69.53 (67.99, 71.07)	71.78 (70.50, 73.07)	69.75 (68.07, 71.43)	
Low	1.51 (1.33, 1.70)	0.98 (0.71, 1.25)	1.64 (1.32, 1.95)	2.44 (1.98, 2.90)	
Comorbidity CHF (%)	2.23 (2.00, 2.46)	1.09 (0.87, 1.32)	2.96 (2.53, 3.39)	3.39 (2.91, 3.88)	<0.0001
Comorbidity CHD (%)	3.32 (2.95, 3.68)	2.86 (2.44, 3.28)	3.99 (3.47, 4.51)	3.12 (2.69, 3.54)	<0.001
Comorbidity hypertension (%)	38.08 (36.15, 40.01)	36.29 (34.70, 37.89)	40.04 (38.74, 41.34)	38.47 (36.81, 40.14)	<0.001
Comorbidity ASCVD (%)	7.68 (7.14, 8.22)	5.44 (4.94, 5.94)	9.13 (8.33, 9.92)	9.93 (9.17, 10.69)	<0.0001
Comorbidity angina (%)	2.14 (1.89, 2.39)	1.50 (1.19, 1.81)	2.59 (2.23, 2.96)	2.71 (2.33, 3.09)	<0.0001
Comorbidity heart attack (%)	3.26 (2.94, 3.58)	2.41 (2.01, 2.80)	3.59 (3.17, 4.01)	4.48 (3.95, 5.02)	<0.0001
Comorbidity stroke (%)	2.84 (2.60, 3.08)	1.55 (1.31, 1.80)	3.55 (3.09, 4.01)	4.34 (3.87, 4.81)	<0.0001
Comorbidity arthritis (%)	25.99 (24.44, 27.55)	24.82 (23.50, 26.15)	27.10 (25.76, 28.45)	26.55 (24.85, 28.26)	0.02
Comorbidity COPD (%)	4.55 (4.10, 5.01)	3.91 (3.37, 4.45)	4.72 (4.20, 5.25)	5.61 (4.83, 6.39)	<0.001
Comorbidity diabetes (%)					<0.0001
No	81.69 (78.06, 85.33)	84.29 (83.25, 85.33)	80.02 (78.87, 81.17)	79.10 (78.14, 80.05)	
Diabetes	13.37 (12.59, 14.14)	10.92 (10.03, 11.82)	14.91 (13.88, 15.94)	15.87 (14.92, 16.81)	
IGT	4.94 (4.54, 5.34)	4.79 (4.27, 5.31)	5.07 (4.48, 5.65)	5.03 (4.44, 5.63)	
Comorbidity PD (%)	0.94 (0.78, 1.10)	0.67 (0.46, 0.87)	1.10 (0.84, 1.36)	1.23 (0.93, 1.52)	0.003

[a]Data are expressed as weighted proportions and corresponding 95% confidence intervals for categorical variables and as weighted means and associated standard deviations (SDs) for continuous variables. Two-sided *P*s-values show results of univariate comparisons between different socioeconomic status. All categorical variables were tested with the χ^2-test. Continuous variables were tested with Analysis of variance (ANOVA). The aforementioned χ^2-test and ANOVA were survey-weighted models.

CHF, congestive heart failure; CHD, coronary heart disease; ASCVD, arteriosclerotic cardiovascular disease; COPD, chronic obstructive pulmonary disease; IGT, impaired glucose tolerance; PD, Parkinson's disease.

TABLE 2 Crude and adjusted association socioeconomic status and increased arteriosclerotic cardiovascular disease risk.

Model	Socioeconomic status (SES)			*P*-value for trend
	High income (%) = 20.60 (19.44, 21.76)	Middle income (%) = 35.72 (33.79, 37.66)	Low income (%) = 43.68 (40.70, 46.66)	
Model 1 (OR)	1.00 (Reference)	1.75 (1.53–2.00)	1.92 (1.69–2.17)	<0.001
P-values		<0.001	<0.001	
Model 2 (OR)	1.00 (Reference)	1.34 (1.16–1.55)	1.92 (1.65–2.23)	<0.001
P-values		<0.001	<0.001	
Model 3 (OR)	1.00 (Reference)	1.31 (1.13–1.51)	1.80 (1.55–2.10)	<0.001
P-values		<0.001	<0.001	

Model 1: Unadjusted model; Model 2: Adjusted for age (continuous), sex (male or female), and marital status (Married, Living with partner, Separated, Divorced, Widowed, Never married), educational level (divided into <9th grade, 9–11th grade, high school graduate, some college or AA degree, college graduate or above), depression severity (None, Mild, Moderate, Moderately Severe, Severe); Model 3: Further adjusted for the American Heart Association's Life's Simple 7 (continuous).
OR, odds ratio.

TABLE 3 The weighted prevalence of leading causes of death in different socioeconomic status.

Cause of death	High income	Middle income	Low income
Diseases of heart (%)	1.00	2.33	2.41
Cerebrovascular diseases (%)	0.20	0.48	0.44
Influenza and pneumonia (%)	0.08	0.12	0.15
Chronic lower respiratory diseases (%)	0.22	0.50	0.69
Nephritis, nephrotic syndrome and nephrosis (%)	0.02	0.18	0.23
Diabetes mellitus (%)	0.17	0.29	0.44
Malignant neoplasms (%)	1.36	2.26	2.24
Alzheimer's disease (%)	0.10	0.30	0.15
Accidents (unintentional injuries) (%)	0.19	0.33	0.36
All other causes (residual) (%)	1.15	2.55	3.08
All-cause (%)	4.49	9.34	10.19

after controlling for covariates, the hazards of all-cause death increased by 43% (HR = 1.43, 95% CI = 1.25–1.63) in middle income levels and 84% (HR = 1.84, 95% CI = 1.58–2.15) in low-income levels, compared to high income group. And trend analyses were all statistically significant (all *P* for trend < 0.001).

Similarly, a series of weighted Cox regressions analyses result in Table 5 consistently suggest that the hazards of cardiovascular mortality increased, with the decrease of each additional income level. Taking the weighted multivariable Cox regressions model 3 as an example, compared to high income group, the risks of cardiovascular death were increased by 43% (HR = 1.43, 95% CI = 1.13–1.81), and 81% (HR = 1.81, 95% CI = 1.41–2.33) for middle- and low-income participants, respectively, after multivariable adjustment. And statistical significance was found in all trend analyses (all *P* for trend < 0.001).

Likewise, the weighted Cox regressions analyses results were shown in Table 6, estimating the associations between the SES and the hazards of having malignant neoplasms mortality. A series of multivariable adjusted weighted Cox regressions consistently revealed that SES may contribute much to the risks of malignant neoplasms mortality. As a result of model 3, participants with middle and low income had increased hazards of malignant neoplasms mortality by 27% (HR = 1.27, 95% CI = 1.01–1.63) and 58% (HR = 1.58, 95% CI = 1.17–2.13), respectively, compared to participants with high income. And the trend analyses all showed statistical significance (all *P* for trend < 0.05).

Sensitivity analysis

Results of weighted Logistic regressions analyses of SES in relation to the risk of the ASCVD for the 2005–2006 and 2007–2018 survey periods were presented in Table 7. The result showed that participants with the middle and low income, the risks of having ASCVD increased by 42% (OR = 1.42, 95% CI = 1.10–1.83), 103% (OR = 2.03, 95% CI = 1.22–3.36) in NHANES 2005–2006, and 29% (OR = 1.29, 95% CI = 1.10–1.51), 77% (OR = 1.77, 95% CI = 1.51–2.07) in NHANES 2007–2018, respectively, compared with participants in the high-income level after full adjustment. And there was statistical significance in all of the trend analyses (all *P* for trend < 0.05).

Discussion

Participants with lower incomes, were younger, female, had lower Life's Simple 7 cardiovascular health scores, low BMI, and were current smokers, as well as higher rates of mild to severe

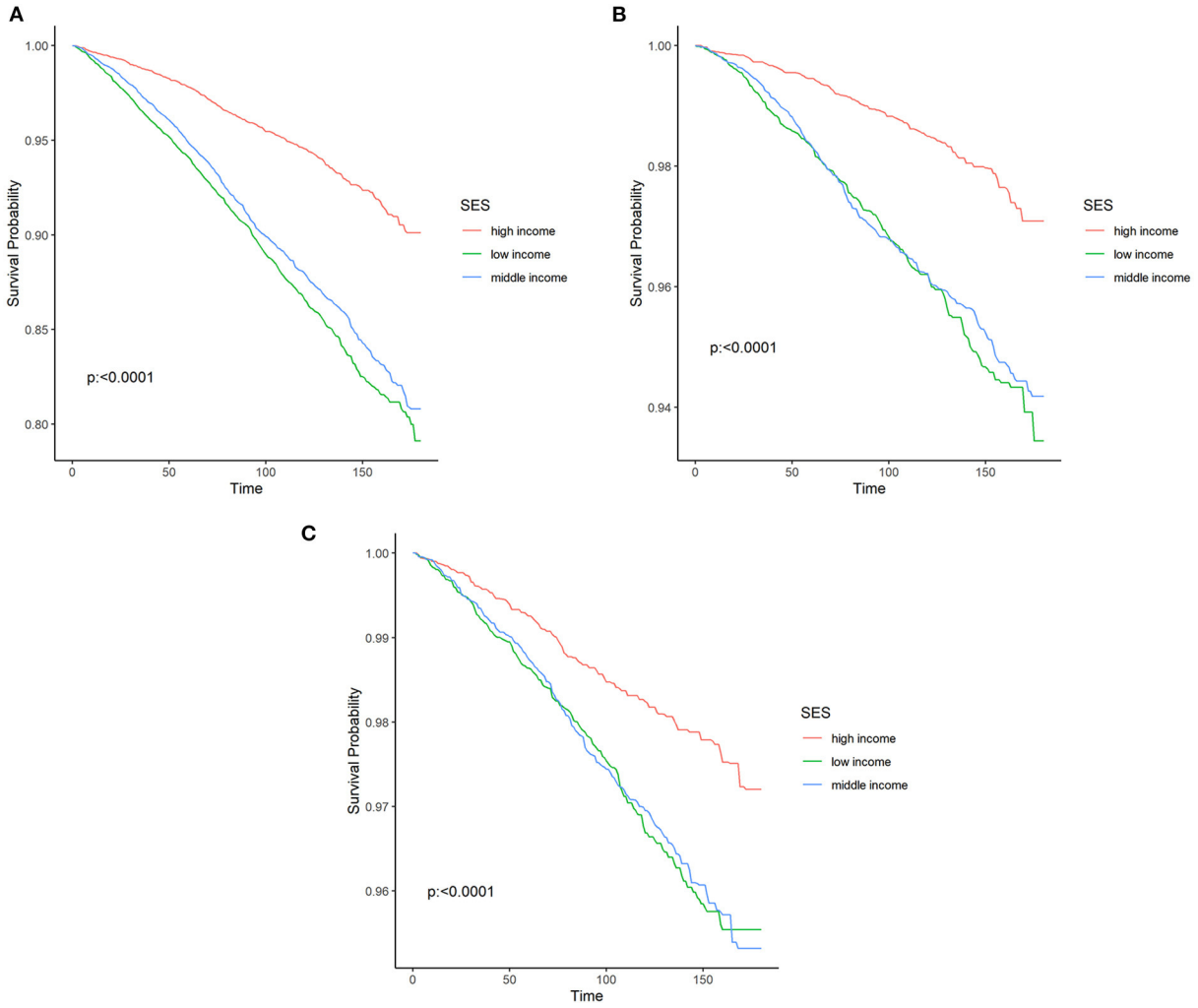

FIGURE 1
Kaplan–Meier curves were depicted to show the association of the socioeconomic status with all-cause **(A)**, cardiovascular **(B)**, malignant neoplasms **(C)** mortality, with follow-up in months. SES, socioeconomic status.

depressive symptoms, which was in agreement with previous research findings (6, 37).

The results of our study indicated that SES had a linear association with ASCVD risk and cause-specific and all-cause mortality, which were consistent with those of the following studies: In developed nations such as the United States, several recent studies have indicated that the ORs for the association between CVD risk and low- and middle-incomes over the high-incomes were 1.49 (95% CI = 1.16–1.91) and 1.27 (95% CI = 1.10–1.47), respectively. Adults with lower incomes had a greater risk of death from all causes than adults with a high SES (HR = 2.13, 95% CI = 1.90–2.38) (37). People with self-reported income in the lowest income bracket between the ages of 35 and 64 were twice as likely to die from myocardial infarction and CHD as those in the highest quartile (38). There were disparities in CHD mortality between men and women, but both were nearly twice as common in the low-income group compared to the high SES group. Moreover, Odutayo et al. reported that the cardiovascular risk decreased in the high-income group from 1999 to 2014, but not in the low-income group (39).

Similar findings were observed in developing nations: as one of the middle-income nations, China has more than 17 million CVD patients (40). Total CVD prevalence was lower in high- and middle-income regions than in low-income regions (P = 0.0064; 7.46, 7.42, and 8.36%, respectively) (41).

The strong effect of SES cannot entirely be explained by the dependence of CVD risk factors. For example, as evidenced in the Whitehall study, men with the lowest incomes have a 10-year CHD death risk 2.7 times that of their highest incomes, which has been reduced to 2.1 after adjusting for conventional risk

TABLE 4 Crude and adjusted association between socioeconomic status and all-cause mortality.

Model	Socioeconomic status (SES)			*P*-value for trend
	High income (%) = 20.60 (19.44, 21.76)	Middle income (%) = 35.72 (33.79, 37.66)	Low income (%) = 43.68 (40.70, 46.66)	
Model 1 (HR)	1.00 (Reference)	2.19 (1.92–2.49)	2.46 (2.15–2.82)	<0.001
P-values		<0.001	<0.001	
Model 2 (HR)	1.00 (Reference)	1.46 (1.28–1.66)	1.93 (1.66–2.25)	<0.001
P-values		<0.001	<0.001	
Model 3 (HR)	1.00 (Reference)	1.43 (1.25–1.63)	1.84 (1.58–2.15)	<0.001
P-values		<0.001	<0.001	

Model 1: Unadjusted model; Model 2: Adjusted for age (continuous), sex (male or female), and marital status (Married, Living with partner, Separated, Divorced, Widowed, Never married), educational level (divided into <9th grade, 9–11th grade, high school graduate, some college or AA degree, college graduate or above), depression severity (None, Mild, Moderate, Moderately Severe, Severe); Model 3: Further adjusted for the American Heart Association's Life's Simple 7 (continuous).
HR, hazard ratio.

TABLE 5 Crude and adjusted association between socioeconomic status and cardiovascular disease mortality.

Model	Socioeconomic status (SES)			*P*-value for trend
	High income (%) = 20.60 (19.44, 21.76)	Middle income (%) = 35.72 (33.79, 37.66)	Low income (%) = 43.68 (40.70, 46.66)	
Model 1 (HR)	1.00 (Reference)	2.45 (1.94–3.10)	2.58 (2.02–3.28)	<0.001
P-values		<0.001	<0.001	
Model 2 (HR)	1.00 (Reference)	1.47 (1.16–1.87)	1.90 (1.48–2.45)	<0.001
P-values		0.002	<0.001	
Model 3 (HR)	1.00 (Reference)	1.43 (1.13–1.81)	1.81 (1.41–2.33)	<0.001
P-values		0.003	<0.001	

Model 1: Unadjusted model; Model 2: Adjusted for age (continuous), sex (male or female), and marital status (Married, Living with partner, Separated, Divorced, Widowed, Never married), educational level (divided into <9th grade, 9–11th grade, high school graduate, some college or AA degree, college graduate or above), depression severity (None, Mild, Moderate, Moderately Severe, Severe); Model 3: Further adjusted for the American Heart Association's Life's Simple 7 (continuous).
HR, hazard ratio.

factors (42). This indicates that the CVD risk imparted by low SES is relatively independent of major CVD risk factors. Even at best, classical risk factors seem to be responsible for only 15–30 percent of the CVD risks associated with SES (43). It is evident that there are other unappreciated societal factors at work that could explain the relationships between ASCVD and SES.

Numerous resources (access to knowledge, wealth, power, prestige, and positive social relationships, recreational facilities), protective factors (access to healthy lifestyle and health care services), education, medical compliance, stress, nutritious food, safe communities, physical activity, smoking, alcohol consumption, drug use, and air pollution were among the potential mechanisms (43–46). For instance, extensive evidence from animal models supports the link between air pollution exposure and ASCVD, demonstrating that increased exposure to concentration ambient particles increases atherogenesis in controlled conditions (47); food insecurity was related to greater metabolic risk (48); and lifestyle factors accounted for 12.3% of the association between SES and death, according to a study (37).

Furthermore, Lower adherence to hospital visits, poorer blood pressure control, and higher risk of in-hospital mortality and post-discharge events in patients with heart failure may contribute to cardiovascular death in low-income participants (49, 50). Biological, behavioral, and psychological risk factors contribute to the occurrence of all-cause death in participants with lower incomes (51). The above explains was a host of reasons why the people with self-reported income in the low-income bracket would be at greater risk of ASCVD and cause-specific mortality and all-cause mortality.

The greatest impact of ASCVD was felt by socially disadvantaged groups. Therefore, immediate actions are required to eliminate socioeconomic health disparities and improve population resilience. Consequently, there was a need to target low-income groups with specific ASCVD management advice.

There are some limitations to the present study that deserve attention. First, the application of competitive risk model in the survival analyses was limited due to complex,

TABLE 6 Crude and adjusted association between socioeconomic status and malignant neoplasms mortality.

Model	Socioeconomic status (SES)			*P*-value for trend
	High income (%) = 20.60 (19.44, 21.76)	Middle income (%) = 35.72 (33.79, 37.66)	Low income (%) = 43.68 (40.70, 46.66)	
Model 1 (HR)	1.00 (Reference)	1.74 (1.36–2.23)	1.77 (1.37–2.29)	<0.001
P-values		<0.001	<0.001	
Model 2 (HR)	1.00 (Reference)	1.29 (1.01–1.65)	1.63 (1.22–2.18)	0.001
P-values		0.042	0.001	
Model 3 (HR)	1.00 (Reference)	1.27 (1.01–1.63)	1.58 (1.17–2.13)	0.003
P-values		0.045	0.003	

Model 1: Unadjusted model; Model 2: Adjusted for age (continuous), sex (male or female), and marital status (Married, Living with partner, Separated, Divorced, Widowed, Never married), educational level (divided into <9th grade, 9–11th grade, high school graduate, some college or AA degree, college graduate or above), depression severity (None, Mild, Moderate, Moderately Severe, Severe); Model 3: Further adjusted for the American Heart Association's Life's Simple 7 (continuous).
HR, hazard ratio.

TABLE 7 Full Adjusted association socioeconomic status and increased arteriosclerotic cardiovascular disease risk for the 2005–2006 and 2007–2018 survey periods.

Model	Socioeconomic status (SES)			*P*-value for trend
	High income	Middle income	Low income	
NHANES 2005–2006 (OR)	1.00 (Reference)	1.42 (1.10–1.83)	2.03 (1.22–3.36)	0.010
P-values		0.012	0.009	
NHANES 2007–2018 (OR)	1.00 (Reference)	1.29 (1.10–1.51)	1.77 (1.51–2.07)	<0.001
P-values		0.002	<0.001	

Models were adjusted for age (continuous), sex (male or female), and marital status (Married, Living with partner, Separated, Divorced, Widowed, Never married), educational level (divided into <9th grade, 9–11th grade, high school graduate, some college or AA degree, college graduate or above), depression severity (None, Mild, Moderate, Moderately Severe, Severe), and the American Heart Association's Life's Simple 7 (continuous).
OR, odds ratio.

stratified multistage, probability cluster design of NHANES survey. The second point to consider was whether there was any possibility that some residual and unmeasured confounders exist, which might bias the findings of our study, even though we have controlled most of the cardiovascular risk factors using weighted logistic regressions and Cox proportional hazards regressions. Third, PIR and ASCVD were all obtained from self-report, which may result in recall bias or interviewer bias. Last but not least, this was a cross-sectional study, so causality should not be claimed on the basis of these findings.

Conclusion

Our study confirmed that the SES was strongly linked to living with ASCVD, and cause-specific and all-cause mortality, even after adjusting for other factors that could impact risk, such as the AHA's Life's Simple 7 cardiovascular health score and variables of age, sex, marital status, education, and depression severity.

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.

Ethics statement

The studies involving human participants were reviewed and approved by the NCHS Research Ethics Review Board (ERB) for the presented surveys years: Protocol #2005–06 (NHANES 2005–2006), Continuation of Protocol #2005–06 (NHANES 2007–2010), Protocol #2011–17 (NHANES 2011–2012), Continuation of Protocol #2011–17 (NHANES 2013–2016), and Protocol #2018–01 (NHANES 2017–2018). More information about the NHANES database can be found at https://www.cdc.gov/nchs/nhanes/irba98.htm. The patients/participants provided their written informed consent to participate in this study.

Author contributions

RS had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. RS and NZ contributed equally as co-first authors. RS, NZ, and JW: concept and design. RS and NZ: drafting of the manuscript. RS, NZ, TZ, JW, PG, and SS: critical revision of the manuscript for important intellectual content. RS and SS: statistical analysis. TZ: obtained funding and supervision. TZ, DeL, and PG: administrative, technical, or material support. All authors: acquisition, analysis, or interpretation of data. All authors contributed to the article and approved the submitted version.

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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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1017271/full#supplementary-material

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Gender differences in income among psychiatrists in China: Findings from a national survey

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Background: Gender income disparity in healthcare settings is a longstanding issue around the globe, but such evidence among Chinese psychiatrists is scarce. This study investigated whether gender income differences exist among physicians in China.

Methods: Data came from the 2019 national survey data of 4,520 psychiatrists in major public psychiatric hospitals across China. Self-reported monthly income after tax (in Chinese Yuan, CNY) by participants at all professional ranks was assessed. Average monthly income by gender was reported. Adjusted income differences between male and female psychiatrists were examined using multivariable regression models, adjusting with inverse probability of treatment weights and controlling for psychiatrist demographics (e.g., gender, professional rank, marital status, educational level, and work hours) and hospital fixed effects.

Results: The unadjusted mean difference in monthly income after tax by gender was 555 CNY (about $86; 95% CI, −825 to −284; mean [SD] for men: 8,652 [4,783] CNY and for women: 8,097 [4,350] CNY) in all psychiatrists. After regression adjustments, the income difference by gender among all psychiatrists reduced substantially and became insignificant. However, gender income difference was still observed among senior-level psychiatrists, where female psychiatrists earned 453 CNY (about $70; 95% CI, −810 to −95) significantly less than male psychiatrists.

Conclusion: China achieved gender equity in income for psychiatrists overall, the observed income differences among senior level psychiatrists, however, reveal the persistence of gender inequity at the highest level of professional hierarchy. These findings call for policy attention to the issue of gender income disparity among psychiatrists in China's healthcare system.

KEYWORDS

income difference, gender difference, psychiatrists, health workforce, China

Introduction

Gender income disparity in healthcare settings is a longstanding issue around the globe. In many countries, female physicians have often been demonstrated to earn significantly less than their male peers (1–5). However, publicly available data on physician income in China is scarce, not even mention evidence about gender income disparity. To the best of our knowledge, there was only one national survey that systematically investigated physician salaries in China (6). The study found a salary difference between female and male physicians, although such a difference became insignificant after regression adjustments. Another regional survey study of physicians in county-level healthcare facilities in rural western China also observed descriptively income differences between female and male physicians (7).

There are many factors contributing to income differences, such as age, marital status, educational level, specialty, work hours, and administrative position (3, 5, 8–10). In China's healthcare system, professional rank, a recognition of the level of technical expertise and work ability for healthcare professionals, is also associated with physician income (6). Similar to the faculty rank that is more commonly used in the globe, professional rank for physicians in China contains three levels: junior-level (i.e., often new graduates and residents), middle-level (i.e., attending physicians), and senior-level (i.e., chief physicians who are exceptional experts of their specialty and have reached the highest level of professional hierarchy in their areas). Senior-level physicians usually have longer work years and are often in leadership positions (some may also be in a management position, such as department chair or vice chair, which may allow them to earn more than their peers).

Like other leadership positions or occupational ranks, gender inequity exists in this professional hierarchy, with women less likely to be promoted to the senior level (6). Even among physicians at the same rank, such kind of gender inequity is likely to contribute to gender income differences. In the United States, gender differences in salary were found at all faculty ranks and were the largest among full professors among academic physicians (11). Another study also revealed gender differences in salaries of clinical department chairs in US public medical schools, with women earning less than men (12). Whether gender income differences exist at the highest level of professional hierarchy in China's healthcare system is, however, unknown.

In this study, we focused on exploring income differences among psychiatrists—the specialty that has not yet been examined in any China's physician income studies. Even globally, evidence on gender income differences among psychiatrists is scarce, and the data used in existing studies were mostly out-of-date (13); for example, a study published in 2007 used 1992–2001 data to examine gender differences in annual income of psychiatrists in the United States (14). Therefore, in this study, we used more recent data from a national survey of psychiatrists in 41 psychiatric hospitals across China to explore whether gender income differences exist among Chinese psychiatrists, and in particular to investigate whether such differences exist among psychiatrists at the senior level. Findings of this study can add to existing evidence on income difference of psychiatrists in China, as such evidence is not currently available in healthcare research, and calls for policy attention to the issue of income disparity in China's context.

Methods

Data and study participants

We retrieved data from the supplement of the National Hospital Performance Evaluation Survey sponsored by China National Health Commission in 2019. The supplement was conducted from March 18 to 31 in 2019, and collected individual information of 4,708 psychiatrists from 41 psychiatric hospitals across 29 provinces in China, including participants' demographic characteristics, work status, and other workforce-related information. The questionnaire was distributed and filled anonymously *via* a widely used smartphone application in China. Informed consent was taken from every participant before the survey and personal privacy was completed protected during the whole study process.

A total of 4,520 psychiatrists completed the survey, yielding a response rate of 96%. In China, almost 90% psychiatrists work in psychiatric hospitals. Because the 41 psychiatric hospitals covered all tertiary psychiatric hospitals in China, our study sample should be taken into account as nationally representative of China's psychiatrists from tertiary hospitals.

Outcome

The outcome of interest was the self-reported monthly income after tax (in Chinese Yuan, CNY) by participants. The survey asked participants to report their income after tax, which included the basic salary, benefits, bonuses, medical practice earnings, and other compensations.

Control variables

The following available participants' demographic information were included in the analysis as control variables in the regression analysis: gender (female vs. male), professional rank (junior, middle, and senior), marital status (married vs. unmarried), educational level (bachelor's degree or below vs. master's or doctoral degree), work hours per week, years of practice, whether being at an administrative position (e.g.,

department chair or vice chair), and whether working in outpatient settings. These variables were included based on data availability and prior literature that indicated their associations with physician income (3, 5, 8–10, 14).

Statistical analysis

Since the income data were self-reported by participants, outliers may exist due to input error or recall bias. To reduce the impact of outliers on data accuracy, we cleaned the income data by dropping outliers that were outside quartile 1 and 99 ($N = 70$), as did in other studies that used income data (15, 16). Our final analytical sample included 4,450 individual psychiatrists. We reported the average monthly income and income differences for female and male psychiatrists by different professional ranks.

To estimate the adjusted gender income differences, we constructed a multivariable linear regression model, where the self-reported monthly income was the outcome variable, and gender was the key explanatory variable. To account for differences in demographic characteristics between female and male psychiatrists, we used the propensity score weighting approach. The specific method we used was the inverse probability of treatment weighting, where weights were calculated using the estimated propensity scores. The propensity score was the probability of a participant being in the treatment group (in this study, the female group), given its observable baseline characteristics, and used to balance all observable characteristics. The propensity scores were estimated using the following characteristics: professional rank, marital status, educational level, administrative position, whether having outpatients, work hours per day, and years of practice. These variables were available in the dataset and could affect the probability of being a female while contributing to differences in income. We calculated the inverse probability of treatment weights using the propensity scores, in which the weight was equal to the inverse probability of receiving the treatment that was actually received (17, 18). Thus, the weight for females was 1/(propensity score) and the weight for males was 1/(1-propensity score). We stabilized the weights to a mean of one and trimmed at the 99th percentile. After applying the inverse probability weights, we successfully balanced all but one of the observable characteristics within our weight sample (years of practice), which we directly controlled for in our model. This approach creates a synthetic distribution of female and male participants, where female and male participants are weighted to be as similar as possible based on observable demographic characteristics, and thus approximates a randomized experiment by isolating the effects caused by gender difference rather than the effects by underlying differences between groups (19, 20).

We applied the inverse probability of treatment weights to the regression model and also directly controlled for participant characteristics that were used in generating the propensity scores. We also included hospital fixed effects in the model to account for hospital-level variations (such as hospital size, location, workforce, and patient volumes). Standard errors were clustered by participants' working hospital to account for autocorrelation among participants. We repeated the model for junior-, middle-, and senior-level psychiatrists. Significance level was set at 0.05 with two-tail tests. All analyses were performed using Stata version 16 (StataCorps, Inc.).

Results

Characteristics of study participants

Of the 4,450 participants, 2,591 (58%) were female (Table 1). A total of 1,370 (31%) were junior psychiatrists, 1,536 (35%) were middle-level psychiatrists, and 1,544 (35%) were senior psychiatrists. More females were at the junior level, unmarried,

TABLE 1 Participant characteristics.

Characteristics	No. (%)		*P*-value[a]
	Male	Female	
Total no.	1,859 (41.8)	2,591 (58.2)	NA
Professional rank			<0.01
Junior level	480 (25.8)	890 (34.3)	
Middle level	629 (33.8)	907 (35.0)	
Senior level	750 (40.3)	794 (30.6)	
Marital status			<0.01
Married	1,584 (85.2)	2,036 (78.6)	
Unmarried	275 (14.8)	555 (21.4)	
Educational level			<0.01
Associate degree or below	69 (3.7)	122 (2.0)	
Bachelor's degree	1,260 (67.8)	2,814 (60.0)	
Master's or doctoral degree	530 (28.5)	1,514 (38.0)	
Administrative position			<0.01
No	1,325 (71.3)	2,187 (84.4)	
Yes	534 (28.7)	404 (15.6)	
Having outpatients			<0.01
No	620 (33.4)	1,017 (39.3)	
Yes	1,239 (66.6)	1,574 (60.7)	
Work hours per day			
Mean (SD)	9.41 (2.29)	9.31 (1.94)	0.12
Years of practice			
Mean (SD)	16.30 (10.05)	12.66 (9.07)	<0.01

NA, not applicable.
[a]P-values were from Pearson Chi-square tests comparing percentages or from two-tail t-tests comparing means between men and women.

had a master or doctoral degree, were less likely to be at an administrative position, and have fewer years of practice compared to male participants.

Unadjusted and adjusted results of gender differences in income

Overall, the average monthly income after tax was 8,097 (SD = 4,350) CNY for Chinese female psychiatrists and 8,652 (SD = 4,783) CNY for male psychiatrists (Table 2). The unadjusted mean difference in income was significant by gender in all psychiatrists (555 CNY, about $86; 95% CI, −825 to −284). However, this difference reduced substantially and became insignificant after adjustments (income difference = −31, 95% CI = −206 to 143).

We observed gender income differences among senior-level psychiatrists in both unadjusted analysis and adjusted regression. On average, the monthly income was 10,480 (SD = 5,261) CNY for female senior psychiatrists and 11,101 (SD = 5,684) CNY for male senior psychiatrists. The unadjusted mean income difference was significant between female and male psychiatrists (621 CNY, about $96; 95% CI, −1,168 to −75). This difference persisted in the model after we adjusted with the inverse probability of treatment weights and controlled for demographic characteristics and other factors. After adjustments, the mean difference in income by gender among senior-level psychiatrists was 453 CNY (about $70, 95% CI = −810 to −95). We did not observe significant gender income differences in junior- and middle-level psychiatrists, neither in the unadjusted analysis nor adjusted regression. Full regression results were presented in the Appendix Table A1.

Discussion

This study, for the first time to our knowledge, used recent data from a nationally representative sample to investigate gender income differences among physicians in China. Overall, we observed that significant income differences exist between female and male psychiatrists in the unadjusted analysis but not in the adjusted regression. When we looked at income differences by professional rank, we found significant gender income differences among senior-level psychiatrists, where female earned 453 Yuan (about $70) monthly less than male psychiatrists after regression adjustments. Our findings suggest that although China achieved gender equity in income for psychiatrists overall, gender inequity still persists at the highest level of professional hierarchy, even under the context that women at this rank have demonstrated the same level of technical expertise and work ability in their areas as men.

Our study was observational and cannot answer why such differences exist. A common explanation might be that such differences are rooted in socio-cultural structures that restrict the opportunities of women in the labor market (4). It is possible that even when female physicians have reached the highest level of professional rank, they may still be less likely to receive recognition for achievements than male physicians which restricts their career opportunities. Other socio-cultural factors could also contribute to such differences, for example, differential household responsibilities and childrearing between women and men could lead women to place less emphasis on their career but more on family compared to their male counterparts in subsequent career development (21–23). Future research is warranted to explore in-depth reasons and other factors (such as years of practice) that drive such differences in China's context.

TABLE 2 Multivariable linear regression analyses on gender differences in income, adjusted with inverse probability of treatment weights.

	Monthly income, in Chinese Yuan Mean (SD)		Gender differences in income [F–M] (95% CI), in Chinese Yuan			
	Female	Male	Unadjusted	*P*-value[a]	Adjusted	*P*-value[b]
All psychiatrists[c]	8,097 (4,350)	8,652 (4,783)	−555 (−825 to −284)	<0.001	−31 (−206 to 143)	0.72
Junior-level psychiatrists[d]	6,106 (2,759)	5,972 (2,500)	135 (−162 to 432)	0.37	−47 (−252 to 158)	0.65
Middle-level psychiatrists[d]	7,964 (3,677)	7,776 (3,311)	188 (−171 to 548)	0.30	90 (−227 to 407)	0.57
Senior-level psychiatrists[d]	10,480 (5,261)	11,101 (5,684)	−621 (−1168 to −75)	0.03	−453 (−810 to −95)	0.01

F, female; M, male.
[a]P-values were from two-tail t-tests comparing means between female and male.
[b]P-values were from regression adjusted with inverse probability of treatment weights. Full regression results were presented in the Appendix Table A1.
[c]Adjusted for professional rank, marital status, educational level, work hours per week, years of practice, administrative position, working in outpatient settings and hospital fixed effects. Standard errors were clustered by participants' working hospital.
[d]Adjusted for marital status, educational level, work hours per week, years of practice, administrative position, working in outpatient settings and hospital fixed effects. Standard errors were clustered by participants' working hospital.

Notably, our study did not find significant gender income differences among psychiatrists at the junior and middle level. It is likely that both female and male physicians at the junior or middle level have less flexible time to leave clinical work, and therefore, have less opportunities to increase their income through other revenues. It is also worth to note that, the income levels for junior and middle level psychiatrists in general are much lower than senior psychiatrists. This issue is critical in China, as many young physicians are turning over healthcare industries because of low income (24–26). Research has also demonstrated that low income is the major reason for turnover intention among China's psychiatric residents (27). Young physicians often have heavier workloads, but workloads and work hours are not tied to income in China's healthcare system. Heavy workloads plus the income that do not match workloads lead to severe turnover issue in healthcare settings, which partly links to shortages of physicians in China (28–30).

Our study calls for policy attention to gender income disparity among senior-level physicians in China's healthcare system. Efforts to monitor and reduce income gaps, for example, can be through publicly reporting salary information and increasing data availability and transparency. In recent years, the Chinese central government has begun to focus on adjusting physician salaries in public hospitals and improving the benefits of physicians in order to stabilize physician workforce (31). Unified governance of physician payment and a more comprehensive compensation plan for senior-level physicians may also minimize gender income gaps.

Limitations

This study has several limitations. First, the income data are self-reported by survey participants, and we lack actual data on real salary of hospital employees. Participants could likely underreport their income, or the actual income level of psychiatrists in China may be less than what we found because our study participants were from tertiary hospitals that tend to have a higher income level. In future research, it is worth to revisit our study using administrative data such as payroll data or income tax data. Second, since this study only used data at the psychiatric setting, caution must be paid when generalizing our findings to other clinical areas. Third, due to data availability, we were unable to control for other physician productivity, such as research grants, publications and teaching, which are also important source of physician income.

Conclusion

In this national survey study of a large sample of China's psychiatrists, we did not observe gender income differences among found existing gender income differences among Chinese physicians. However, we did find differences existing among senior physicians who have reached the highest level of professional hierarchy in their areas. These findings call for actions to address such differences in China's healthcare system. Future research is also needed to understand in-depth mechanisms that drive such differences.

Data availability statement

The datasets presented in this article are not readily available, because it involves privacy information. Requests to access these datasets should be directed to the corresponding author and the National Hospital Performance Evaluation Survey Group (fengjiang@sjtu.edu.cn).

Author contributions

JZ: conceptualization, methodology, validation, resources, writing—review and editing, and supervision. XH: methodology, formal analysis, and writing—original draft. LS: writing—review and editing. JT: formal analysis. FJ: resources, investigation, and writing—review and editing. HL: resources and investigation. All authors contributed to the article and approved the submitted version.

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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.

Publisher's note

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Appendix

Table A1 Multiple linear regression results of gender income differences by professional rank.

	Total		Professional rank					
			Junior		Middle		Senior	
	Coff.	95% CI	Coff.	95% CI	Coff.	95% CI	Coff.	95% CI
Gender								
Female	−31	(−206 to 143)	−47	(−252 to 158)	90	(−227 to 407)	−453*	(−810 to −95)
Male	Ref.		Ref.		Ref.		Ref.	
Professional rank								
Senior	1,388***	(1,003 to 1,772)						
Middle	334*	(12 to 655)						
Junior	Ref.							
Marital status								
Married	307	(−37 to 651)	496***	(223 to 769)	−104	(−515 to 307)	−692	(−1,393 to 10)
Unmarried	Ref.		Ref.		Ref.		Ref.	
Educational level								
Master's or doctoral degree	553*	(116 to 990)	688**	(231 to 1,145)	355	(−25 to 735)	309	(−162 to 779)
Bachelor's degree or below	Ref.		Ref.		Ref.		Ref.	
Administrative position								
Yes	2,087***	(1,694 to 2,479)	1,294	(−1,259 to 3,847)	1,618***	(1,035 to 2,201)	2,235***	(1,896 to 2,573)
No	Ref.		Ref.		Ref.		Ref.	
Working in outpatient settings								
Yes	640***	(390 to 890)	353*	(12 to 694)	538***	(304 to 772)	1,111***	(575 to 1,647)
No	Ref.		Ref.				Ref.	
Work hours per day	−44	(−96 to 8)	1	(−65 to 66)	−91	(−189 to 8)	−38	(−142 to 66)
Years of practice	84***	(53 to 116)	50**	(17 to 84)	33**	(13 to 52)	113***	(79 to 146)
Hospital fixed-effects	Yes		Yes		Yes		Yes	
Observations	4,394		1,345		1,521		1,529	
R-squared	0.601		0.508		0.607		0.576	

Coefficients and 95% confidence intervals (CI) were presented in this table. Standard errors were clustered by hospital. All models adjusted with inverse probability of treatment weights, generating from the propensity score weighting approach. ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.

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Ethical allocation of scarce vaccine doses: The Priority-Equality protocol

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Background: Whenever vaccines for a new pandemic or widespread epidemic are developed, demand greatly exceeds the available supply of vaccine doses in the crucial, initial phases of vaccination. Rationing protocols must then fulfill a number of ethical principles balancing equal treatment of individuals and prioritization of at-risk and instrumental subpopulations. For COVID-19, actual rationing methods used a territory-based first allocation stage based on proportionality to population size, followed by locally-implemented prioritization rules. The results of this procedure have been argued to be ethically problematic.

Methods: We use a formal-analytical approach arising from the mathematical social sciences which allows to investigate whether any allocation methods (known or unknown) fulfill a combination of (ethical) desiderata and, if so, how they are formulated algorithmically.

Results: Strikingly, we find that there exists one and only one method that allows to treat people equally while giving priority to those who are worse off. We identify this method down to the algorithmic level and show that it is easily implementable and it exhibits additional, desirable properties. In contrast, we show that the procedures used during the COVID-19 pandemic violate both principles.

Conclusions: Our research delivers an actual algorithm that is readily applicable and improves upon previous ones. Since our axiomatic approach shows that any other algorithm would either fail to treat people equally or fail to prioritize those who are worse off, we conclude that ethical principles dictate the adoption of this algorithm as a standard for the COVID-19 or any other comparable vaccination campaigns.

KEYWORDS

rationing, vaccines, COVID-19, pandemics, medical ethics

1. Introduction

When vaccines for the COVID-19 pandemic first became available, countries around the world rushed to secure as many doses as possible, with little or no attempt at coordination (1–5). To mitigate the ensuing chaos, and to provide global, equitable access to vaccines, the World Health Organization (WHO), the Coalition for Epidemic Preparedness Innovations (CEPI), and the Vaccine Alliance (Gavi) proposed the multilateral initiative Covax Facility (COVAX). The European Union also acted on behalf of all its member states (6), and the U.S. allocated vaccines among jurisdictions (7). In those and many other cases, vaccines were centrally acquired and had to be distributed among the territories.

The allocation of a centrally-acquired stock of (scarce) medical resources to individual territories is, however, a complex problem which is encountered in different environments. In the case of COVID-19, the various organizations referred above implemented different procedures on the basis of their political support rather than objective, scientific criteria (8). As a result, an ethical debate erupted, pointing out a number of serious flaws in the implemented procedures (9, 10). For example, some territories received enough vaccines to start inoculating lower-priority groups while other territories were not able to fully immunize higher-priority ones (11, 12). Further, individuals noticed that they would in practice receive higher priority if they simply moved from one territory to the next (13, 14).

According to a prominent strain of the medical ethics literature (15–18), the key ethical desiderata (or "fundamental values") to take into account when facing the rationing of scarce medical resources are four: "(i) maximizing the benefits produced by scarce resources, (ii) treating people equally, (iii) promoting and rewarding instrumental value, and (iv) giving priority to the worst off" [(17), p. 2051]. If we restrict our attention to the allocation of scarce vaccines, the first and the third fundamental values are relevant to establish the different priority classes. In other words, priority classes should be defined to reflect medical and scientific evidence as, for example, the different effects of treatments on individuals in different health states (12), and practical considerations as those dictating preferential treatment of medical personnel. In contrast, the challenges arising from the distributional aspects of vaccine allocation involve the second and the fourth fundamental values above.

In this contribution, we shed light on these distributional aspects of the allocation of scarce vaccines. In other words, we assume that the priority classes have already been decided (e.g., by experts in medical ethics and organizations like the WHO). The remaining key ethical desiderata are two. First, priority should be given to worse-off groups (as the elderly or otherwise at-risk) and to those with instrumental value (as, e.g., medical personnel). Second, equal people, that is, those with the same priority, should be treated equally, meaning that they should have the same likelihood of being vaccinated.

There exist many frameworks addressing distributional fairness in healthcare (4, 16–22), but they typically remain unspecified, that is, they discuss desiderata but stop short of identifying actual distribution mechanisms. For the case of vaccine allocation, at this point, society needs an allocation procedure or *vaccine rationing protocol* fulfilling the two key requirements discussed above. That is, higher-priority classes should receive vaccinations before lower-priority ones, and people within the same priority class should be treated equally.

The rationing protocols used to distribute vaccines in the case of COVID-19 failed on all accounts. Indeed, the dispersion in vaccination rates for given priority classes in EU countries was remarkable. In the 12th week of 2021, 99.6% of all healthcare workers were vaccinated (primary course) in Hungary,[1] 71.5% in Romania, and 66.9% in Estonia, while the rates of fully-vaccinated health care workers were much lower in Denmark (36.8%), Czechia (42.7%), Ireland (54%), or Iceland (21.5%) (Figure 1A). Note that the vaccination rates for the healthcare workers in these countries were near 100% in January 2022, demonstrating that healthcare workers of those countries had a clear preference for being vaccinated, and hence that equal people were far from being treated equally.[2]

It is also clear that prioritization was violated. Figure 1B reports a simple exercise performed using publicly-available vaccination numbers from the European Center for Disease Prevention and Control and the size of population groups (healthcare workers and age groups) from the OECD (Table 1). Respecting priority means that, say, all healthcare workers in the entire EU should have been vaccinated (or it should have been possible to vaccinate them if willing) before immunization of other classes started, that no 70-year old should be vaccinated before all those aged above 80 were vaccinated in the entire EU, etc. In reality, in week 22, Spain and Belgium had received enough vaccines to vaccinate all healthcare workers and those aged 70 or older, while Denmark, France, and Greece only had received enough to immunize those older than 80, and Hungary already had enough to immunize all above 60. Even ignoring the

1 Starting in February 2021, Hungary decided to buy Sputnik V and Sinopharm vaccines from Russia and China, respectively (23, 24), considering that the EU scheme was too slow. This helps explain both the high rate of vaccinated healthcare workers on the 12th week of 2021 as well as Hungary's high performance, in Figure 1B, in terms of the classes that each country could have immunized at every point in time along the year 2021. We thank an anonymous referee for this insightful comment.

2 In the 12th week of 2021, Bulgaria had a rate of only 13.4% fully-vaccinated healthcare workers. However, this rate was still 28.7% in early March 2022, suggesting that Bulgaria's issue is orthogonal to these considerations, and most likely related to the widespread vaccine hesitancy in this country (25–27).

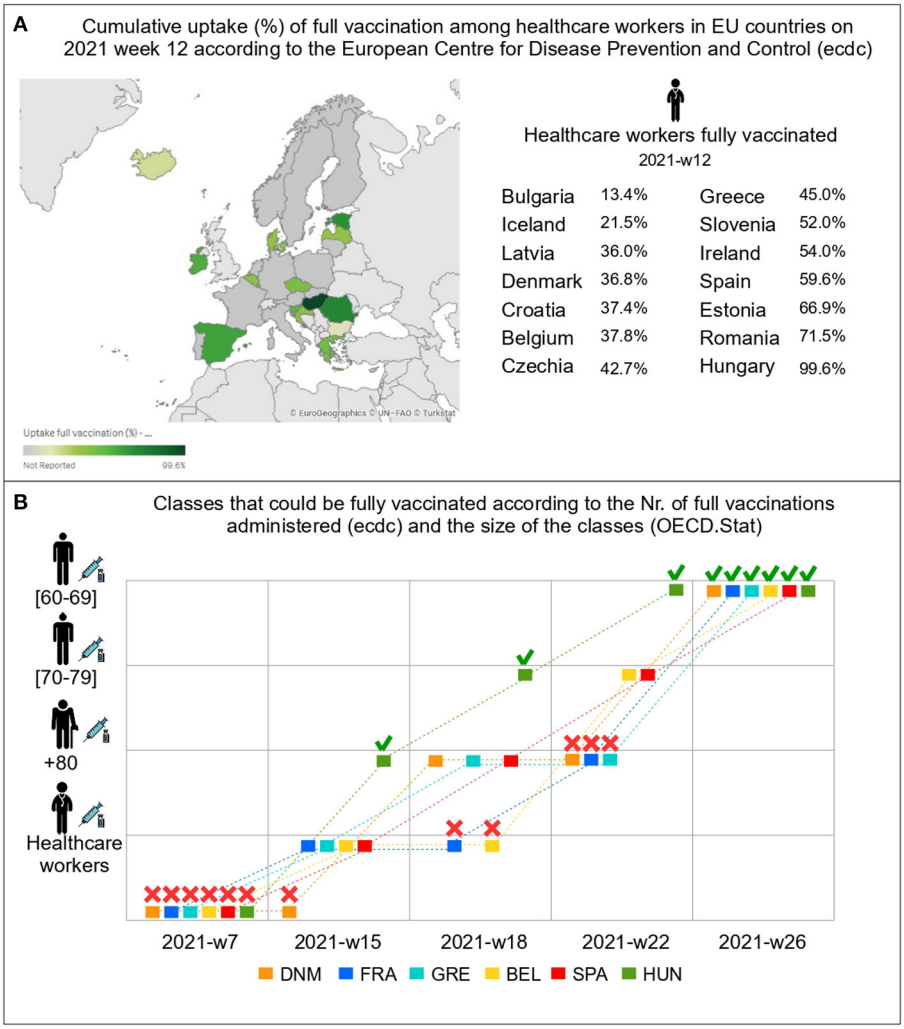

FIGURE 1
Data and map from the European Center for Disease Prevention and Control (ecdc) and OECD.Stat. **(A)** shows a high dispersion in the vaccination rates of healthcare workers within the EU in week 12/2021, showing that *Prioritizing According To Needs* was violated. **(B)** uses OECD data (Table 1) and shows which priority classes could have been fully immunized at different points in time (2021) according to ecdc data on full vaccinations administered (primary course) in each territory. This exercise shows that *Treating Equal People Equally* was violated. For example, on week 22*nd*, beyond the case of Hungary (which decided to buy vaccines from third countries on top of the agreement with the EU), we observe that Belgium and Spain could have started immunizing citizens from 60 to 69 years while France, Greece, or Denmark did not have enough vaccines to have immunized all citizens above 70 years. Icons made by `Freepik` from `Flaticon`.

case of Hungary (which had bought additional vaccines), this illustrates that the allocation protocol did not respect priority classes, as within the same vaccination alliance (the EU) people from lower-priority classes were being immunized while higher-priority classes had still not been fully vaccinated.

We make use of the axiomatic approach proper of the mathematical social sciences. Formally, one translates ethical desiderata into analytical properties to be satisfied by protocols (themselves defined as mathematical functions), and then reverse-engineers the protocols fulfilling those properties. Very often, when using this methodology, one ends up with an impossibility theorem which reveals that the desiderata are mutually incompatible or too exacting. In this contribution, we demonstrate that the problem to find a vaccine allocation protocol fulfilling prioritization and equal treatment can be solved analytically. The failures illustrated above were not borne out of lack of competence at any level, or of inefficiency in administering a protocol. Rather, they are inherent failures of the protocols that were used. We show analytically that those protocols cannot fulfill the requirements of prioritization and equal treatment. We go even further and show that there exists one and only one protocol that satisfies both requirements.

TABLE 1 Table reporting actual data about full vaccinations administered (primary course) at weeks 15, 18, 22, 26 of 2021 and the population by priority class according to the OECD.Stat.

	Nr. of full vaccinations administered				OECD statistical data			
EU members	**2021-w15**	**2021-w18**	**2021-w22**	**2021-w26**	**Healthcare W.**	**Age +80**	**Age [70–79]**	**Age [60–69]**
Hungary	1,362,623	2,460,201	3,929,646	4,958,419	318,508	441,525	867,394	1,282,913
France	4,534,880	7,875,751	12,630,071	22,593,343	3,899,000	4,137,718	5,823,662	8,002,188
Spain	3,447,162	6,278,419	10,956,826	19,121,368	1,527,500	2,856,102	3,986,744	5,427,445
Greece	769,325	1,215,279	2,306,762	3,966,764	266,627	774,369	1,012,738	1,292,835
Belgium	762,582	1,138,287	2,593,255	4,230,452	646,600	652,184	936,587	1,357,188
Denmark	488,572	848,769	1,351,828	2,094,482	525,000	277,977	570,642	664,621

This means that *any other* protocol, already-existing or yet-to-be-designed, will either fail to respect priority classes or treat people within the same priority class unequally. This includes all protocols that have been used to distribute vaccinations for the COVID-19 pandemic. We pin down the new protocol to the algorithmic, ready-to-use level, and offer it for use by any vaccine alliance.

Intuitively, the protocol identified by our approach proceeds as follows. First, one must consider the size of the different priority classes *jointly across territories*, and distribute (on paper) vaccines to classes according to their priorities. Second, for each priority class, one distributes the vaccines to the territories proportionally to the size of the class in each territory. This protocol can be applied to any multi-territory organization, ranging from current multi-jurisdiction countries and alliances to the ideal of a global vaccine distribution (19, 20, 28–30). In contrast, currently-used protocols have been essentially based on an approach where, first, vaccines are allocated to territories proportionally to population (7, 31, 32), and then allocated to classes following priority within each territory (33, 34). As we show below, these methods violate both desiderata described above, and hence are inherently flawed, both technically and ethically.

2. Materials and methods

The formal-analytical proof of the existence and uniqueness result given below is in the Supplementary material.

3. Results

3.1. Vaccine rationing problems and ethical desiderata

There are $T \geq 2$ territories, indexed by $t = 1, \ldots, T$, and P priority classes, $p = 1, \ldots, P$. A total of $V > 0$ vaccinations are available and must be allocated across territories and priority classes. For simplicity, a "vaccination" refers to a unit containing the number of doses required to immunize a single individual (e.g., two doses for most of the initial COVID-19 vaccinations, one for booster campaigns, etc.).

Territorial authorities report or request the number of vaccinations required for each class in each territory. Denote by c_t^p the corresponding *claim* for class p in territory t. Let $c^p = c_1^p + \cdots + c_T^p$ and $c_t = c_t^1 + \ldots + c_t^P$ be the total claims for class p and territory t, respectively. The total claim is $C = c^1 + \ldots + c^P = c_1 + \ldots + c_T$. A *Vaccine Rationing Problem* appears when $C > V$, that is, the total claim exceeds the available number of vaccinations and hence the latter must be rationed and distributed across territories and priority classes.

Let n_t^p be the number of individuals belonging to priority class p in territory t, which is observable through administrative records. Denote by $n_t = n_t^1 + \ldots + n_t^P$ the total population of territory t, and by $N = n_1 + \ldots + n_T$ the total population across all territories. Obviously, claims are constrained so that $c_t^p \leq n_t^p$ for each p and t. To simplify notation, write c and n to denote the matrices containing all c_t^p and all n_t^p, respectively.

The solution for Vaccine Rationing Problems is a *Vaccine Rationing Protocol* which takes as inputs the claims c_t^p and the population sizes n_t^p, and delivers as outputs the vaccinations allocated to each p and t, denoted by $R(c, V)$. This is in itself a matrix, that is, given claims c_t^p and total available vaccinations V, the protocol R allocates $R_t^p(c, V)$ vaccinations to priority class p in territory t. The only requirement is that the $R_t^p(c, V)$ sum up to V, i.e., all vaccinations are allocated. Formally, every protocol R is a mathematical mapping between well-defined spaces (see Supplementary material A.1). The key of our contribution is that ethical desiderata can be translated into formal properties which such protocols should fulfill, and the axiomatic approach from the mathematical social sciences (see Supplementary material A.3) allows to pin down an exact protocol as the only one which satisfies the desiderata.

Among the ethical desiderata discussed in the introduction, the technical aspects of the requirement to maximize the benefits of scarce vaccinations are already encompassed in

the definition of Vaccine Rationing Protocol, and specifically into the condition that the $R_t^p(c, V)$ add up to V, that is, no vaccinations are wasted. The requirement to promote and reward instrumental value means that priority classes should take into account professional groups as e.g., clinical or security personnel—since we take the priority classes as given, for our purposes this requirement is subsumed in the requirement to prioritize worse-off groups, which means that classes with higher priority (lower p) should receive vaccinations before the immunization of classes with worse priority starts.

Say that a class in a territory is *rationed* if it does not fully receive its claim, i.e., $R_t^p(c, V) < c_t^p$, and that it is *excluded* if it receives zero, i.e., $R_t^p(c, V) = 0$. The requirement that priority classes are honored is the following.

Prioritizing According To Needs. If a class in a territory is rationed, then every class with worse priority (in *any* territory) is excluded.

Formally, this can be written as follows: If $R_t^p(c, V) < c_t^p$ for some p and some t, then $R_{t'}^{p'}(c, V) = 0$ for all $p' = p + 1, \ldots, P$ and for all t'. In other words, if there are not enough vaccinations to immunize all the individuals in a priority class for a given territory, then the protocol must not have allocated vaccinations to any lower-priority class in *any* territory. The requirement that this holds for any territory is crucial; as we will see below, standard allocation procedures during COVID-19 violated this desideratum.

The second desideratum is that (equal) people should be treated equally. Obviously, it is impossible to treat everybody equally while respecting priority of different classes, and what is actually meant by this desideratum is that two different people belonging to the same class should not face different constraints, and specifically should not be treated differently across territories. To formulate this principle, let the *vaccination rate* of a priority class be the proportion of people in the class that can be inoculated, given the number of allocated vaccinations, i.e., $R_t^p(c, V)/c_t^p$.

Treating Equal People Equally. The vaccination rates of priority classes do not differ across territories.

Formally, this means that, for every priority class p and any two territories t, t',

$$\frac{R_t^p(c, V)}{c_t^p} = \frac{R_{t'}^p(c, V)}{c_{t'}^p}$$

provided $c_t^p > 0$ and $c_{t'}^p > 0$.

The ratios can also be interpreted as the probability of being vaccinated for priority class and territory. Thus, this desideratum implies that individuals cannot increase their vaccination chances by moving from one territory to another.

3.2. Why COVID-19 protocols violated ethical desiderata

Generally speaking (as, e.g., in the case of COVAX or the EU), COVID-19 vaccinations were distributed in a two-stage fashion where first vaccinations were allocated to territories (31, 32), and then those allotments were redistributed across the priority classes in each territory (33, 34).

These naïve protocols violate both ethical principles, *Prioritizing According To Needs* and *Treating Equal People Equally*. To see this, we first define the procedure sketched above formally. This is a simplified procedure sharing the defining characteristics of the methods actually used in the case of COVID-19, and it suffices to see why such methods are problematic. For this purpose, we describe the procedure used by the European Union to allocate vaccines among their Member States proportionally to their population, with the simplifying assumption that in the second stage all Member States treat the priority classes the same way.

The Territorial Allocation protocol (TA). This protocol, which mimics those actually used for COVID-19 in a simplified way, proceeds as follows (Figure 2A). In the first stage, the available vaccinations V are distributed among the territories proportionally to the territories' population, unless the territorial claim can be fulfilled. Specifically, each territory t receives a total allotment of

$$R_t(c, V) = \min\left\{c_t, \lambda \frac{n_t}{N}\right\}$$

where $N = n_1 + \ldots + n_T$ is the total population across all territories and λ is a constant computed to guarantee that the vaccinations are exhausted, i.e.,

$$\sum_{t=1\ldots,T} \min\left\{c_t, \lambda \frac{n_t}{N}\right\} = V$$

In words, the procedure allocates V proportionally to the population of the territories, but reduces the allocation to the actual claim if that is exceeded, reallocating the excess vaccinations to other territories. Hence, λ is the proportion of the total population that can be vaccinated for those territories that are actually rationed.

In the second stage, the TA protocol distributes the allotment $R_t(c, V)$ of each territory t among the priority classes in t following the order of the priority classes. That is, for each territory, the highest-priority class is vaccinated, with the remaining vaccinations (if any) going to the second class, and so on until the doses are exhausted. Formally, let $p^*(t)$ be the unique class such that $c_t^1 + \ldots + c_t^{p^*(t)-1} \leq R_t(c, V)$ but $c_t^1 + \ldots + c_t^{p^*(t)} > R_t(c, V)$, i.e., the first class in order of decreasing

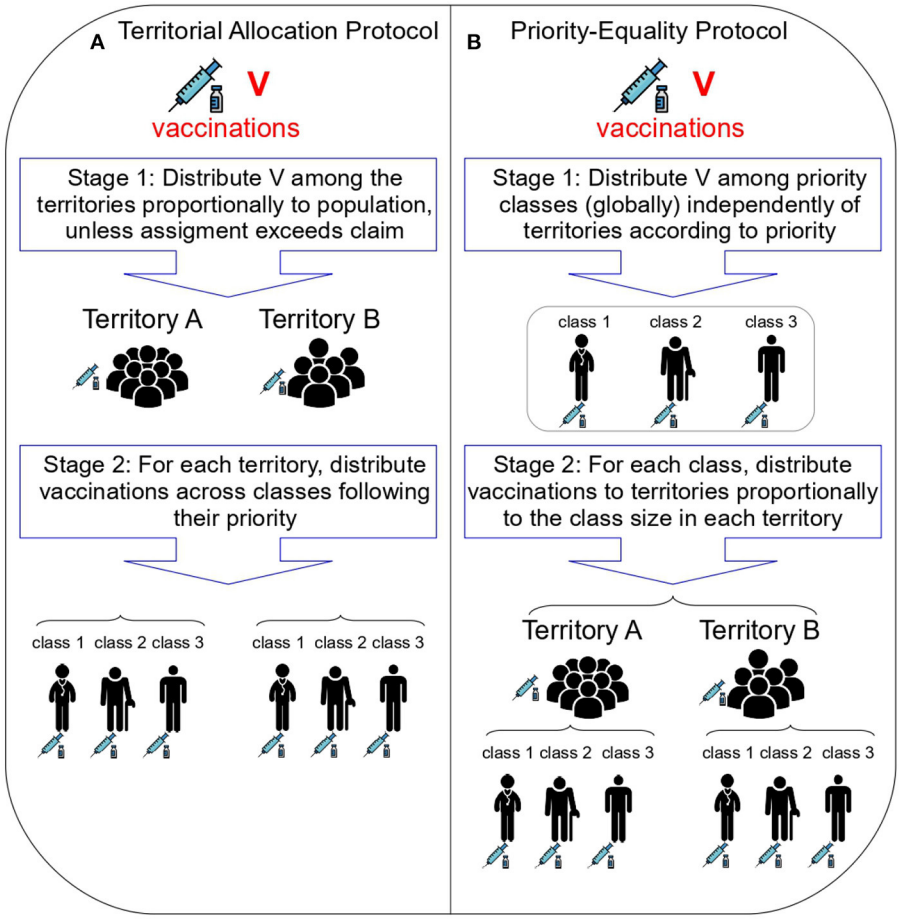

FIGURE 2
The Territorial Allocation and Priority-Equality protocols. **(A)** (left) shows the two stages of the Territorial Allocation protocol, which captures the essential features of those actually used for COVID-19. **(B)** (right) shows the two stages of the Priority-Equality protocol, which we identify in this work as the only one satisfying fundamental ethical principles. Icons made by `Freepik` from `Flaticon`.

priority such that available vaccinations in the territory do not allow for full coverage. Then,

$$R_t^p(c,V) = \begin{cases} c_t^p & \text{if } p < p^*(t) \\ R_t(c,V) - c_t^1 - \ldots - c_t^{p^*(t)-1} & \text{if } p = p^*(t) \\ 0 & \text{if } p > p^*(t). \end{cases}$$

This intuitive protocol violates not one but both of the ethical principles described above. To see this a counterexample suffices. Figure 3 shows an example of Vaccine Allocation Problem where the second priority class in a territory receives vaccinations while the first priority class in another territory is still rationed, hence violating Prioritizing According To Needs (Figure 3A). Further, vaccination rates per class are strictly better in the first territory, violating Treating Equal People Equally (Figure 3B).

3.3. Main result

Our main result shows that it is possible to satisfy both ethical desiderata. Strikingly, the axiomatic approach actually pins down the protocol (and the algorithm) which makes this possible. In other words, any other conceivable protocol, currently extant or not, *will* violate one of the principles.

Theorem 1. *There exists one and only one Vaccine Rationing Protocol which satisfies Prioritizing According To Needs and Treating Equal People Equally. This is a two-stage procedure as follows:*

- Stage 1: *Allocate vaccinations to priority classes (globally) independently of territories according to priority.*
- Stage 2: *For each priority class, reallocate vaccinations across territories proportionally to the size of the class in them.*

We refer to this two-stage procedure as the **Priority-Equality protocol** (PE; Figure 2B). Algorithmically, this

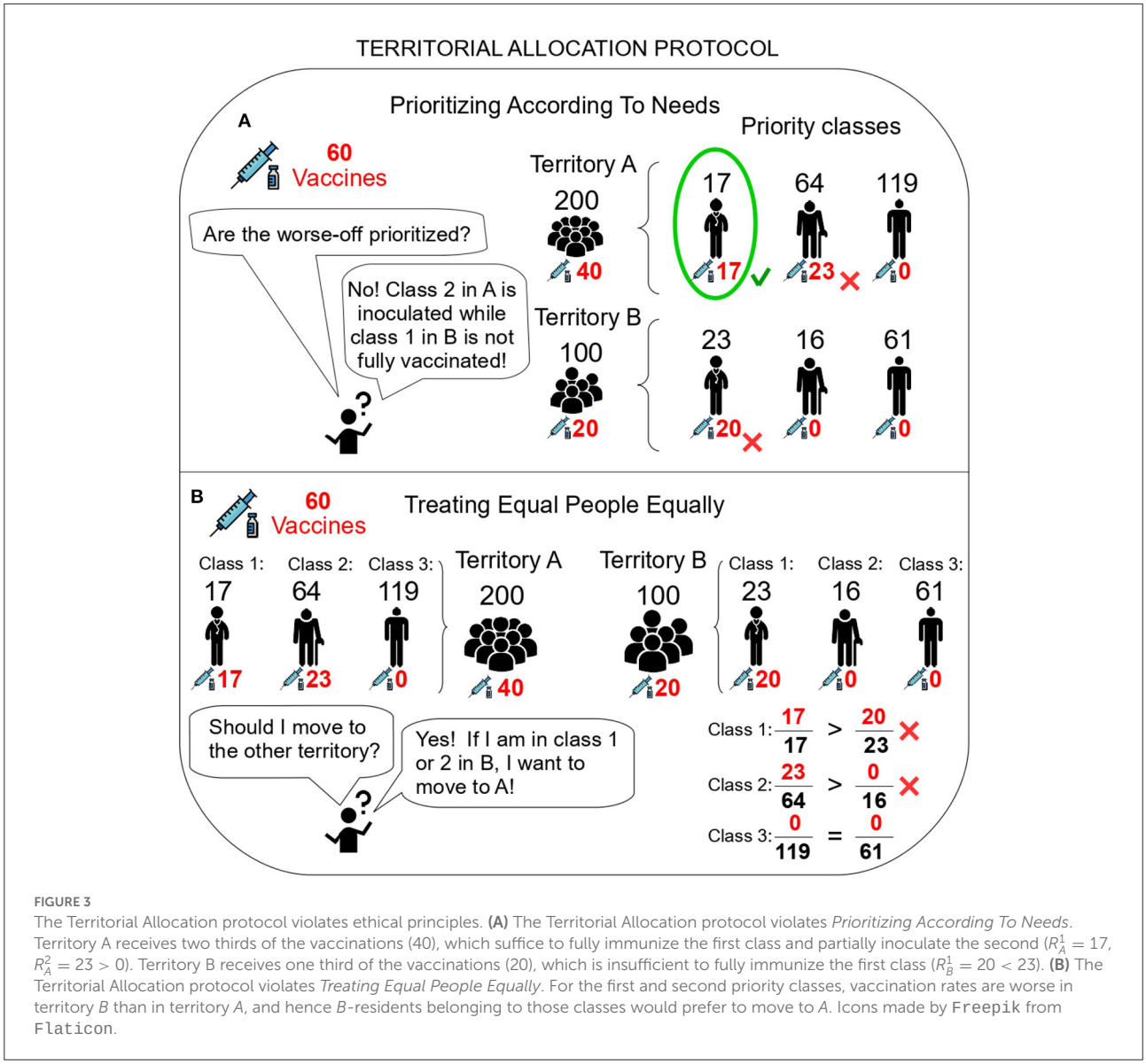

FIGURE 3
The Territorial Allocation protocol violates ethical principles. **(A)** The Territorial Allocation protocol violates *Prioritizing According To Needs*. Territory A receives two thirds of the vaccinations (40), which suffice to fully immunize the first class and partially inoculate the second ($R_A^1 = 17$, $R_A^2 = 23 > 0$). Territory B receives one third of the vaccinations (20), which is insufficient to fully immunize the first class ($R_B^1 = 20 < 23$). **(B)** The Territorial Allocation protocol violates *Treating Equal People Equally*. For the first and second priority classes, vaccination rates are worse in territory *B* than in territory *A*, and hence *B*-residents belonging to those classes would prefer to move to *A*. Icons made by `Freepik` from `Flaticon`.

protocol is as follows (see Figure 4 for an example). In Stage 1, the available vaccinations V are distributed following the order of the priority classes (without any distinction across territories). That is, the highest-priority class is vaccinated in all territories, with the remaining vaccinations (if any) going to the second class, and so on until the doses are exhausted. Formally, let p^* be the unique class such that $c^1 + \ldots + c^{p^*-1} \leq V$ but $c^1 + \ldots + c^{p^*} > V$, i.e., the first class in order of decreasing priority such that overall available vaccinations do not allow for full coverage. Then, each class p is allocated

$$R^p(c,V) = \begin{cases} c^p & \text{if } p < p^* \\ V - c^1 - \ldots - c^{p^*-1} & \text{if } p = p^* \\ 0 & \text{if } p > p^* \end{cases}$$

In the second stage, the total allocation to class p, $R^p(c,V)$, is distributed across territories (or, more properly, among their respective p-priority classes). This is done proportionally to the territorial claims for each priority class,

$$R_t^p(c,V) = \frac{c_t^p}{c^p} R^p(c,V)$$

for the classes with $c^p > 0$ [if for any class there were no claims, $c^p = 0$, then $R_t^p(c,V) = 0$ for all t].

Figure 4 illustrates with an example how this protocol fulfills both desiderata. The mathematical proof of our result is provided in Supplementary material A.2. It first shows that the PE protocol fulfills both desiderata for all problems. Crucially, it

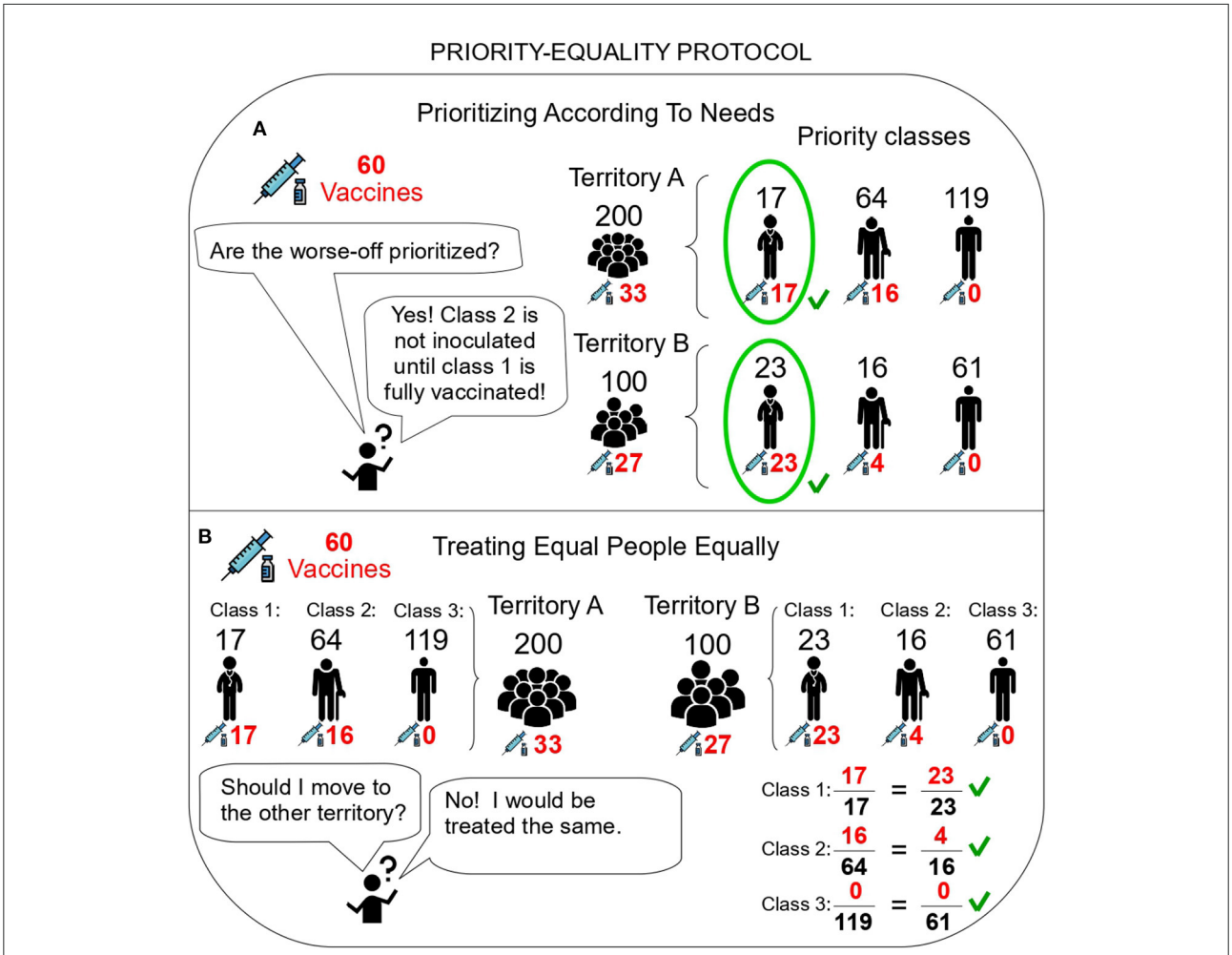

FIGURE 4
The Priority-Equality protocol satisfies ethical principles. **(A)** *Prioritizing According To Needs*. The highest priority class is fully covered in both territories. The remaining vaccinations (20) do not suffice to cover the second priority class, hence that class is rationed in both territories. Other classes are excluded. **(B)** *Treating Equal People Equally*. For the second class, vaccinations are allocated proportionally to the size of that class across the territories ($R_A^2 = 16 < 64$, $R_B^2 = 4 < 16$). Hence, vaccination rates are identical. Icons made by `Freepik` from `Flaticon`.

then shows that any other hypothetical protocol that also fulfills those must be identical to PE.

It is easy to show that the two fundamental ethical desiderata considered here are logically independent (see Supplementary material A.4). Finally, we remark that the PE protocol also fulfills other appealing properties that the TA protocols violate, e.g., robustness to decentralization, equal treatment of territories with identical claims for a given class, or robustness to sequential vaccination campaigns (see Supplementary material A.5).

4. Discussion

We offer a possible approach to the problem of allocating scarce vaccines from an ethical perspective. More concretely, we focus on the prominent work "Fair allocation of scarce medical resources in the time of COVID-19" (17). We restrict our attention to this ethical framework for two reasons. First, this is one of the most influential ethical frameworks in the literature. And second, this framework adapts existing, well-known paradigms for the ethical analysis of the allocation of scarce medical resources (16, 18) to the specific crisis of the COVID-19 pandemic. Our contribution consists in converting the ethical desiderata in this framework into formal axioms to analyze their potential compatibility. Our main result is that they are indeed compatible and single out one and only one protocol, which differs from the previously used ones.

The problem we analyze here is of course not limited to the allocation of vaccines during an epidemic. Rather, the protocol is applicable whenever scarce medical resources need to be allocated across different territories or organizations while

respecting the ethical principles of prioritization and equal treatment of equals. More generally, the allocation of scarce medical resources is often decided *ad hoc* on the basis of heuristic approaches that often oversimplify the problem (35). The protocol we present here is derived from the formal analysis of the constraints arising from universally-appealing ethical principles, and hence provides a more nuanced approach. Of course, this protocol is not a universal recipe to be blindly applied to every ethical allocation dilemma. Our algorithm is well-suited for the normative allocation of scarce resources whenever three conditions are fulfilled. First, the demand exceeds the resources at hand. Second, administrative records of the patients or resource claimants are available. Third, there is an uncontroversial prioritization of the claimants (as decided by medical experts and the legitimate authority on the basis of scientific evidence). Note that these properties can be fulfilled at multiple levels, from allocations across countries in a supranational alliance or across states in a country to those across healthcare areas in a region or between hospitals in a local network.

The present work is complementary to an important strand of the literature that studies how to allocate priority depending on the societal objective function.[3] For instance, other studies show that older groups should be vaccinated first if the target is minimizing deaths, but younger groups should be vaccinated earlier if the target is to minimize confirmed cases (37), that the allocation of vaccines among the different sociodemographic groups depends on the stated goal (38), or that infections and economic losses can be minimized combining the optimal vaccine prioritization and the optimal stay-at-home policy (39).

Our approach is, of course, not exempt of limitations. For instance, it has been noted that many rationing methods are too rigid to be applied in very-dynamic crises (40), and this criticism also applies to the protocol we identify. A more important limitation is that, necessarily, our formal approach takes the priority classes *and their priority order* as given. Our paper does not focus on vaccine prioritization, but rather on territorial and class allocation (fulfilling key ethical principles) given the priority classes. Ultimately, the consequences of the protocol might be judged in conjunction with a given definition of priority classes, which is beyond the scope of our contribution. For instance, one might argue that if healthcare workers are prioritized, the protocol implies allocating (relatively) more vaccines to countries that are already in the fortunate situation of having more healthcare workers per capita. This might be problematic from a deontological perspective, since these countries are already better placed to cope with a health crisis. On the contrary, one might counter that this very same fact makes engaging in a global, worldwide supra-national alliance more politically acceptable for the governments of these favored countries, since they are the ones paying the largest share of the bill at the end of the day. Obviously, the protocol we identify will prescribe different allocations depending on the final prioritization decided by the experts in the field. However, our result is orthogonal to these considerations. We only state that, given the priority classes (which are exogenously given and ideally determined by medical experts), there exists one and only one algorithm that allocates vaccines satisfying the ethical desiderata. If a given definition of priority classes is changed on the basis of ethical or political arguments, the ethical principles we discuss still pin down the same algorithm for vaccine allocation across the territories and the new classes.

A further limitation is that our work concentrates on the implications of specific ethical desiderata (17) for allocation procedures. Of course, a myriad of other dimensions are important in practice, ranging from logistic considerations to political constraints. However, it is important to understand that our result is a full characterization. Suppose that one considered some other, further desideratum to be crucial, e.g., arising from political or logistical considerations. Since there is one and only procedure satisfying the two key ethical desiderata, the question of whether there is a procedure satisfying those desiderata and also the additional one is immediately solved: if the PE protocol fulfills that desideratum, the answer is positive. If the PE protocol fails this further desideratum, the answer is negative.

Hence, our result can be seen as either good news or bad news. On the one hand, there exists a procedure fulfilling the fundamental ethical desiderata identified by a wide consensus. On the other hand, there exists only one such procedure, and hence adding any further constraints or wishes is likely to result in an impossibility theorem. We see our result mostly on the positive side. First, it shows that the allocation of scarce medical resources to multi-territorial areas (from medical districts to the whole planet) under priority constraints is feasible while respecting ethical principles. This does not mean that the implementation of such allocations will be logistically simple or politically uncontroversial. The result shows possibility, and hence hope that other difficulties can be overcome. Second, not all possible, additional desiderata will affect the allocation in itself. For example, logistical considerations might impose constraints on which specific vaccine batches can be allocated to which territories, or on the exact timing of delivery. However, if such difficulties can be overcome without affecting the allocation totals derived from the procedure, the properties of the allocation in itself are unaffected. That is, some additional (but of course important) dimensions of the allocation problem might concern implementation and be orthogonal to the properties considered here.

5. Conclusion

We show that elementary ethical desiderata can be fulfilled by Vaccine Rationing Protocols. This was by no means a

3 Other works look at more operational aspects of vaccine distribution. For example, the optimal number of doses to hold in an inventory (36).

given. The mathematical social sciences are ripe with examples where putting together a number of desiderata results in an impossibility theorem, as (to cite but one example) the celebrated Arrow's impossibility theorem (41) which shows that there exists no democratic voting method fulfilling a number of innocent-looking, ethically-appealing properties.

Our result actually pins down a protocol. If several protocols fulfilled the ethical desiderata, we would have opened Pandora's box and started a discussion about the relative virtues of one or another protocol. On the contrary, there exists only one protocol fulfilling the targeted properties. Using any other protocol, or any variant of PE (no matter how seemingly small the deviation) will result in a procedure which violates either Prioritizing According to Needs or Treating Equal People Equally. Hence, as long as those principles are deemed desirable, the protocol we identify shows the only way to implement them. It is important to note that the protocol is algorithmic and readily implementable. Our analysis provides not a discussion of a framework, but an actual method, down to the specific computations, ready to be implemented out of the box.

Our results lead to immediate recommendations. If decision makers wish to implement the ethical principles reflected by Prioritizing According to Needs and Treating Equal People Equally, currently-used allocation protocols as the Territorial Allocation protocol need to be replaced by the Priority-Equality protocol. This creates the need for territorial authorities to formally agree to the protocol and its implementation. Of course, this will be easier for certain territorial alliances (states within a single country) than others (heavily decentralized multinational entities).

We conclude by remarking that our algorithm is a general tool to allocate any scarce medical resources, including of course vaccines but also newly-developed, expensive treatments, or preventive treatments from a national stockpile (e.g., iodine pills in the face of nuclear threats).

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

CA-F, JG-S, and MG-V conceptualized the project, proposed the formal model, and drafted the paper. CA-F and JG-S revised the manuscript and added examples based on real data. All authors contributed to the article and approved the submitted version.

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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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.986776/full#supplementary-material

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Waterborne diseases and ethnic-related disparities: A 10 years nationwide mortality and burden of disease analysis from Ecuador

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Background: Despite worldwide progress in terms of clean water supply, sanitation, and hygiene knowledge, some middle and most of low-income countries are still experiencing many diseases transmitted using unsafe water and the lack of sanitation.

Methods: To understand the impact of all waterborne diseases (WBD) registered in Ecuador. We performed a population-based analysis of all cases and deaths due to WBD in Ecuador based on the national public databases of hospital discharges as a proxy of incidence, in-hospital mortality, and countrywide general mortality rates from 2011 to 2020.

Results: In Ecuador, mestizos (mixed European and Indigenous American ancestry) had the greatest morbidity rate (141/100,000), followed by indigenous (63/100,000) and self-determined white patients (21/100,000). However, in terms of mortality, indigenous population have the greatest risk and rates, having a 790% additional mortality rate (2.6/100,000) than the reference group (self-determined white populations) at 0.29/100,000. The burden of disease analysis demonstrated that indigenous had the highest burden of disease caused by WBD with 964 YLL per every 100,000 people while mestizos have 360 YYL per 100,000 and self-determined white Ecuadorians have 109 YYL per 100,000.

Conclusions: In Ecuador, waterborne diseases (WBD) are still a major public health problem. We found that indigenous population had higher probability of getting sick and die due to WBD than the rest of the ethnic groups in Ecuador. We also found that younger children and the elderly are more likely to be admitted to the hospital due to a WBD. These epidemiological trends are probably associated with the lower life expectancy found among Indigenous

than among the rest of the ethnic groups, who die at least, 39 years earlier than the self-determined white populations, 28 years earlier than Afro-Ecuadorians and 12 years earlier than the mestizos.

KEYWORDS

diseases, water, sanitation, hygiene, disparities, inequalities, WaSH

1. Introduction

During the last 50 years, the world has experienced a notable increase in wealth in almost every country and region; nevertheless, the rise of inequality has been unparalleled and continuous (1). Several countries' economic prosperity and health development have led to decreased mortality, increased life expectancy, and a continuous struggle to maintain the general state of health (2). However, those on the lower ends of the socioeconomic spectrum have less ability to access optimal welfare conditions such as nutrition, housing, and education. Therefore, they are more likely to suffer from pathogenic infectious diseases caused by micro-organisms such as bacteria, virus or parasites, all responsible for what is known as waterborne diseases (WBD) (1).

WBD are considered an essential indicator of health in the most deprived populations (3). The World Health Organization (WHO) estimates that 844 million people lack a basic drinking water supply services (4). According to UNICEF in 2017, 2.1 billion people in the world did not have access to safe drinking water, which can be contaminated by feces and other wastes, causing diseases such as cholera, dysentery and typhoid fever (5). About 842,000 people die each year from diarrhea due to contaminated water, of which 361,000 are children under 5 years old (6). WHO estimated that 10.6, 15.4, and 45.8 per every 100,000 deaths were attributed to water, sanitation and Hygiene (WaSH) preventable diseases in the Eastern Mediterranean, South East Asia and Africa continents, respectively (7). In Latin America, the consumption of contaminated water and the lack of access to improved sanitation services is related to more than 4,000 premature deaths (8). One important factor is that Latin America is one of the fastest urbanizing regions of the world, where only an average of 30% of the wastewater is treated and most of it is dumped in the natural waterways that are source of water for productive activities and production downstream (9, 10).

Ecuador is one of the most affected countries by this reality, with 15.4% of its urban and 31.8% of the rural population consuming contaminated water with fecal coliforms, and only an average of 20% of wastewater treated (11). In a country like Ecuador, which shares similar characteristics to other countries in the region such as Peru, Colombia, Bolivia or Brazil, a large part of the indigenous population lives in remote areas without adequate access to basic services such as clean-running water, electricity or sewage services (12, 13). It has been reported that Indigenous groups suffer a heavier burden of communicable and non-communicable diseases compared to the rest of the population (14). In Ecuador, only 20.9% of indigenous children have WaSH measures, meaning that 8 out of 10 indigenous children simultaneously lack safe water, basic sanitation or supplies for handwashing (15). The overall low basic sanitation coverage (70.9%) of the indigenous population does not represents the reality of some Amazonian or Andean communities (15). For instance, WaSH within the Amazon region (eastern region of Ecuador), only reaches 24.8%, while in the highlands (central region of Ecuador) and the Coast (western region of Ecuador), this indicator rises to 55.1 and 52.8%, respectively (15).

According to the identifiable Objectives of Sustainable Development of Water, Sanitation and Hygiene of Ecuador, access to safe water is influenced by the ethnicity of Ecuadorians. For instance, only 59.1% of the Afro-Ecuadorian population have access to clean and potable drinkable water, that number raises to 58.7% among Montubios (a group made up of peasant farmers on the Ecuadorian Coast region), 73.4% for mestizos and >95% for self-determined white population (16). In terms of running water, 86.9% of Afro-Ecuadorians, 86.7% of mestizos and 85.6% of Montubios have a constant supply of water for washing their hands and for their lavatories (16).

After 2015, the Sustainable Development Goals (SDG) broadened the spectrum of targets focusing on water, sanitation and hygiene (WaSH), inviting the member states, including Finland in first place with a human development index (HDI) = 0.938, Chile in first place among American countries with HDI = 0.851, followed by Uruguay with HDI = 0.817, while for Ecuador the HDI is 0.759, to fulfill their obligation to bring better services to its population on this matter (17). Unfortunately, the effect of these achievements on health is hard to measure. In Ecuador, two studies found that access to basic services, better living conditions and access to health services reduce morbidity and mortality, both in newborns and in adults (18, 19). Nonetheless, to our best knowledge, there are no studies that explore the national distribution of waterborne diseases and related problems. This information is crucial to guide and to prioritize interventions to address WaSH and WBD related problems among vulnerable populations.

In this context, the aim of this study was to analyze the impact of waterborne diseases on Ecuadorian population and their population differences (age, gender, ethnics, and social health determinants) from 2011 to 2022.

2. Methodology

2.1. Study design

A country-wide comparison of the total number of cases and deaths attributed to WBD from the 24 provinces and the 221 cantons in Ecuador was performed from 2011 to 2020. We performed a secondary data analysis of publicly available data from the Ecuadorian National Institute of Statistics and Census (INEC) at https://aplicaciones3.ecuadorencifras.gob.ec/sbi-war/.

2.2. Setting and participants

Ecuador with an area of more than 283,000 km^2 is the smallest country in the Andean mountainous region in South America. The country is divided into four geographical regions, the coast, the highlands, the Amazon region, and the Galapagos Islands. The political division encloses 24 provinces, 10 from the highlands, seven from the coast, six from the Amazon region, and one from the insular region of Galapagos. Ecuador has 221 political divisions called cantons and they are comparable to cities elsewhere. In the 2010 Population Census, most of the population self-identified as mestizo (71.9%), followed by those who considered themselves Montubios (7.4%), Afro-Ecuadorians (7.2%), indigenous (7.0%) and white/Caucasians (6.1%). However, mathematical projections as 2021 developed from data of the National Survey on Employment, Unemployment and Underemployment (ENEMDU) 2021 are described in Table 1.

2.3. Variables

We constructed measurements for disease occurrence using hospital admission rates as a proxy for incidence. In terms of mortality, sex-age and ethnicity specific rates were computed using in-hospital mortality and death certificates as numerators and the population at risk as denominators. The lists of diseases used for the analysis was obtained from the INEC databases (including the variables of year of registration, sex, age, ethnicity, pathology, hospital discharge status, and geographic location) based on The International Statistical Classification of Diseases and Related Health Problems in its 10th version (ICD-10) (Table 2). Due to data source incompleteness determined by the absence of data for the cases studied corresponding to variables such as ethnicity and location especially in the first years reported in this research (2011, 2012, 2013) and underreporting, the proportion of entries with missing data on ethnic identity and educational attainment did not match the cumulative incidence and mortality for sex, age, and place of residence. The data was retrieved as it was documented within the reporting system.

2.4. Data source and measurement

We used the latest estimated projections based on the 2010 National Population Census to compute incidence and mortality sex-age specific rates with a yearly resolution from 2011 to 2020. Information by ethnicity was retrieved directly from the variable "ethnic background" from the official National Institute of Statistics and Census (INEC) databases.

2.5. Bias

To reduce the likelihood of incurring in any type of confirmation bias, data was retrieved directly from the official source by two members of the research team. They performed independent analysis and compared the results with the rest of the team. If controversies were observed, the entire team met up to solve any inconsistency.

2.6. Statistical analysis

We performed descriptive statistics based on demographic variables to obtain absolute and relative variations. We also constructed measurements for disease occurrence, including in-hospital mortality (%), incidence, and countrywide mortality rates. For the burden of disease analysis, the "lillies" package of the R was used to estimate YLL for patients with a given condition (20), the calculation methodology was based on the number of cases in a population with the diagnosis of a specific disease or condition, using the age of diagnosis of the disease for the cases studied, the Ecuadorian population, and the annual projection for each year based on the life expectancy of the population studied for Ecuador (21).

The analysis of the data was performed using the SPSS statistics software for Mac (IBM Corp. 2014, version 24.0. Armonk, NY, USA) and R version 3.6.2. Figures and graphs were performed in Prism 8 GraphPad Software version 8.2.0 (2365 Northside Dr. Suite San Diego, CA 92108). The basic cartography maps were generated using QGIS Development Team 180 2.8 (Creative Commons Attribution-ShareAlike 3.0 license CC BY-SA).

TABLE 1 Population distribution by ethnicity in Ecuador.

Ethnic self-determination	White-Caucasian	Afro-Ecuadorian	Montubio	Indigenous	Mestizo
Population (*N*)	215,499	582,838	744,461	1.401,315	13.458,965
%	1.30	3.60	4.50	8.50	82.10
Urban (*N*)	179,079	436,233	320,110	302,036	9.957,615
Rural (*N*)	36,420	146,606	424,351	1.099,278	3.501,349
Men (*N*)	103,748	280,978	376,331	692,399	6.543,623
Women(*N*)	111,751	301,861	368,130	708,916	6.915,342
Suitable employment (%)	40.10	29.40	18.60	15.10	35.30
Unemployment (%)	7.10	10.20	2.10	1.80	5.60
Underemployment (%)	19.90	26.60	31.20	21.20	22.90
Income poverty rate (%)	16.90	37.70	38.30	52.70	24.60

2.7. Ethical considerations

According to the local and international regulation, secondary, fully anonymized publicly available data analysis do no required ethical approval for any kind. All procedures performed in our study were in accordance with the ethical standards of the Minister of Public Health (MoH) and with the Helsinki Declaration and comparable ethical standards.

2.8. Availability of data and materials

The datasets generated and/or analyzed during the current study are available in the following link: https://github.com/covid19ec/WASH.

3. Results

In the last 10 years of available data, Ecuador officially registered 361,457 cases and 1,870 deaths due to waterborne diseases. Women accounted for 51.8%. The overall incidence rate was 223 cases [CI95% 118–295] per 100,000 people and 1.1 deaths [CI95% 0.7–1.7] (Table 3).

TABLE 2 ICD-10 Classification of waterborne diseases (WBD).

ICD-10 classification
A00 Cholera
A01 Typhoid and paratyphoid fevers
A02 Other salmonella infections
A03 Shigellosis
A04 Other bacterial intestinal infections
A05 Other bacterial foodborne intoxications, not elsewhere classified
A06 Amoebiasis
A07 Other protozoal intestinal diseases
A08 Viral and other specified intestinal infections
A09 Other gastroenteritis and colitis of infectious and unspecified origin
A71 Trachoma
B15 Acute hepatitis A
B58 Toxoplasmosis
B68 Taeniasis
B69 Cysticercosis
B75 Trichinosis
B77 Ascariasis
B78 Strongyloidiasis
B79 Trichuriasis
B80 Enterobiasis
B81 Other intestinal helminthiases, not elsewhere classified
B82 Unspecified intestinal parasitism

3.1. WBD-related morbility

3.1.1. Age and gender differences

The average age of all water borne disease related cases for the mestizo group was 21.2 years. Meanwhile, the indigenous, Afro-Ecuadorian and Montubio groups were younger than mestizos with means of 21.3, 18.6, and 18. One years, respectively. On the other side, the white population recorded a mean of 28.9 years.

In terms of cases by age, we found that 39.9% of all WBD in Ecuador were among children younger than 4 years, followed by those from 5 to 9 years of age with 12.6% of the overall number of cases (Table 4).

TABLE 3 Number of WaSH related cases and deaths in Ecuador from 2011 to 2020.

	Cases	%	Incidence Rate/100,000	CI 95%	Deaths	%	Mortality rate/100,000	CI 95%
Men	177,704	49.16	221	[115–292]	919	49.14	1.1	[0.8–1.78]
Women	183,753	50.84	224	[120–298]	951	50.86	1.1	[0.75–1.75]
Total	361,457	100.00	223	[118–295]	1,870	100.00	1.1	[0.78–1.75]

TABLE 4 Age differences among patients with Wash related diseases.

Age	Pop. at risk	Hospital admissions (*N*)	Relative (%)	Incidence rate/100,000	CI <95%	CI > 95%	Deaths (*N*)	Relative (%)	In hospital mortality (%)
0–4	1,658,115	144,188	39.9	89.18	38.75	124.42	581	31.1	0.4
5–9	1,676,535	45,420	12.6	27.85	16.68	33.43	70	3.7	0.2
10–14	1,682,311	22,429	6.2	13.79	8.18	17.22	37	2.0	0.2
15–19	1,619,198	13,938	3.9	8.62	4.46	12.16	18	1.0	0.1
20–24	1,515,761	14,813	4.1	9.17	4.6	13.16	25	1.3	0.2
25–29	1,397,212	15,554	4.3	9.61	5.18	13.31	23	1.2	0.1
30–34	1,287,159	14,259	3.9	8.81	4.91	12.04	30	1.6	0.2
35–39	1,189,296	11,970	3.3	7.38	4.31	9.65	37	2.0	0.3
40–44	1,076,995	10,354	2.9	6.4	3.48	8.74	31	1.7	0.3
45–49	951,067	9,434	2.6	5.83	3.12	8.22	43	2.3	0.5
50–54	833,293	9,301	2.6	5.74	3.14	7.55	39	2.1	0.4
55–59	719,133	8,703	2.4	5.36	3.13	7.0	48	2.6	0.6
60–64	594,271	8,191	2.3	5.05	2.87	6.53	55	2.9	0.7
65–69	465,854	7,627	2.1	4.7	2.82	5.94	79	4.2	1.0
70–74	347,342	7,091	2.0	4.36	2.71	5.45	90	4.8	1.3
75–79	240,977	6,241	1.7	3.84	2.42	5.01	107	5.7	1.7
80+	256,124	11,944	3.3	7.35	4.54	9.11	557	29.8	4.7
Total	17,510,643	361,457	100.0	223.03	118.32	295.33	1,870	100.0	0.5

Furthermore, in the subgroup analysis (by age), substantial differences in morbidity among patients under 5 years old per ethnic group were found (Figure 1). In this case, the under 5 years hospital discharge rates showed a 118% increase in hospital discharges rates among mestizos (60/100,000) than indigenous children (27/100,000) and 1,032% more than self-reported white children (5/100,000). In terms of morbidity among those older than 65 years of age, mestizos have a significantly higher incidence rate (13/100,000) than indigenous (6/100,000) and self-reported white elderly (2/100,000) (Figures 1A,B).

3.1.2. Morbidity rates by ethnic groups

The mean overall morbidity rate of WBD in Ecuador was 223 (CI95% 118–295) cases per 10,000 inhabitants (Figure 1). We found that in Ecuador, mestizo people had the greatest morbidity rate (141/100,000) followed by indigenous (63/100,000) and self-determined white patients (21/100,000). However, in terms of mortality, indigenous population have a 790% increase in mortality rate (2.6/100,000) compared to self-determined white populations (0.29/100,000) and 176% more compared to mestizos (0.94/100,000) (Figures 1A,B).

3.2. WBD-related mortality

In Ecuador, a total of 1,870 deaths were recorded from 2011 to 2020, 951 (51%) were women and 919 (49%) were men. The mean mortality rate of WBD was 1.1 per 100,000 (CI95% 0.7–1.7). From 2011 to 2020, we observed an average decline of 70% in the number of WBD hospital admissions, ranging from 67% from indigenous to 73% among Afro-Ecuadorians (Figure 2A).

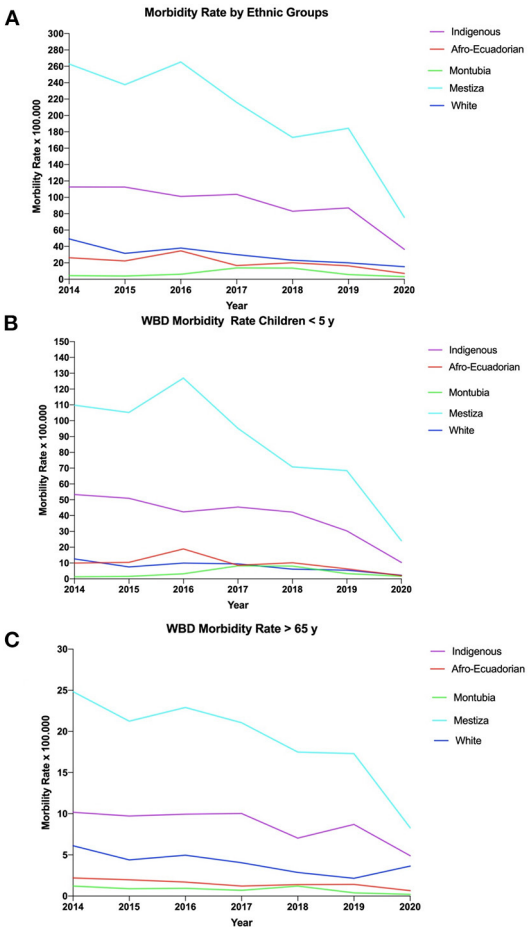

FIGURE 1
Morbidity due to waterborne diseases in Ecuador from 2011-2020. **(A)** Overall Morbility rate in Ecuador. **(B)** Morbility Rate by ethnic group in children from 0 to 5 years. **(C)** Morbility rate by ethnic group in patients over 65 years of age.

3.2.1. Age and gender differences

The average age of death due to WBD in Ecuador as 42.4 for men and 49.6 for women. The difference among ethnic group is significant at 95% confidence level ($p < 0.001$). Most of deaths were found among children younger than 4 years of age, representing 31.07% ($n = 581$) of the total universe, followed by those patients older than 80 years of age, representing 29.79% ($n = 557$).

3.2.2. Mortality rates by ethnic group

In Ecuador, indigenous people have the highest mortality rates due to waterborne diseases per every 10,000 inhabitants. This group has a mortality rate from 2011 to 2020 of 2.6 per 100,000 (CI 95% 1.1–5.2), while Afro-Ecuadorians have a rate of 0.8 per 100,000 (CI95% 0.1–3.0), Mestizos the highest rate of 0.9 per 100,000 (CI95% 0.7–1.2) and self-reported white population with the lowest rate of 0.2 per 100,000 (CI95% 0.08–0.56) (Figure 2C).

Furthermore, in the subgroup analysis per age, substantial differences in mortality among under 5 years old per ethnic group were found (Figure 2D). In this context, the mean mortality rate among indigenous children was 1.2 per 100,000 (CI95% 0.3–2.6), while Afro-Ecuadorians have a rate of 0.3 per 100,000 (CI95% 0.1–1.0), Mestizos with 0.25 per 100,000 (CI95% 0.1–0.3) and self-reported white people with 0.04 per 100,000 (CI95% 0.1-0.19) (Figure 2B). Regarding mortality among the elderly, the trends follow the same pattern than among children (Figure 2C).

3.2.3. Life expectancy

In Ecuador, the all-causes mean age at death was 62.3 years while for the WBD the mean age at death was 45.6 years. The average age of death among self-reported white people with a WBD was 63.3 years, while indigenous people died 29.3 years younger than self-reported white people, followed by Afro-Ecuadorians with 28.2 years, Mestizos 12.1 years and Montubios with 5.1 years of age (Figure 3).

3.2.4. In-hospital mortality

Overall, in Ecuador we found an average in-hospital mortality proportion of 5.6% of the total number of admissions. Trichinosis (B75) resulted in the most lethal when admitted to the hospital with 60.0 % of patients dying, followed by Strongyloidiasis (B78) with 12.50 % and other intestinal helminthiases, not elsewhere classified (B81) with 11.76 % (Table 5).

3.3. Sociodemographic analysis around WBD

3.3.1. Educational attainment

In Ecuador, the number of cases of waterborne diseases, when plotted by educational attainment, demonstrated that from the 100% of deceased people, most of the indigenous have no formal education at all (62%) (Figure 2B). In contrast, self-determined White Ecuadorians with no formal education accounted for <5% in the control group (Figure 2B).

3.3.2. Rural vs. urban differences

The percentage of patients affected by waterborne diseases who lived in urban areas is greater for all groups except for indigenous, where 54% of them are reported to be living in rural areas during the time of diagnosis.

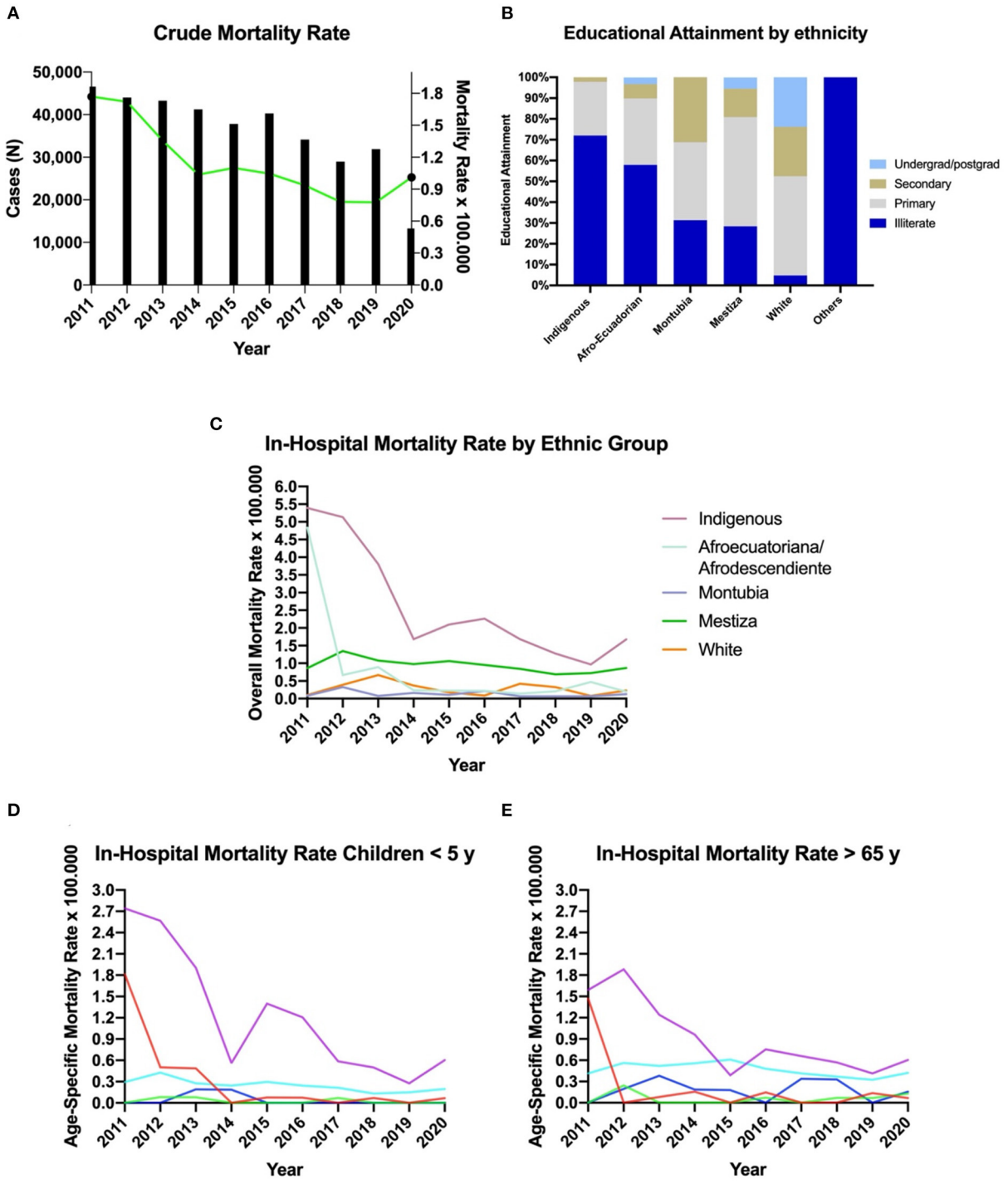

FIGURE 2
Mortality due to waterborne diseases in Ecuador from 2011 to 2020. **(A)** Mortality rate due to WBD in Ecuador from 2011 to 2020. **(B)** Educational attainment by ethnic group in Ecuador. **(C)** Overall mortality rate by ethnic group. **(D)** Mortality rate by ethnic group in among children younger than 5 years of age. **(E)** Mortality rate by ethnic group in people older than 65 years of age.

3.3.3. Geographical differences

In terms of provinces, the most affected province in Ecuador was Morona Santiago with 446.23 cases per 100,000 inhabitants, followed by Cañar with 346.47 cases per 100,000 inhabitants and El Oro province with 327.16 cases per 100,000 inhabitants (Table 6).

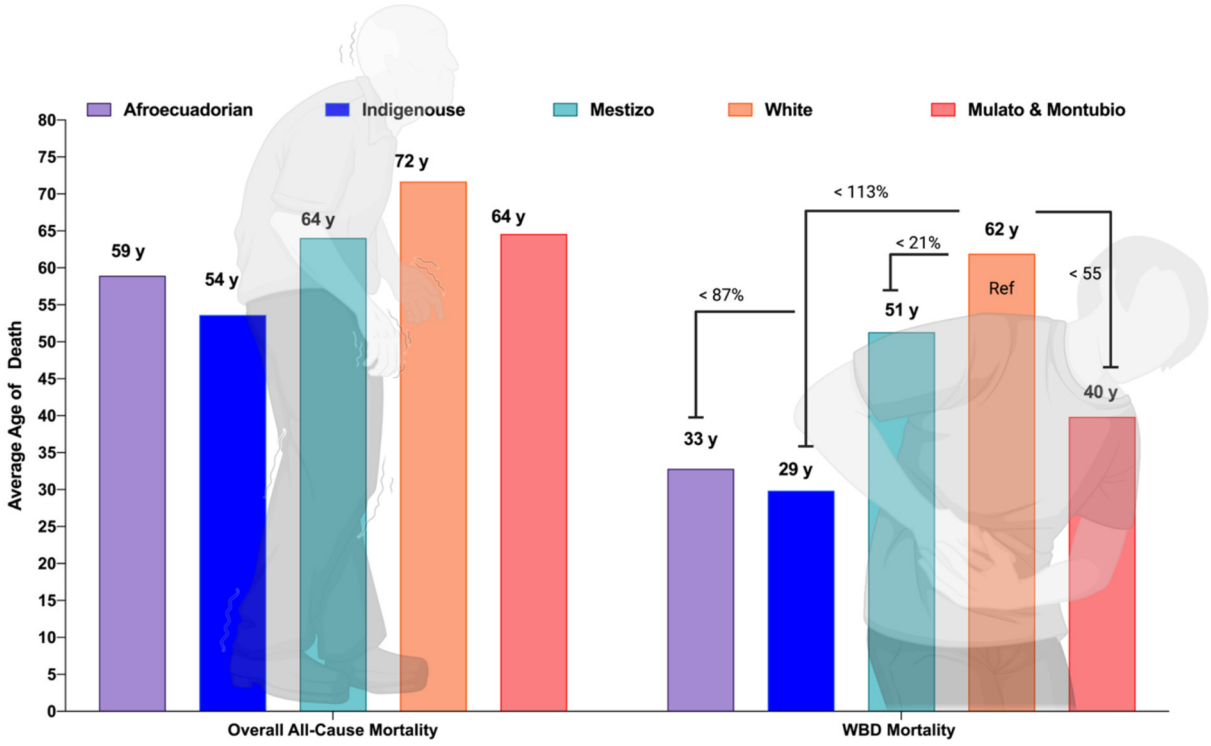

FIGURE 3
Average age of death due to all cause's mortality and WBD in Ecuador by ethnic group.

In relation to mortality, Napo Province had the highest mortality rate with at least 2.98 deaths per 100,000 inhabitants, followed by Cotopaxi with 2.46 deaths per 100,000 inhabitants and Chimborazo with 2.31 deaths per 100,000 inhabitants. The most affected cantons (cities) by WBD in Ecuador were Santiago (Morona Santiago) with an incidence rate of 897.33 cases per 100,000 inhabitants, followed by Limon Indanza (Morona Santiago) with 844.98 cases per 100,000 inhabitants and El Chaco (El Napo) with 771.73 cases per 100,000 inhabitants (Figure 4A). In relation to mortality, the canton of Saquisili (Cotopaxi) presented the highest mortality rate with more than 10.59 deaths per 100,000 inhabitants, followed by the canton of Oña (Azuay) with 7.63 deaths per 100,000 cases and Putumayo (Sucumbios) with 4.48 deaths per 100,000 cases (Figure 4B).

3.3. WBD burden analysis

Overall, in Ecuador, 56,507 years of life have been lost prematurely due to WBD from 2011 to 2020. Although the majority of the population studied in this analysis was of mestizo ethnicity with 9,822 YLL, the adjusted calculation of YLL per capita (100,000 inhabitants), showed that the indigenous ethnicity group had the highest burden (964/100,000) of disease caused by WBD, followed by mestizos (360/100,000), Afro-Ecuadorians (287/100,000) and self-determined white Caucasians (109/100,000) (Table 7).

Consequently, when comparing the indigenous ethnicity with the other ethnic groups, the indigenous were more affected showing an excess of 236.2% of YLL prematurely compared to Afro-Ecuadorians, 2,374.4% compared to Montubios, 167.3% compared to mestizos, and 777.3% compared to White-Caucasians.

4. Discussion

The results of our research show that in Ecuador there is a high incidence rate of waterborne diseases. In general terms, the burden of disease of these WBD is greater among indigenous populations than among mestizos or self-reported white/Caucasians. This is evident when we analyze the years of life lost prematurely (YYL) due to these infectious diseases related to the consumption of poor-quality water or the lack of sanitation, especially among indigenous populations. We found significant differences between indigenous populations and other ethnic groups in Ecuador, probably linked to higher poverty index rates, lower access to clean water and

TABLE 5 In hospital mortality (%) caused by WBD in Ecuador from 2011 to 2020.

Disease	ICD-10	Deaths (*N*)	Hospital admissions (*N*)	In hospital mortality (%)
Typhoid and paratyphoid fevers	A01	13	6,162	0.2
Other salmonella infections	A02	22	11,080	0.2
Shigellosis	A03	1	451	0.2
Other bacterial intestinal infections	A04	229	35,304	0.6%
Other bacterial foodborne intoxications, not elsewhere classified	A05	24	9,259	0.3
Amoebiasis	A06	19	6,413	0.3
Other protozoal intestinal diseases	A07	1	959	0.1
Viral and other specified intestinal infections	A08	9	12,485	0.1
Other gastroenteritis and colitis of inf. and unspecified origin	A09	1,300	262,914	0.5
Acute hepatitis A	B15	46	8,017	0.6
Toxoplasmosis	B58	43	683	6.3
Cysticercosis	B69	123	1,968	6.3
Trichinosis	B75	3	5	60.0
Ascariasis	B77	15	1,282	1.2
Strongyloidiasis	B78	5	40	12.5
Other intestinal helminthiases, not elsewhere classified	B81	2	17	11.8
Unspecified intestinal parasitism	B82	15	4,418	0.3
Total	N/A	1,870	361,457	0.5

reduces access to health systems as depicted in our conceptual framework (Figure 5).

According to the local authorities, indigenous people are more likely to live in rural areas, areas with poorer infrastructure, no potable water treatment plants and scarce or none waste management (22, 23). This trend might be related to the fact that rural area has cheaper housing and makes it possible to cultivate the land (24). Therefore, they do not have access to all other favorable social conditions, including education and adequate hygiene habits, since most of them cannot afford housing in urban centers, continuing the vicious circle of poverty among indigenous. Also, these lands suffer high degrees of deforestation, with a consequent loss of water quality that have been linked to gastrointestinal diseases (25, 26).

Apart from that, these populations have low levels of educational attainment which increases the risk of incurring in unhygienic practices such as not washing hands after going to the bathroom or before eating, open defecation and river defecation as well as poor waste management (27, 28). Another finding comes along to the fact that despite having lower WBD incidence rates, indigenous population have higher mortality rates, an indirect indicator of poorer healthcare access increasing the risk of more severe illness, thus, increasing death rates (29).

This study found that the average mortality rate in Ecuador was 1.1 per 10,000 inhabitants, while the hospitalization rate was 223 per 10,000 inhabitants. Countries with a very high Human Development Index, such as Canada, report lower mortality and hospitalization rates from transmitted diseases, on average 0.52 and 12 per 10,000, respectively (30). Regarding nearby realities, in Colombia, the mortality rate for children under 5 years old due to acute diarrheic disease was 2.69 per 10,000 inhabitants during the years 2011–2014. This value did not considered ethnicity as a risk factor, neither age-sex adjusted rates, reducing our chances to fairly compare WBD incidence between countries (31).

It is known that the main factors that contribute to waterborne disease outbreaks are the poor treatment of consumption and waste water, being higher on underground water sources than in other sources (58.6% vs. 53.7%) (32). In Ecuador, 27% of the population consumes polluted water, regardless of the source, being higher in rural and amazon areas where almost 45.3% have inadequate water quality (33). More development in the control of the factors contributing to outbreaks should be considered to achieve the 6th goal in the Sustainable Development Goals (SDGs). Ecuador has made a considerable improvement since the 1990s by increasing some health indicators, such as the percentage of rural population with access to improved water, from 61.4% in 2003 to 75.5% in 2014 (34). In addition, accomplishing the objective of sustainable development in WaSH practices, then water

TABLE 6 Incidence and mortality rate due to waterborne diseases by province in Ecuador from 2011 to 2020.

Province	Hospital admissions	Incidence rate/100,000	CI<95%	CI>95%	Deaths	Mortality rate/100,000	CI<95%	CI>95%	In hospital mortality (%)
Azuay	22,218	275.81	147.85	388.48	164	2.03	0.89	3.09	0.74
Bolivar	3,999	198.66	120.08	243.91	20	0.98	0	2.43	0.50
Canar	8,943	346.47	204.29	437.83	37	1.45	0.38	3.53	0.41
Carchi	2,512	139.65	82.27	183.24	21	1.16	0	2.53	0.84
Chimborazo	15,029	300.56	151.26	408.46	116	2.31	1.25	3.37	0.77
Cotopaxi	10,689	234.24	125.33	302.75	109	2.46	0.1	6.73	1.02
El oro	21,935	327.16	162.77	410.04	52	0.78	0.21	1.57	0.24
Esmeraldas	7,190	121.09	59.49	202.07	65	1.09	0.34	2.51	0.90
Galapagos	589	202.20	79.29	302.29	0	0	0	0	0.00
Guayas	97,223	239.03	122.98	333.74	304	0.74	0.57	0.96	0.31
Imbabura	7,408	167.25	86.75	238.23	55	1.23	0.64	1.83	0.74
Loja	9,450	191.40	101.43	272.73	67	1.37	0.17	2.8	0.71
Los rios	22,656	263.72	119.20	395.87	68	0.79	0.35	1.45	0.30
Manabi	30,972	208.25	89.65	311.52	97	0.64	0.35	0.97	0.31
Morona Santiago	7,779	446.23	259.82	589.84	37	2.13	0.81	4.3	0.48
Napo	3,085	263.33	78.96	465.17	34	2.98	0	10.44	1.10
Orellana	2,071	137.85	65.97	215.34	25	1.76	0	8.3	1.21
Pastaza	3,030	307.37	134.46	468.22	10	0.95	0	2.82	0.33
Pichincha	41,315	140.25	82.81	175.97	341	1.15	0.82	1.56	0.83
Santa Elena	11,157	311.18	156.11	397.31	41	1.15	0	2.07	0.37
Sto. Domingo DLT	9,474	227.16	148.26	336.32	51	1.2	0.6	1.65	0.54
Sucumbios	4,843	237.96	74.90	372.28	43	2.15	0.88	4.7	0.89
Tungurahua	15,110	271.86	155.55	378.97	104	1.87	0.77	2.99	0.69
Zamora C.	2,780	255.41	177.22	310.17	9	0.84	0	2.44	0.32
Total	361,457	223.55	118.60	296	1,870	1.19	0.83	1.78	0.52

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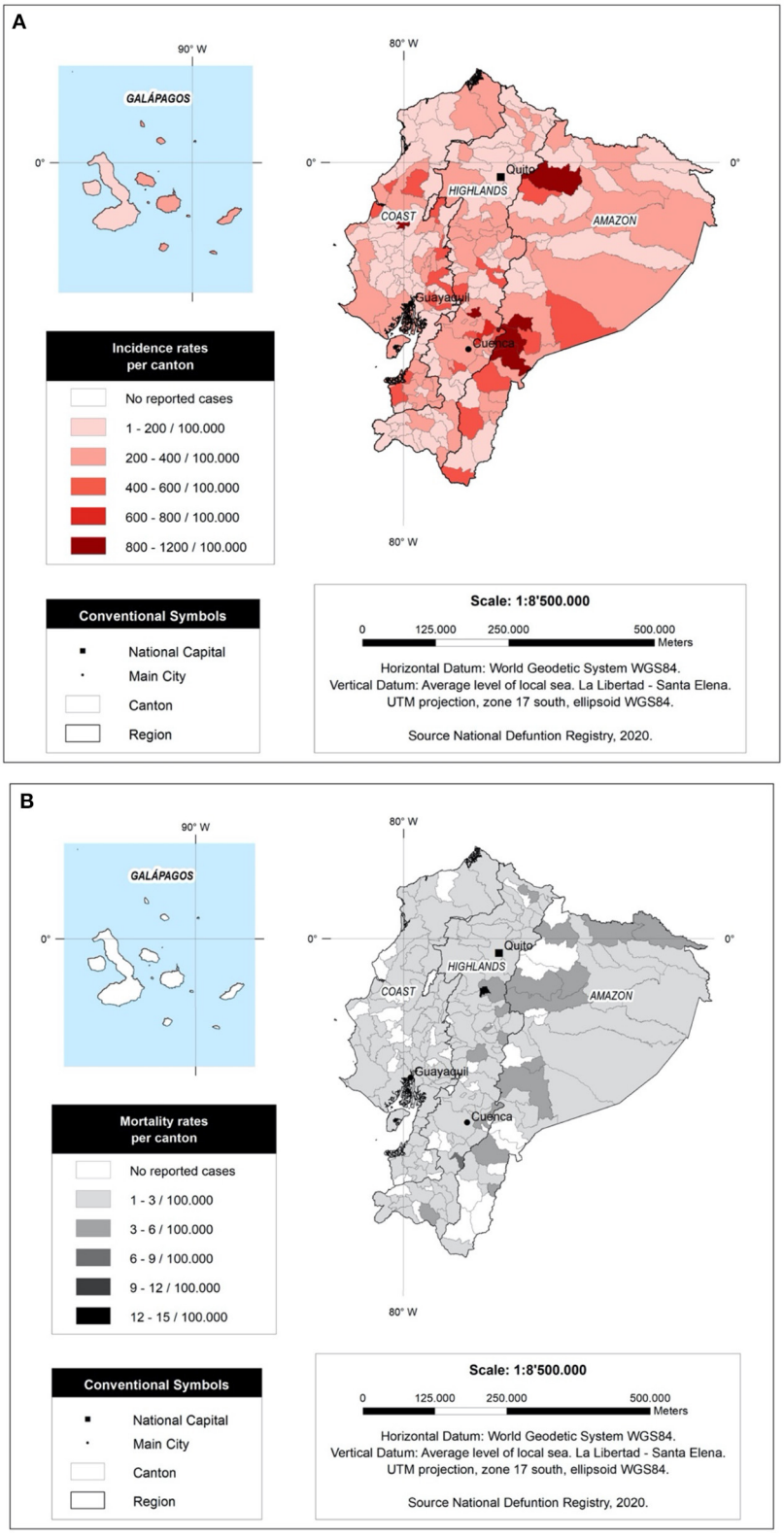

FIGURE 4
Incidence and mortality rate per 100,000 per canton in Ecuador from 2011 to 2020. **(A)** WaSH related Incidence Rate per canton **(B)** WaSH related mortality rate per canton.

TABLE 7 Burden of WBD and years of life lost (YLL) prematurely caused by WBD in Ecuador from 2011 to 2020.

	White-Caucasian	Afro-Ecuadorian	Montubio	Indigenous	Mestizo	Other	Total
Total cases (*N*)	23	5	1	847	1,101	27	2,004
Urban (*N*)	718,589	774,486	434,007	218,571	6,904,554	40,579	9,090,786
Rural (*N*)	163,794	267,073	636,721	799,605	3,512,745	12,775	5,392,713
Total (*N*)	882,383	1,041,559	1,070,728	1,018,176	10,417,299	53,354	14,483,499
YLL	967	2,992	422	9,822	37,587	4,717	56,507
YLL/100.000	**109.6**	**287.3**	**39.5**	**964.7**	**360.8**	**8,840.3**	

Bold values are the total Years of Life Lost Prematurely per 100,000 people.

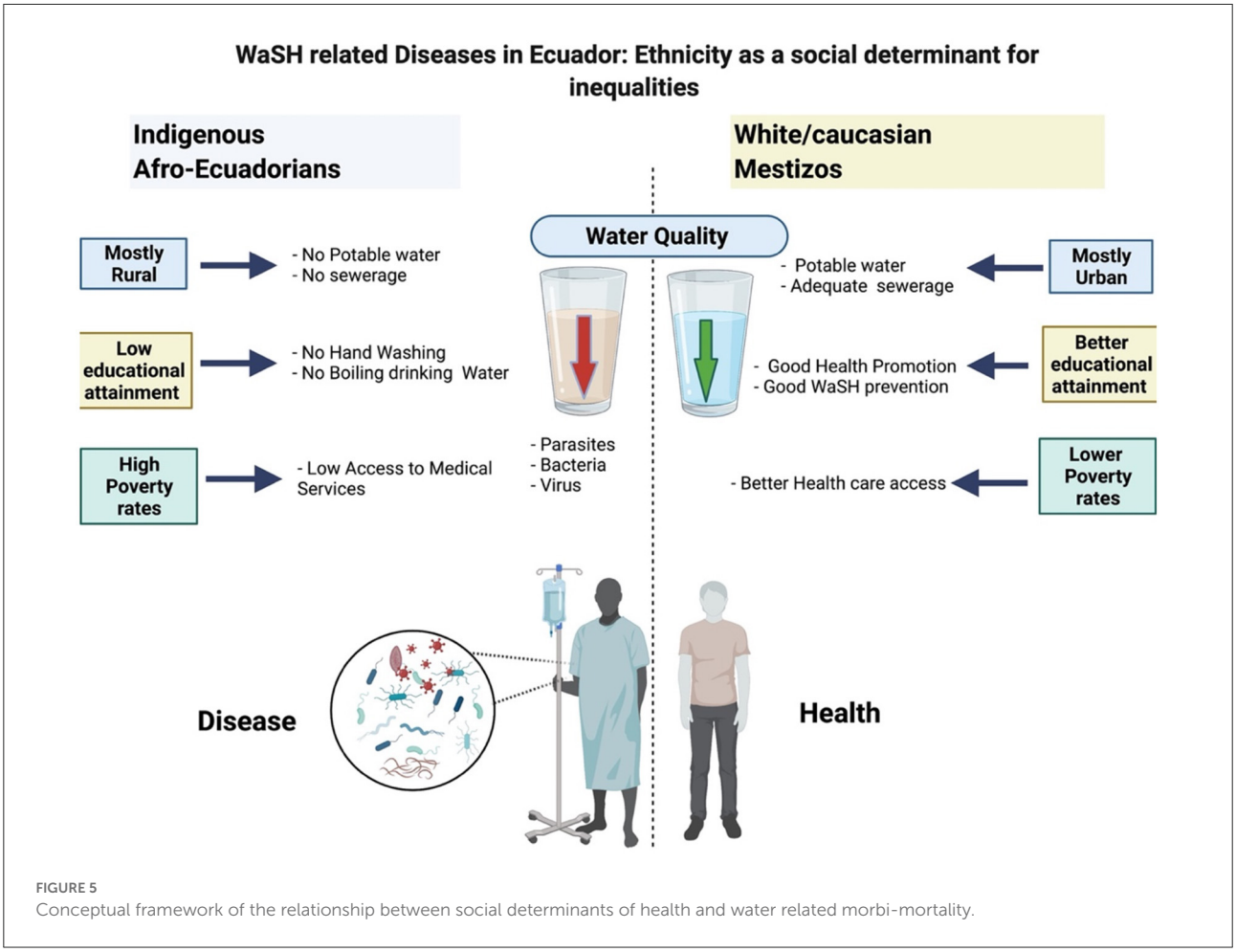

FIGURE 5
Conceptual framework of the relationship between social determinants of health and water related morbi-mortality.

availability seemed to be assured. However, several factors in terms of access and coverage vary, which is the cause of significant disparities. The investment in aqueduct and sewerage systems in Colombia during 2011–2014 were not enough reduce the incidence of waterborne diseases (31). In Argentina and Brazil, although mortality cases decreased, the measure was not enough to eradicate waterborne diseases, neither in the long nor in the medium term (35). In fact, in Colombia and Argentina only 12 and 10 % of the population, respectively, are connected to wastewater treatment facilities (10), which means that wastewaters are dumped in natural waterways without treatment, which can be the source of water for other populations downstream. For example, in Ecuador, a study in Quito, where 98 % of wastewater is dumped directly to waterways, found 26 viral species associated with infections in humans (36).

Indigenous people have limitations to access healthcare, such as geographical isolation and poverty (37). This may be the reason why they show lower rates of hospital discharges but higher rates of mortality due to WBD. Disease progression

is another consequence of having poorer access to the health system among indigenous and Afro-Ecuadorian populations. For example, a previous otherwise treatable roundworm infection caused by the ingestion of *Trichinella larvae* becomes severe trichinosis in cases of heavy infestation (38, 39). In addition, several reports show that vital organ complications such as myocarditis, encephalitis, or meningitis, caused by foodborne parasitic diseases increase in-hospital mortality, something that we observed in our results (40, 41).

According to the latest statistics from the National Institute of Statistics, poverty was reduced significantly, especially extreme poverty (42). About WaSH resources, the share of the population using improved drinking water resources in 2015 was 92.6%, and sanitation facilities was 86.1% (34). Despite these achievements, the reduction was not equitable among all ethnic groups in the country. This study shows that WBD in the indigenous population is significantly greater than the one reported among mestizos, Afro-Ecuadorians, and white populations, as shown in another work by Morales and Mideros (43). Living under poverty in rural areas and limited access to clean water, secure food sources and other basic needs have affected this ethnic group. Moreover, there is a strong relationship on land conservation and children's health, especially in rural areas. It has been stated that forest cover is associated with less diarrheal disease in children in developing countries (25). Studies across tropical countries have demonstrate that land conservation is a crucial factor preventing WBD and improving child health. Therefore, land conversion can have tremendous effects on vulnerable population living on rural areas, like indigenous groups in Ecuador.

On the other hand, the diagnosis of less-lethal infectious diseases such as respiratory endocrine and metabolic diseases is more frequent in proportion in the white population, possibly due to better access to health resources and medicines (44). In Ecuador, diseases related to poor hygiene and lack of potable water, clean and safe for health, mainly affect the indigenous population. In a report from the INEC, it was evidenced that the houses with adequate access to clean water did not exceed 80%, while in other groups such as mestizos and white population, it surpassed 97% (42). In general, Ecuadorian indigenous groups have reduced access to safe drinking water and appropriate sanitation and wastewater treatment facilities, which influences greater morbidity and mortality caused by diseases transmitted by the water. All this information is available from the countrywide databases that includes data from indigenous populations that live in Ecuador and have access to health services. In the country however, as well as in other parts of the Amazon rainforest there are indigenous populations living in voluntary isolation that drink water directly from the rivers (45, 46). Those groups could be affected by the poor quality of the water that might arrive through the tributary streams, thus, the importance of WBD is fundamental not only to reduce the prevalence of water-related infectious diseases but also to prevent the potential extermination of indigenous groups living in voluntary isolation (47). The information provided in this investigation seeks to set a precedent and serve as an input to generate public policy related to health prevention and health promotion in the context of WBD.

The effect of WBD on economic and social development was evidenced by a significant number of deaths and a total of 56,507 YLL between 2011 and 2020; while with regard to analyses corresponding to 2016, the disability-adjusted lost years (DALYs/1,000) for low- and middle-income countries in the Americas was much higher (DALY = 799/1,000) compared to countries in the high-income continent (DALY = 25/1,000); However, the regions that were shown to be most affected by diseases related to inadequate water, sanitation and hygiene behaviors were sub-Saharan Africa, and Southeast Asia (48). Although the first analysis exposed the mestizo ethnic group as the most affected by WBDs, the per capita adjusted analysis exposed that the group that truly feels the most WBD burden effects is the indigenous (YLL/100,000 = 964.7), no analyses have been reported that evaluate the effects of ethnic inequities on the disease burden of waterborne diseases, however, we consider that these effects cannot be present only in Ecuador since several developing countries in the world and the region have reported ethnic inequities (49–51).

Finally, we believe that it is essential that both local and national governments focus on providing clean, drinking and readily available water to all the populations that are currently living in regions with not access to it. All the strategies should also aim to achieve adequate management of water sanitation and hygiene with a holistic perspective, including wastewater treatment and land management and to improve other socioeconomic factors within communities.

5. Limitations

One of the main limitations we encountered in this study was the quality of the national disease reporting system. As a result, we cannot differentiate the number of people getting sick from the number of events (hospital admissions) that required hospitalization. The same patient could have entered the hospital twice in the same week, but the database cannot differentiate these events. At the same time, we could not purge the database from the presence of garbage codes, which might hinder the accurate analysis of this type of information.

6. Conclusion

In Ecuador, waterborne diseases (WBD) are still a major public health problem. We found that indigenous population had higher probability of getting sick and die due to WBD than the rest of the ethnic groups in Ecuador. We also found that younger children and the elderly are more likely to be admitted

to the hospital due to a WBD. These epidemiological trends are probably associated with the lower life expectancy found among Indigenous than among the rest of the ethnic groups, who die at least, 39 years earlier than the self-determined white populations, 28 years earlier than Afro-Ecuadorians and 12 years earlier than the mestizos.

7. Recommendations

We recommend that all the efforts in terms of public policy need to be directed to improve sanitation and access to clean water based on good data, including the ecological quality of freshwater resources, that provide holistic indicators of water quality and land use (52, 53). In the next 10 years it will be the only chance to overcome disparities and probably make a difference in terms of health outcomes. This is especially relevant in climate change scenarios that can reduce the water availability but also increase the incidence of WBD. Since cultural and social factors are more difficult to change, improving access to basic services such as potable water, waste management and more hygienical environments will represent progress toward equality among groups, preventing infectious diseases with epidemic or pandemic outbreaks such as the one we are currently experiencing with SARS CoV-2 virus, due to, among other causes, the weakness on improved water sanitation systems and good WaSH practices (54).

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.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

EO-P is fully responsible for the conceptualization of the study. EO-P, LG-B, and KS-R contributed to data collection, data extraction data analysis, and data visualization. EO-P, KS-R, LG-B, and GC were responsible for the elaboration of the first draft of the manuscript. DC, JV-G, and JI-C contributed with the discussion section and the final revision of the manuscript. AL and BR-T added important insights from a public health and the water quality-ecological perspective. All authors contributed to the article and approved the submitted version.

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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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Access to healthcare for disabled individuals: An analysis of judgments of the European Court of Human Rights from an ethical perspective

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Introduction: Individuals with disabilities (ID) suffer from restricted access to healthcare. This contributes to their poorer health status and constitutes an ethical challenge. The aim of this research was to systematically analyze judgments of the European Court of Human Rights (ECtHR) to illustrate examples of restricted access to healthcare for ID.

Methods: Through a search in the ECtHR's database we identified judgments dealing with access to healthcare for ID. The search resulted in $n = 329$ judgments, of which $n = 55$ were included in the analysis. A descriptive statistic was performed on Articles of the European Convention on Human Rights and violation of these articles. Qualitative thematic analysis was conducted to group the judgments in thematic categories.

Results: Most applications were filed against Russia ($n = 23$), followed by Poland ($n = 8$) and Ukraine ($n = 7$). The youngest applicant was 18, the oldest 72 years old. An overwhelming majority of cases dealt with disabled prisoners. Most of the judgments involved Article 14 and Article 8. We identified seven partially overlapping categories representing thematic patterns in the analyzed judgments.

Discussion: Any restriction of access to healthcare can be considered a violation of human rights. However, the results show a relatively low total number of judgments dealing with limited access to healthcare for ID. This could be a further confirmation of the fact that ID still experience too little attention in our societies. Especially in the context of detention, ID is restricted from receiving the healthcare they require. Indirect ways of a restricted access to healthcare should not be overseen.

KEYWORDS

disabled persons, access to healthcare, medical ethics, international law, human rights

1. Introduction

There are at least 1 billion individuals with disabilities (ID) worldwide, which corresponds to about 15% of the world's population (1). Originally, disability was seen as an illness that had to be diagnosed and treated and thus primarily fell within the sphere of the action of medicine. With the establishment of the social model of disability in the 1970s, disability has increasingly been considered a result of social limitations, making it society's task to remove these limitations (2). The Convention on the Rights of Persons with Disabilities (CRPD) of the United Nations (UN) conceives disability as resulting from an interaction between persons with limitations on the one hand and social limitations on the other hand. Therefore, the task to alleviate the restrictions of ID in numerous areas of life shall be assigned both to medicine and to society (3).

In the CRPD, the UN declared that ID have the right to receive the same range and quality of healthcare as other persons. Furthermore, the text of the CRPD explicitly states that there must be no restriction of access to healthcare for ID (3). Despite this, the preservation of their dignity and autonomy and the abolition of inequalities for ID have been demanded at least since the 1960s (4). The current COVID-19 pandemic once again illustrated that the interests of ID in accessing healthcare are not being considered to the same extent as those of other persons (5). To counteract the danger of discrimination against ID, the German Federal Constitutional Court even felt compelled in December 2021 to stipulate that ID must not be disadvantaged if a triage would be necessary (6).

Restricted access to healthcare of ID represents a serious social limitation (7, 8). Various factors contribute to a limited access to healthcare for ID: stigmatization (9), comorbidities and difficulty in communication (10), misconceptions and negative attitudes toward ID (11), lack of knowledge or attention on part of healthcare providers (11, 12), insufficient research activities (13), lack of integration of disability-specific content in medical curricula (14), difficulties regarding the transport of ID to medical facilities and associated high costs (7, 11), insufficient flexibility of the medical care system that frequently overlooks specific needs of ID (12), poverty (11), barriers in access to medical facilities (15), and a lack of integration of the voices of ID in service design (8).

As ID often have higher healthcare needs (16), limited access to healthcare certainly contributes to the poorer health status of ID than those without disabilities (1). From the ethical point of view, the right to health is one of the human rights, inseparably connected with the ethical principles of human dignity and social justice. This standpoint is represented and anchored in numerous international treaties, i.e. the Universal Declaration of Human Rights (17), and the Constitution of the World Health Organization (18).

Abbreviations: ID, individuals with disabilities; ECtHR, European Court of Human Rights.

The European Court of Human Rights (ECtHR) is the instance that deals with violations of human rights when the legal instances of the respective member state have been exhausted. Thus, the ECtHR's judgments are normative acts dealing with central medico-ethical questions of human dignity, justice, and equity in access to healthcare. The jurisdiction of the ECtHR should be binding for the 46 member states of the Council of Europe. The judgments of the ECtHR include not only legal but also normative considerations on central ethical issues. They can thus serve as a valuable source to explore in what ways access to healthcare for ID is restricted in individual member states. Therefore, the aim of this research was an analysis of the judgments of the ECtHR with consideration of the following questions: (i) How many ECtHR judgments deal with a restriction of access to healthcare for ID? (ii) How can these judgments be grouped thematically? (iii) How does the ECtHR assess these cases, in particular regarding their ethical content?

2. Materials and methods

We used HUDOC, a database of the ECtHR's case law, to retrieve all relevant judgments for our study (accessible under https://hudoc.echr.coe.int/eng#{%22documentcollectionid2%22:[%22GRANDCHAMBER%22,%22CHAMBER%22]}). On 4th January 2022, we performed a search with the following search terms' combinations: "disability" and "access" and "healthcare", or "disability" and "access" and "health care", or "disabled" and "access" and "healthcare", or "disabled" and "access" and "health care".

Our search yielded $n = 329$ judgments. $N = 130$ duplicates could be identified and eliminated. The remaining $n = 199$ judgments were read thoroughly to examine their relevancy with respect to our research questions. We identified $n = 55$ judgments relevant to our investigation. We excluded $n = 144$ judgments that were either not concerned with restricted access of ID to healthcare at all or in which the disability status of the applicant was not explicitly mentioned (Figure 1). We only included judgments that clearly dealt (1) with individuals that have been granted a disability status and (2) restricted access to healthcare of those individuals.

2.1. Descriptive statistics

We performed descriptive statistics on the Articles of the Convention that were involved in the judgments. All articles which the ECtHR ruled on as well as violation of these articles were counted. The judgments of the ECtHR often involve different articles in one case or even different paragraphs of the same article. For example, a judgment could state that one sub-paragraph of an article was violated while other sub-paragraphs were not breached or the substantive aspect of an article was violated while the procedural aspect

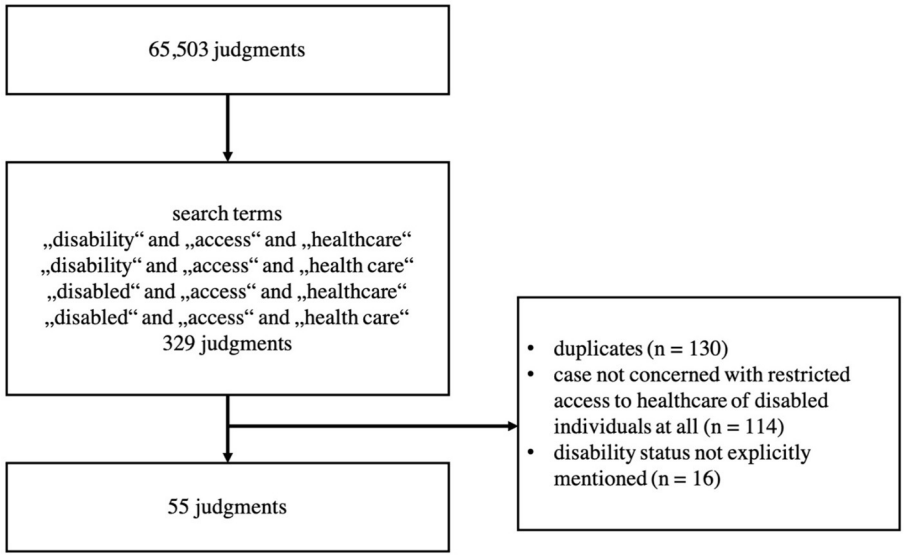

FIGURE 1
Flowchart of the search.

was not. We counted a violation of an article if at least one violation of one of its sub-paragraphs or aspects was held by the ECtHR. This procedure involves a certain limitation of our investigation.

2.2. Thematic analysis

We performed a thematic analysis on all 55 relevant judgments. This is a quantitative approach for identification of recurring themes or patterns in narrative or text materials (19, 20). We inductively formulated and critically discussed thematic categories that could be derived from the analysis of the textual content of the judgments. Or research team was multiprofessional and included a psychiatrist (T.S.), a physician and expert in the history, philosophy and ethics of medicine (F.S.), and a political scientist (M.O.). The identified categories represent important thematic patterns of the judgments with regard to the research aim and research questions and do not depend exclusively on quantifiable measurements. We illustrate each of the categories by presenting representative examples of the analyzed judgments.

3. Results

3.1. Countries and time period of analyzed judgments

The $n = 55$ judgments derived from $n = 15$ countries. The most applications were filed against Russia ($n = 23$), followed by Poland ($n = 8$) and Ukraine ($n = 7$) (Table 1). Although the database of the ECtHR contains judgments from the year 1960 on, we could only identify judgments deriving from the time period between 2001 and 2021. With regard to the annual number of judgments during this period, we could not identify any trends or visible patterns.

TABLE 1 Overview of the countries the analyzed judgments derive from and numbers of analyzed judgments.

Country	No. of judgments
Russia	23 (41.82%)
Poland	8 (14.55%)
Ukraine	7 (12.73%)
United Kingdom	3 (5.45%)
Romania	3 (5.45%)
Switzerland	2 (3.64%)
Serbia	1 (1.82%)
Denmark	1 (1.82%)
Greece	1 (1.82%)
Bulgaria	1 (1.82%)
Czech Republic	1 (1.82%)
Germany	1 (1.82%)
Latvia	1 (1.82%)
Belgium	1 (1.82%)
Lithuania	1 (1.82%)

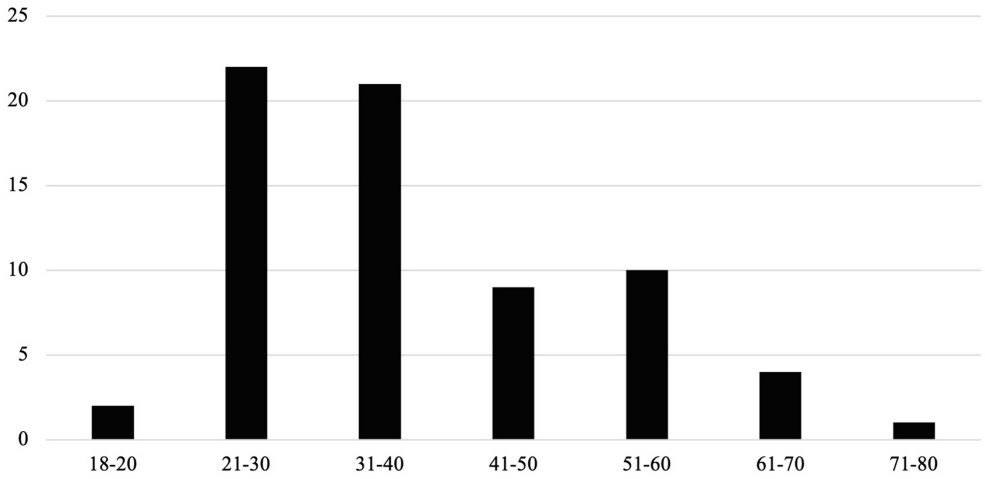

FIGURE 2
Distribution of age of applicants in our analyzed judgments (2001–2021). On the horizontal axis, we depict age frames, and on the vertical axis the number of judgments.

3.2. Age of applicants at the time of the alleged violation of the convention

We analyzed all judgments regarding the age of the applicants at the time of the first alleged violation of an Article of the ECtHR. In the case of detained applicants appealing against the circumstances of the detention, we applied the date of the placement into detention; in all other cases, we used the point of time we first found a hint to an alleged violation of the Convention. As some judgments are dealing with more than one applicant, the sum of all applicants in our analyzed judgments is 70. In one case we were not able to determine the age of the applicant. The youngest applicant was 18, the oldest 72 years old. We did not find any cases dealing with applicants younger than 18 years (Figure 2).

3.3. Attribution of applicants to other minority groups

In $n = 43$ cases (78.18%) we could attribute the applicants not only to the minority group of ID but also to other minority groups. In $n = 2$ judgments (3.64%) the disabled applicant was a migrant respectively an inhabitant of a social care home. The overwhelming majority of judgments ($n = 41$, 74.55%) dealt with applicants that were disabled prisoners.

3.4. Articles of the European Convention on Human Rights

In Table 2 we present frequencies of the Articles of the Convention involved in the analyzed judgments. Most of the judgments involved Article 14 (prohibition of discrimination) and Article 8 (right to respect for private and family life).

3.5. Categories

We identified seven partially overlapping categories representing thematic patterns in the analyzed judgments (Figure 3). These categories describe in what way access to healthcare is restricted for ID. The categories are not mutually exclusive – often judgments were classified as belonging to several categories. The access to healthcare for ID was found to be restricted by (i) denial of medical treatment and/or examinations ($n = 39$, 70.91%), (ii) denial of adequate support ($n = 34$, 61.82%), (iii) conflicting opinions of need ($n = 26$, 47.27%), (iv) provision of insufficient medical facilities ($n = 15$, 27.27%), (v) denial of access to information ($n = 11$, 20%), (vi) denial of insurance grant/reimbursement ($n = 6$, 10.91%) and (vii) denial of investigation of complaints ($n = 4$, 7.27%). We regard all these categories as phenomena that are either directly restricting the access to healthcare for ID (categories i, ii, iii, vii) or that exclude ID from full participation in the medical healthcare system (categories iv, v, vi).

3.5.1. Judgments involving a restriction of access to healthcare for ID by denial of medical treatment and/or examinations

As an example might serve case *Reshetnyak v. Russia* (appl. no. 56027/10). This case deals with an applicant that is arrested for robbery. Suffering from tuberculosis, he was admitted to a correctional colony primarily occupied by inmates infected with tuberculosis. Although he was examined by prison doctors on several occasions, his state of health deteriorated constantly.

TABLE 2 Frequencies of articles on rights and freedom (Section 1, Articles 1–18) and protocols of the European Convention on Human Rights in the $n = 55$ judgments included into this analysis.

Articles of the European Convention on Human Rights	Name of the article	Judgments involving this article	Judgments in which at least one violation of this article was found (either alone or in conjunction with other articles)
Article 1	Obligation to respect human rights	$n = 1$ (1.82%)	$n = 0$
Article 2	Right to life	$n = 1$ (1.82%)	$n = 1$ (100%)
Article 3	Prohibition of torture	$n = 47$ (85.45%)	$n = 38$ (80.85%)
Article 5	Right to liberty and security	$n = 16$ (29.09%)	$n = 8$ (50%)
Article 6	Right to a fair trial	$n = 18$ (32.73%)	$n = 9$ (50%)
Article 8	Right to respect for private and family life	$n = 17$ (30.91%)	$n = 7$ (41.18%)
Article 13	Right to an effective remedy	$n = 16$ (29.09%)	$n = 11$ (68.75%)
Article 14	Prohibition of discrimination	$n = 7$ (12,73%)	$n = 1$ (14.29%)
Article 17	Prohibition of abuse of rights	$n = 2$ (3.64%)	$n = 0$
Article 34	Individual applications	$n = 5$ (9.09%)	$n = 4$ (80%)
Art 1 of Protocol No. 1	Protection of property	$n = 4$ (7.27%)	$n = 1$ (25%)
Art 1 of Protocol No. 12	General prohibition of discrimination	$n = 1$ (1.82%)	$n = 0$
Art 2 of Protocol No. 7	Right of appeal in criminal matters	$n = 1$ (1.82%)	$n = 0$

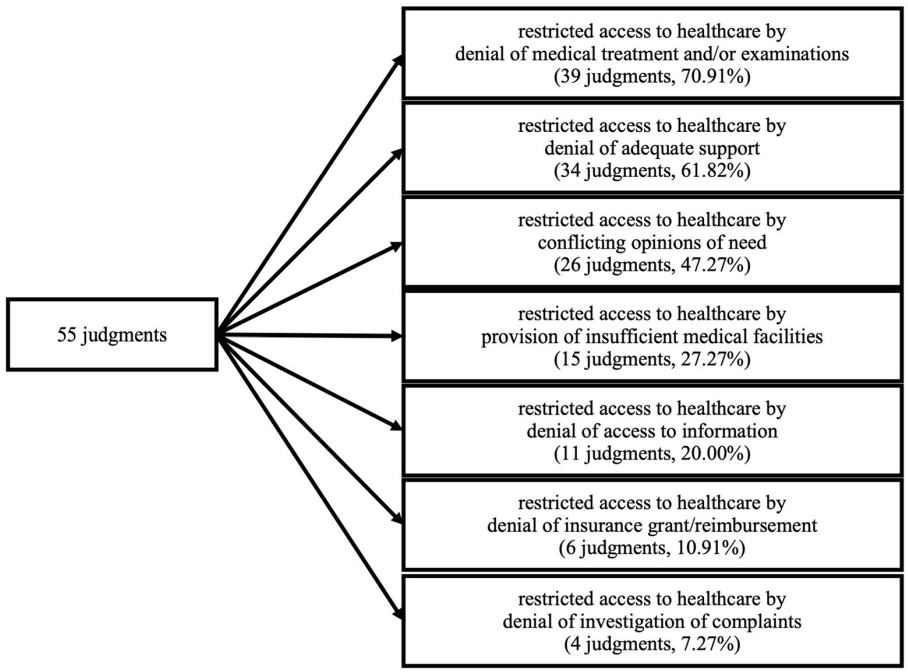

FIGURE 3
General count and percentages of judgments we found regarding each category.

Even though he proved to be smear-positive (meaning that the bacterium causing tuberculosis could be detected in his sputum), he was not provided with drugs that had a serious prospect of improving his health status. Instead, the prison doctors kept administering the same drugs in various combinations that had proved to be ineffective (amongst others, antihistamines,

multivitamins and muscle relaxants, which have no effect on tuberculosis). Moreover, there were long delays between deteriorations of the applicant's health and the reaction of the colony doctors. Finally, the applicant was diagnosed with a destructive tuberculosis and a tubercular intoxication. Only after about 5 years, a much-needed drug susceptibility testing was performed by the prison doctors, revealing the applicant to suffer from multi-drug-resistant tuberculosis, tempting them to acknowledge that the drug regimen administered so far was ineffective. In the opinion of the ECtHR, it is highly unsatisfactorily that the detention facility, which primarily was accommodated by tuberculosis patients, obviously lacked proper drugs to provide an adequate therapy. It stated that the mere fact that a prisoner is seen by a doctor and prescribed a treatment is not enough to qualify a detention facility's medical care as adequate. Moreover, the Court did not accept any problems concerning the supplementation with effective drugs on the side of the detention facility as excuse for not being able to provide the healthcare needed by the applicant. Hence, it saw a violation of Article 3 (besides Article 13).

3.5.2. Judgments involving a restriction of healthcare for ID by denial of adequate support

We regard "support" as having a broader meaning than "medical treatment": While "support" incorporates any form of specific attention a disabled individual may need, "medical treatment" refers to specific interventions usually ordered by a medical doctor.

Example: The applicant in the case *Patranin v. Russia* (appl. no. 12983/14) suffered from progressive multiple sclerosis and was recognized as being disabled. In 2012, he was arrested on suspicion of several crimes, including murder. He then experienced a significant deterioration of his health. Finally, he was found to suffer from left-sided hemiplegia, right-sided hemiparesis, partial atrophy of the visual nerves, symptomatic epilepsy, arterial hypertension and myopathy of both eyes. Although the prison doctors stated he should be released early on health grounds, his respective request was dismissed. He mentioned that he relied on constant assistance which he was in no way provided within the penal system. Being severely restricted in his movement, he had to stay in bed all day long. This was due to the fact that he even needed help when he wanted to be placed in his wheelchair. He had to endure significant unsanitary conditions as he had not been bathed for months, although he suffered from involuntary urination due to urethral dysfunction. Moreover, he received food only once a day as he was not able to eat or drink unaided. Being not able to defecate and being provided with an enema only every fortnight he had to bear severe pain. In numerable occasions, he did not receive necessary medical treatments. He was only released in 2015 after extensive proceedings concerning his state of health which was not compatible with the care the penal system provided. In its judgement, the ECtHR stated that any torture or inhuman or degrading treatment is prohibited regardless of the applicant's behavior and the circumstances. Such treatment would violate a person's human dignity. Moreover, also in prison anything should be done to treat health issues of a detainee or to prevent their aggravation. In the case at hand, the applicant was exposed to such inhuman and degrading treatment diminishing his human dignity. Therefore, the ECtHR stated a violation of Article 3 (in addition to a breach of articles 13 and 34).

3.5.3. Judgments involving a restriction of access to healthcare for ID by conflicting opinions of need

In our analysis, we considered conflicting opinions of need as a situation, in which the applicant claimed specific care that others did not provide, as they seemed to have a different interpretation with respect to the care required. Basically, any denial of medical treatment or support can be reduced to conflicting opinions regarding the specific need of a person. However, we use this category separately and in contrast to the categories (i) "denial of medical treatment" and (ii) "denial of adequate support" to emphasize that in some cases the restriction of access to healthcare is the result of different and conflicting assessments regarding the specific need of an ID.

Example: In the case *G. v. Russia* (appl. no. 42526/07) the applicant was suffering from severe rectal cancer (amongst other illnesses) and was arrested on suspicion of committing bank fraud. Although his state of health deteriorated significantly during his time in prison, he was not released on medical grounds. About a month after his arrest, a large part of his sigmoid colon prolapsed which caused not only fecal incontinence, but also severe pain. He even lost consciousness on several times during his detention due to the intensity of pain he had to endure. He was not provided with absorbent briefs and was hardly able to perform basic hygiene measures he urgently needed. Although his situation worsened constantly and independent medical specialists demanded at several times that the applicant needed colorectal surgery, the prison doctor found his condition satisfactory not calling for immediate surgery. In the end, surgery was delayed for nearly a year. The ECtHR stated in its judgment that the medical problems of the applicant were not sufficiently addressed which not only led to a significant deterioration of the applicant's quality of life, but also had to be regarded as life-threatening. Moreover, the authorities did not provide adequate alternative treatment to ameliorate the applicant's suffering. Furthermore, denying the applicant the much-needed absorbent briefs caused significant distress and embarrassment for the applicant. Consequently, the Court saw a breach of Article 3 (in addition to a violation of Article 5).

3.5.4. Judgments involving a restriction of access to healthcare for ID by provision of insufficient medical facilities

Insufficient medical facilities could imply the lack of necessary specialists (as in *Bubnov v. Russia*, appl. no. 76317/11), the impossibility to provide required medication (as in *Petukhov v. Ukraine*, appl. no. 41216/13), the lack of medical equipment (as in *G. v. Russia*, appl. no. 42526/07), being kept together with infectious patients (as in *Romokhov v. Russia*, appl. no. 4532/04) and even syringes used more than once (*Ukhan v. Ukraine*, appl. no. 30628/02).

Example: The applicant in *Gurenko v. Russia* (appl. no. 41828/10) suffered two myocardial infarctions before being arrested for beating his female partner to death. Although his medical condition already was unsatisfactory before the arrest and even deteriorating while being in detention, he never was examined by a cardiologist. The medical professions in charge of him included general physicians, a dermatologist, a surgeon, an otolaryngologist, a tuberculosis specialist, a drug addiction specialist, an ophthalmologist and a psychiatrist. Due to lack of knowledge in cardiology, they only were able to treat his problems symptomatically. A significant number of medicines necessary to treat the applicant's medical problems, were not provided by the detention facility, but had to be bought and brought to the applicant by his son. On several occasions, required tests (like ultrasound scanning) were not provided or could not be interpreted (ECG testing). Furthermore, essential recommendations by the attending physician of the prison hospital the applicant was admitted to during his detention, were not followed. Even the prison hospital was not able to provide emergency resuscitation assistance if need be. In its judgment, the ECtHR acknowledged that the applicant did not receive the required treatment and therefore experienced a degradation of his human dignity by persistent mental and physical suffering. Therefore, the ECtHR stated a violation of Article 3.

3.5.5. Judgments involving a restriction of access to healthcare for ID by denial of access to information

We regard a denial of access to information as a form of restricted access to healthcare since full and autonomous participation in any healthcare-related aspect for any patient is dependent on being informed about all necessary circumstances as much as possible. Without being informed about the nature of the medical condition at hand and about interventions that might be possible or that even have taken place, a patient cannot perform an informed consent and cannot adequately claim his or her rights (e. g. during legal procedures). Hence, full access to all relevant information and all medical files is an indispensable aspect of a patient's access to healthcare.

We found several ways in which access to information could be denied: denial of access to information partly or at all (e. g. *Makshakov v. Russia*, appl. no. 52526/07), denial of assistance to read medical files although severe reduction of eyesight (*Tysiac v. Poland*, appl. no. 5410/03), illegible records or denial to record complaints (e. g. *Ukhan v. Ukraine*, appl. no. 30628/02) or discrepant files (e. g. *Reshetnyak v. Russia*, appl. no. 56027/10).

Example: The applicant of *I. N. v. Ukraine* (appl. no. 28472/08) was involuntarily placed in a psychiatric facility by the authorities. The respective documents that argued for the applicant's admission in a psychiatric facility had not been submitted to the Court. He was not allowed to study his medical files to learn about the legal basis of his being subjected to psychiatric treatment. Subsequently, he instituted proceedings against the psychiatric institutions he was placed in. The following proceedings were extensive and lengthy and lasted from 2001 to 2007. During that time, numerous court hearings were scheduled and, in many cases, postponed (due to failure of the defendants to appear in court, non-availability of the court recording equipment or expire of the term of office of the judge in charge of the applicant's case). Obviously, although the applicant could not receive all relevant information about his medical case, his employers had been informed about his state of health. Moreover, he was not informed about the type of medication he was given. In its judgement, the ECtHR argues that there would have been insufficient legal requirements regarding the placement of the applicant in a psychiatric facility. It criticized that it had not been provided with any evidence that the applicant was suffering from a mental disorder at the material time that would present a danger to him or to others justifying his hospitalization. The Court stated that the excessive length of proceedings was unreasonable and caused by facts the authorities were primarily responsible for. In its decision, the ECtHR saw a violation of Articles 5 and 6.

3.5.6. Judgments involving a restriction of access to healthcare for ID by denial of insurance grant/reimbursement

As an example we provide case *Shmalko v. Ukraine* (appl. no. 60750/00). The applicant in this case is a disabled veteran of the Second World War suffering from myasthenia. He instituted proceedings seeking reimbursement of his costs for a drug he needed to treat his medical condition. Being not available in the Ukraine, he had to buy it abroad and cover the costs himself. After several rejections of his claim as being unsubstantiated, the Regional Court of Appeal allowed the applicant's claims in part. However, it lasted more than 1 year for the respective institutions to provide the applicant with the money the litigation demanded. In its argumentation, the ECtHR states that a State's alleged lack of funds cannot be an excuse for not executing a judgment. The State of Ukraine has the obligation to provide medication free of charge for the applicant. Moreover, the age of the applicant and his disability called urgently for an undue payment of his costs caused by his obtaining medication

necessary to treat his medical condition. By causing a significant delay, the authorities furthermore prevented the applicant from a possession of his property. In conclusion, the ECtHR saw a violation of Article 6 and Article 1 of Protocol No. 1.

3.5.7. Judgments involving a restriction of access to healthcare for ID by denial of investigation of complaints

We also regard a denial of investigation of complaints as a form of a restriction of access to healthcare. Full access to healthcare should incorporate a patient's possibility to claim for his or her rights regarding access to healthcare. Without this legal security, a patient would be restricted to passively waiting for access to healthcare to be provided and be restricted of the possibility to actively demand access to healthcare. Thus, the possibility to demand a proper investigation of complaints is a relevant part of full access to healthcare.

A denial of investigation of complaints was done in different ways: refusal of authorities to institute a proceeding to investigate an applicant's complaints (*Ukhan v. Ukraine*, appl. no. 30628/02), letters to Court not dispatched by authorities (*Sergey Babushkin v. Russia*, appl. no. 5993/08), denial of timely provision of information or complaints being non-answered at all (*Gurenko v. Russia*, appl. no. 41828).

Example: Case *Ukhan v. Ukraine* (appl. no. 30628/02) deals with an applicant who claimed to have suffered bodily injuries inflicted by police officers (fractured rib and major head injury) as he was forced to confess his offenses. Subsequently, the prosecutor's office refused to institute criminal proceedings to investigate the applicant's complaints referring on testimonies of the involved police officers. Also, the Regional Court of Appeal dismissed the applicant's appeal concerning ill-treatment. The applicant started suffering from severe headaches, lost mobility in his left side and a partial loss of sight in his left eye. A neurologist diagnosed him with a partial atrophy of the left eye nerve considered to be of traumatic origin. Although complaining about his medical problems and the insufficient medical care on numerous times (even by going on hunger strike), there was no adequate reaction of the authorities. They kept responding that his medical condition was satisfactory. The medical personnel even refused to examine and record his complaints. The ECtHR stated in its judgement that the adequacy of medical assistance provided to a detainee is, amongst others, dependent on the keeping of a comprehensive record including the detainee's medical status and the provided treatment. The Court criticized, that in the case of the applicant, significant aspects of his medical condition remained unreported and unsupervised and that the information provided in the medical records is incomplete. The Court decided that there was a breach of Article 3 and 13.

4. Discussion

4.1. Countries and time period of analyzed judgments

By far the highest number of our analyzed judgments challenged Russia (followed by a considerable margin by Poland and Ukraine). This is in line with the overall statistics of all judgments of the ECtHR: Russia is on second place (behind Turkey) in terms of the total number of judgments considered by the ECtHR, Ukraine is on fourth and Poland on sixth place (21). Numerous human rights violations have been known to take place in Russia (22). Although Russia signed the European Convention of Human Rights, the country often shows a profound disregard for the rulings of the European Court of Human Rights (23). Obviously, respect for the rights of ID is no exception. The fact that ID in Russia find ways to fight for their rights, gives some hope (24). Overall, the results show a relatively low total number of judgments dealing with limited access to healthcare for ID. This and the fact that the oldest judgments relevant to our research are just 11 years old could be a further confirmation of the fact that ID still experience too little inclusion and attention in our societies (25).

4.2. Age of applicants at the time of the (alleged) violation of an article of the ECtHR

The applicants in the analyzed judgments were all adults, the youngest applicant being 18 years old. An unexpected result is that we did not find any cases dealing with disabled children, considering that about one in ten children worldwide has a disability (26). This may reflect the fact that children with disabilities are one of the most neglected and marginalized groups frequently facing challenges in realizing their human rights (26). Regarding healthcare, this may be illustrated by the fact that cuts in services across Europe increased waiting times and lessened the time allotted for each child in the provision of healthcare (27). Even though we did not find a case dealing with disabled children, this does not in any way mean that there are no restrictions on access to healthcare for this group of people. It is rather the contrary: one could take the fact that no such cases end up at the ECtHR as an indication that there are (too) few legal processes regarding the access to healthcare of disabled children in the member states. Furthermore, only a small number of identified judgments were dealing with applicants older than 60. This

could imply that older age might serve as additional factor of discrimination.

4.3. Attribution of applicants to other minority groups

An overwhelming majority of cases ($n = 41$, 74.55%) dealt with disabled prisoners. $N = 22$ (53.66%) of these cases concerned Russia. Various human rights violations in Russian prisons, particularly in relation to overcrowding and poor medical care, have already come to the attention of the ECtHR in numerous cases (28, 29). It is not surprising that ID are among these. However, it is remarkable that in most of these judgments the disability status did not play a central role in the argumentation of the ECtHR. Since the cases that come before the ECtHR are only the tip of the iceberg of all legal cases in a member state, this could be taken as a sign of a significant restriction of the legal rights of individuals who are "only" disabled.

4.4. Articles of the European Convention on Human Rights

Most judgments dealt with Article 3 (prohibition of torture, $n = 47$, 85.45%), followed by Article 6 (right to a fair trial, $n = 18$, 32.73%) and Article 8 (right to respect for private and family life, $n = 17$, 30.91%). Article 3, according to the ECtHR, expresses one of the most fundamental values of democratic societies. It prohibits ill-treatment regardless of the victim's conduct or the circumstances. The ECtHR considers not only "inhumane" conduct such as physical injury or the infliction of intense physical or mental suffering as criteria for ill-treatment, but also any "degrading" conduct that is likely to violate the human dignity of an individual or provoke feelings of fear, anguish or inferiority that may break a person's morals (*G. v. Russia*, appl. no. 42526/07 and *Stanev v. Bulgaria,* appl. no. 36760/06). Thus, any conduct that may violate the dignity of ID may in principle also constitute a violation of Article 3. In particular, the provision of adequate healthcare is seen as a positive obligation arising from Article 3 (29). However, to meet this obligation, adequate healthcare must not only be provided but must also be fully accessible (*Gurenko v. Russia*, appl. no. 41828/10). Thus, any restriction of access to healthcare can also be considered a breach of Article 3 and thus a violation of human rights. The numerous cases of restrictions on access to healthcare for ID depict violations of human rights and urgently need to be stopped. It should be borne in mind that restrictions on access to healthcare are not in every case obvious but often sublime and unnoticed.

4.5. Categories

In most of the analyzed judgments, access to healthcare was restricted in a very direct way, either by a denial of medical treatment and/or examinations ($n = 39$, 61.82%) or by a denial of adequate support ($n = 34$, 61.82%). The availability of only insufficient medical care ($n = 15$, 27.27%) and the restriction of access to healthcare due to conflicting opinions of need ($n = 26$, 47.27%) can also be considered direct restrictions. However, we also found less obvious ways in which ID are denied full participation in healthcare, such as a denial of access to information ($n = 11$, 20.00%), a denial of insurance grant/reimbursement ($n = 6$, 10.91%), or denial of investigation of complaints ($n = 4$, 7.27%). Healthcare should be considered as a concept that not only refers to a direct provision of medical interventions but also includes participation in ethical and legal aspects of the health system. This undoubtedly includes the right of patients to be fully informed, to be insured, and to take legal action if violations of their rights occur. Even though not all forms of disability are per se associated with an increased need for medical support, the risk for ID to suffer from health disorders is nevertheless very high: through secondary and co-morbid diseases, a greater vulnerability to age-related conditions, a higher proportion of health risk behavior and a higher risk of experiencing violence and accidents as well as premature death (1). Hence, ID are dependent on unrestricted access to healthcare. However, the above-mentioned restrictions of access to healthcare contribute significantly to the poorer overall health status of ID compared to non-disabled people (1). Moreover, ID experience stigma and discrimination in different ways (30). We consider any restriction of access to healthcare as a form of stigmatization. Stigma can be associated with the experience of minority stress, which can lead to depressive and anxiety symptoms (31). Therefore, limiting access to healthcare can in turn itself increase the risk of further health disorders.

4.6. Limitations

There are some limitations to our study. First, we included only cases in which any degree of disability officially has been acknowledged. Moreover, we included all cases irrespective of the type or degree of disability the applicant was suffering from. As disability is an extremely variable concept and the criteria for acknowledging a disability status may vary in different states, our analyzed judgments dealt with a variety of health-related phenomena. Second, the judgments included in the analysis do not represent all examples of restricted access to healthcare

for ID. The ECtHR only considers cases that run through all domestic instances. Furthermore, it was not possible for us to make an explicit analysis of the illnesses underlying the disabilities in the individual cases. This was due to the fact that (1) often more than one illness was mentioned and (2) it was not possible to identify in individual cases which illnesses led to the granting of disability status. Finally, our categories were overlapping, making a clear assignment of the complex cases to a particular category a difficult task. The assignment of some cases might be disputable.

4.7. Conclusion

Our research shows that ID suffer from restricted access to healthcare all over Europe, especially through denial of medical treatment and/or examinations ($n = 39$, 61.82%) or by a denial of adequate support. Indirect ways of a restriction of access to healthcare, such as denial of access to information, denial of insurance or reimbursement, or denial of investigation of complaints should not be overseen. Especially in the context of detention, ID are restricted from receiving the healthcare they require. There is an urgent need to facilitate access to healthcare for ID to prevent further widening of the gap regarding the health status of ID compared to non-disabled persons. As restriction of access to healthcare is in itself a form of stigmatization, it may contribute to ID's poor health.

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

TS-E, MO, and FS conceptualized the topic and scope of the research. TS-E and MO performed the data analysis, wrote, and reviewed the original draft. FS supervised the research and reviewed the manuscript. All authors have read and agreed on the submitted version of the manuscript.

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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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Influence of public hospital reform on public health: Evidence from a quasi-natural experiment in China

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Public health is an important symbol of national wealth and prosperity. At present, China's public health is hindered by the poor management of public hospitals, which impacts the demographic structure and socioeconomic development. Therefore, taking the implementation of public hospital reform in China as a quasi-natural experiment, this study employed the time-varying DID model and the mediating effect to evaluate the influence of public hospital reform on public health. The results were as follows: (1) Public hospital reform can significantly improve public health, and a series of robustness tests have also confirmed the effects; (2) Government's financial support is a transmission mechanism for public hospital reform to promote public health; (3) After taking control variables into consideration, the effect of public hospital reform is stronger in the western region with a poorer economy. This research provides a vital policy reference for promoting the scope of reform and improving the health of the general public.

KEYWORDS

public hospital reform, public health, medical expenditure, DID, the mediating effect, China

1. Introduction

Since the reform and opening up, China's economy has achieved significant growth, which has been recognized as a miracle in the history of the world economy (1). However, compared to the speed of economic development, the health level of Chinese people has been relatively slow. The development of the health sector has not been satisfactory. In response to the increasingly serious problems in public health, China launched a new round of healthcare reform in 2009 which not only changed the previous market-oriented and commercialized health service but also enhanced the government's responsibility in the health sector.

The disparity between economic growth and health improvement has plagued China for a long time (2). During the early years of reform and opening up, China's mortality rate was effectively decreased through the improvement of basic living and health conditions, but the overall health status was still slow compared to other countries. In terms of life expectancy, for instance, it had increased in low-, middle-, and high-income countries by three, five, and 4 years, respectively, while it had only increased by 2 years in China (3). In comparison, in India, where the economy is growing as rapidly as China, its infant mortality rate is much lower than that in China (4). At the same time, China's health status has become more polarized within the population, where the low-birth-weight rate in 2000 for children under 5 years was 3% in urban areas but six times more in rural areas. Since 2005, when the State Council issued the report "The Failure of Old Health Care Reform," the subject of

healthcare reform has become the focus of national attention. In addition, the new round of public hospital reform that was launched in 2009 has raised the problems in the national health system to an unprecedented level.

As an essential spatial carrier to implement the strategy of *Health China*, hospitals are a vital node for improving the quality of public health. In China, public hospitals are the leading providers of health services, which significantly affects the direction of the overall health sector and determines the quality of its public health. However, at the beginning of the 21st century, the government's "decentralization" in the healthcare sector led to the collapse of the publicly funded health system which was established at the beginning of the new China. In the face of continuous reduction of medical financial support, public hospitals began to shift toward the profit-seeking path of supply-side induced demand, thus resulting in "difficult and costly medical treatment," creating tension between doctors and patients and other chaotic phenomena that endanger China's healthcare. In response, the Ministry of Health issued the "*Guiding Opinions on the Reform of Public Hospital*" in 2010, which pointed out that public hospitals should adhere to national welfare, put the protection of people's health rights first, and encourage scientific development to meet the health needs of the general public. As the core policy of the "new medical reform," the public hospital reform aims to help accelerate the formation of a medical service system that will be characterized by "serving the people" and achieving the coordination of public health and medical services. Based on this, this study considered the fact that the public hospital reform has been carried out from pilot projects to full-scale implementation as a quasi-natural experiment, explored the impact of public hospital reform on public health, and attempted to answer the following questions: Has public hospital reform significantly improved public health in China? What is the transmission mechanism? Are there any significant differences in the effects of reform between different regions?

2. Literature review

Public health is a significant symbol of national wealth and prosperity. Since the 1950's, health issues, as a pivotal component of human capital, have drawn increasing attention and discussion from economists. After Grossman (5) groundbreaking publication "*On the Concept of Health Capital and the Demand for Health*," the field of health economics has rapidly developed.

At present, academic research on health economics mainly focuses on the influential factors and the character of its public goods. Among them, the influential factors can be divided into individual and social dimensions. In the individual dimension, factors such as family status, living habits, and medical conditions are strongly related to their health level. In particular, the relative deprivation of income, job, or other economic factors hinders the low-income groups' ability to integrate into society resulting in their low health level (6). Currie et al. (7) believed that people with higher socioeconomic status have more convenient opportunities to enjoy a healthy lifestyle because of the "privilege" of obtaining more health support. In addition, an increase in educational attainment can also lead to a higher health status (8), and Mao et al. (9) found that education can contribute to people's health through a combination of mediating and moderating effects. Regarding the social dimension, scholars have mainly studied it from macro perspectives, such as economic growth, level of openness, environmental pollution, urbanization progress, and scientific improvement. Cen et al. (10) argued that economic growth would have a positive impact on public health due to the presence of government incentives for livelihood. The level of openness will promote public health by bringing healthy food and medical equipment to the residents (11). The significant effect of urbanization, an essential modern civilization benchmark, on improving public health has regional differences (12). As for the effect of environmental pollution, Sun et al. (13) used a spatial econometric model to analyze air pollution with a spillover character and found that it has a more significant detrimental effect on public health than other pollutants (14).

The great positive externality of public health determines that its provision must involve the participation of the public sector. Researchers believe that the government must take responsibility for public health investment and fully play the role of public finance in health investment (15). Medical expenditure can improve the equity of healthcare resource allocation, effectively prolong life span and reduce infant mortality (16). Cheng et al. (17) concluded that medical expenditure not only directly improves people's health status but also moderates the health effects of education. This view is further corroborated by Tian et al. (18) from the perspective of government competition. However, several scholars are skeptical of this conclusion, arguing that health fiscal spending does not have a significant effect on health (19) and even leads to an increase in population mortality (20).

Public hospital reform is the core of China's "new medical reform," and scholars have mainly focused on the two aspects of the practices and effects. For one, public hospital reform should establish a robust accountability mechanism and a plausible incentive system to form a health service structure, which can guarantee the national welfare of public hospitals (21). Cao et al. (22) argued that hospitals should separate the management and administration system, reform the performance appraisal system, and strengthen the capabilities of primary medical resources such that the tiered diagnosis and treatment system can be fully formed (23). To break the profit mechanism of "feed doctors with drugs," Ye et al. (24) considered that the multiple compensation system of public hospitals needs to be implemented. Furthermore, scholars believed that public hospital reform could improve the level of medical services and optimize the distribution of medical resources, thus increasing the accessibility and equity of medical care and promoting the improvement of public health (25). The Affordable Care Act, similar to the concept of "new medical reform" in China, has also made substantial contributions to expanding medical insurance coverage and lowering the mortality rate of the population (26, 27).

Public health is the fundamental measurement of people's wellbeing and economic development, and it is of great significance for production. A review of the existing literature shows that scholars have studied public health and public hospital reform from multiple perspectives, including the macro perspective and the micro perspective, and have made considerable research findings, setting a solid foundation for this study. Previous studies have argued that the factors which influence public health are not

only individual participation but also government involvement; however, few studies have examined the impact of external policy shocks as a variable on health. Similarly, while numerous scholars have affirmed the achievements of public hospital reform on questions such as resource allocation and service levels, little attention has been paid to the impact of reform on public health, and only some literature has analyzed the relationship between improvements in health services and public health. Therefore, the impact of public hospital reform as an exogenous variable shock on public health is a question that needs to be answered urgently.

Based on the above questions, this study explored the impact of public hospital reform on public health. The empirical results showed that comprehensive public hospital reform significantly improves the level of public health, the indirect effect of the reform through the increase of financial expenditures on medical care is not as effective as expected, and the promotional effect of the reform on the level of public health shows significant heterogeneity among regions. The marginal contributions of this study are mainly in three aspects. First, regarding the research perspective, previous studies were primarily limited to the provincial level, while the research focus of this study is at a national level and considers the basic implementation of public hospital reform from batch piloting to full roll-out, which makes up for the absence of research in this area to a certain extent. Second, unlike the qualitative analysis method used in previous literature, this study adopted a time-varying DID empirical analysis, which is conducive to overcoming the endogeneity problem arising from model construction and can exclude as much as possible the effects caused by interfering factors other than the reform policy so as to estimate the unbiased net policy effect and reveal the effect of public hospital reform on the public health more comprehensively. Third, based on the fact that China's regional development is imbalanced, the extent of the impact of public hospital reform on public health in the eastern, central, and western regions of China are explored separately, thus making the study more consistent with the reality of China's vast territory and providing policymakers with a better perspective for decision-making.

3. Policy evolution and research hypothesis

3.1. Policy evolution

Even after the founding of New China, people's physical health was generally poor, and their demand for medical care could not be satisfied. Due to this lack of improvement in the healthcare sector, the country proposed to institute a three-tier medical diagnosis and treatment system to ensure the fairness and accessibility of the nationwide medical system. Since then, the labor insurance system and the publicly funded health system have also come into being, which significantly contributed to the development of healthcare in China and basically met people's medical needs. In the early years of the country, public hospitals aimed at general interest and national welfare greatly safeguarded people's right to life and health and fully embodied the government's original intention of working for the wellbeing of the people. The publicly funded health system largely maintained social stability and economic reconstruction for more than 30 years and became one of the most comprehensive medical systems in the world at that time.

In 1978, China officially kicked off the prelude to reform and opening up. Its fundamental goals, improving productivity and promoting economic growth, not only changed the path of the economic sector's development but also influenced the direction of the non-economic sector. The government's gradual withdrawal from the healthcare sector induced the medical system to shift toward a market-oriented path. In the early phase of the reform and opening up, marketization overcame many shortcomings of the public hospitals, such as a lack of competition and enthusiasm, a rigid structure, and poor service efficiency. It encouraged the innovation of public hospitals' management, salary subsidies, and other aspects in a short period and met the diversified medical needs of the people. However, with the government's financial support unable to maintain the regular operation of public hospitals, the profit motive gradually strengthened. Eventually, the loss of national welfare in public hospitals became more apparent and problematic, such as the supply-side induced demand, "high price and poor quality" of medical services, and the intensive relationship between doctors and patients. To resolve this chaotic phenomenon, in 2010, China proposed in the *Opinions* to form a more scientific and standardized public hospital management system. Through the government's financial assistance, the profit-seeking path of public hospitals and the "feeds doctor with drugs" situation were to be eradicated. A reasonable regulatory framework, operational system, and "white angel" image of the doctors were to be established. Hence, the development of public hospitals was to be rectified and the basic healthcare needs of the population were to be satisfied.

In 2010, the Ministry of Health launched public hospital reform to solve these problems. The reform can be separated into three parts. In the first part on management, the document emphasized that the modernization of hospital management must be undertaken and the decisions made by hospitals must be guided by public welfare and supervised by multiple channels. The second part focused on minimizing patient costs, particularly aimed at reducing the cost of medicines and medical consumables, such that the doctor could no longer benefit from prescribing medicines. To narrow the gap between urban and rural medical situations, the third part called for replanning the layout of public hospitals. More medical resources were to be allocated to rural hospitals, and the tier diagnosis service model needed to be established. To implement public hospital reform smoothly, the government selected 16 cities, including Anshan City, Shanghai City, Xiamen City, and Ezhou City, as national pilot cities to explore effective paths. In 2014, 17 cities, including Tianjin City, Ningbo City, Tangshan City, and Liuzhou City were selected as the second batch of pilot cities to carry out reform work. In 2015, the government assigned 66 cities, including Nanjing City, Xuzhou City, and Wenzhou City, to implement the third batch of reform. In May 2015, the government issued the "Guidance on the Comprehensive Reform Pilot of Urban Public Hospital," which focused on breaking the profit-seeking mechanism of public hospitals and required all departments to jointly continue to do a good job in the next comprehensive reform. The fourth batch was formally implemented in 2016, with 100 pilot cities, including Haikou City, Zhongshan City, and Yueyang City. In 2021, the government again issued the *Opinions on Promoting*

the High-Quality Development of Public Hospitals, which proposed that the next stage should adhere to people's health, be government-led, be focused on national welfare, and establish a modern hospital management system. In this way, public health and healthcare infrastructure were to be improved more comprehensively. To date, public hospital reform has been implemented for more than 10 years, and the capacity of China's medical service has significantly improved.

3.2. Research hypothesis

Improving public health is the fundamental goal of public hospital reform. The *Opinions* clearly emphasize the need to improve the public hospital's service system and management structure. It also proposed to augment the medical security payment by deepening the personnel reform and increasing government financial investment in health. We observed that this reform aimed to bring public hospitals back to the goal of national welfare from many perspectives, such as the reasonable mobilization of human capital, the continuous improvement of medical facilities, the innovation of management, the breaking up of the situation of medicine to support medical care, and other strong measures. The general public could, therefore, "dare to see a doctor," have more equitable access to medical and health services, and improve their physical wellness. Therefore, the public hospital reform, in theory, was a significant step forward in improving public health.

Hypothesis 1: The reform of public hospitals will positively affect public health.

As an essential part of this reform, increasing the government's financial investment in health is the key to breaking the situation of public hospitals being "fed by medicines." On the one hand, government financial investment can reduce the revenue channels of public hospitals to service fees and government subsidies but not drug revenues. It can also promote market-based pricing of medical services and establish a service price system that reflects the value of services and technical labor, so the welfare of patients and doctors can be enhanced. Using a doctor-patient relationship model, Chen et al. (28) found that the elimination of drug surcharges not only benefited the quality and supply of medical resources but was also able to reduce the cost of patients. On the other hand, Kou (29) argued that to deal with public health problems in China, it is necessary to rationalize the use of health resources and improve the efficiency of medical services so that social support and healthcare systems can be effectively used. In addition, the increase in financial support can guarantee capital construction and equipment purchase. Research in critical areas, personnel training, and even retiree pension will all be satisfied soundly. With the government's financial support, the service system of medical institutions can be built jointly, and the distribution of medical resources can be handled with necessary approvals. Eventually, public health will be improved.

Hypothesis 2: Public hospital reform affects the level of public health by increasing the government's financial investment in health.

Compared with the central-western regions, the eastern region has a better economic foundation to produce a higher health environment, such as a higher degree of marketization, relatively abundant medical resources, more comprehensive public health services, and a relatively high level of human capital. In the meantime, with the transformation and upgrading of the industrial structure in the eastern region, the negative environmental externalities brought by economic development are decreasing. Therefore, the level of public health in the eastern region is high. However, in central-western regions, with the scarcity of medical resources and the deficiency of infrastructure facilities, the supply of education and medical resources can't catch up with the growing demand for health services from the population. Therefore, theoretically, the impact of public hospital reform on public health in the Chinese regions will exhibit significant differences.

Hypothesis 3: The impact of public hospital reform on public health is regionally heterogeneous.

4. Data sources, variables, and model

4.1. Model selection

This study used a quasi-natural experiment, the public hospital reform that began in 2010, to examine its impact on public health levels. The method used in this study is a frontier research method in economics: the time-varying difference in difference model, intending to obtain plausible causal inferences. The main rationale of this method is to identify the net effects of policy shocks by comparing the policy effects of the treatment group and the control group before and after the policy shock based on the construction of counterfactual events. Specifically, this study took the time dimension as a first difference to compare the effects of public hospital reform before and after. Second, to examine the differences between cities that carried out public hospital reform and other cities, the study used the regional dimension as the second difference. Referring to Wang et al. (30) and Guo et al. (31), this study constructed an econometric model as follows.

$$y_{ct} = \alpha + \beta_1 DID_{ct} + \varphi X_{ct} + \gamma_t + \sigma_c + \varepsilon_{ct}, \quad (1)$$

where y_{ct} is the explained variable, representing the health level of the population in a given city c at the time of year t; DID_{ct} is the core explanatory variable, representing whether the city is under implementation or not; X_{ct} represents the control variables that change with city c or year t and affect public health, including the urbanization level, the education level, government scale, environmental pollution, and openness level; σ_c represents city-fixed effects, controlling all city-level factors that do not change over regions, such as geographical location; γ_t represents a time-fixed effect, controlling time-level features that do not vary from time to time, such as macroeconomic changes; and ε_{ct} indicates the error term. The core explanatory variable DID_{ct} estimated coefficient β_1 is the main focus of this study, which reveals the effect of public hospital reform on public health compared with non-implemented cities.

4.2. Variables description

4.2.1. Explained variable

Public health. Generally, public health is influenced by many complex factors such as ecological environment, economic conditions, education level, lifestyle, social factors, and medical level; therefore, it is difficult to find a multi-dimensional proxy indicator. Most of the indicators, such as population mortality, life expectancy, and infant or maternal mortality, have been used in past studies to measure public health. However, since it is difficult to distinguish structural differences in public health from macro data, based on the definition of health by the World Health Organization and with reference to previous studies, this study used population mortality rate (*PMR*) to measure the public health level in the locality. In general, a lower population mortality rate represents a higher level of public health. In addition, to analyze the mechanism of the effect of public hospital reform on public health, the article adopted the per capita medical fiscal expenditures in cities (*lnmedical*) as a proxy variable to measure the governmental financial investment in health.

4.2.2. Explanatory variable

DID_{ct}. Since the public hospital reform cities are implemented in four phases, this study adopted a time-varying DID model to evaluate the policy of public hospital reform in cities. DID_{ct} is defined as follows: if the city is in the year of policy pilot implementation or subsequent years, then $DID_{ct} = 1$; otherwise $DID_{ct} = 0$, thus forming a treatment group and a control group.

4.2.3. Control variables

To obtain objective estimates of policy effects, this study controlled for variables that varied over time or regions and may affect public health. With reference to previous studies, the following control variables were selected: (1) urbanization rate (*urb*), expressed as the ratio of the resident urban population to the total population; (2) education level (*edu*), expressed as the number of college students per 10,000 people; (3) government scale (*gov*), is replaced by the annual government revenue; and (4) environmental pollution level (*fog*), which is substituted by the annual air emissions of each city. A large number of studies have shown that environmental problems have a negative impact on the health level of residents. The spillover and exogenous determinacy of air pollutants are stronger compared with other pollutants. This study adopted the annual emissions of smoke and dust as a proxy for the level of air pollution, referring to Sun et al. (32). (5) Level of openness (*fdi*) was represented by the total foreign direct investment in the current year. To avoid bias such as heteroskedasticity due to excessive numerical difference, the control variables in this study are all processed logarithmically.

4.3. Data sources and description statistics

In this study, panel data from 269 prefecture-level cities in China from 2008 to 2019 were as the research sample to evaluate the policy effects of the reform of public hospitals. According to the availability and validity of data, data from some cities such as Tibet, Turpan, and Haidong were removed from this article. All data in the article were acquired from the City Statistical Yearbook, Regional Statistical Yearbook, and EPS database, and some missing data were made up by manually collecting annual reports from each prefecture-level city. The data processing and empirical regression were mainly done through Stata16. Table 1 presents the descriptive statistics of each continuous variable.

TABLE 1 Descriptive statistics for the variables.

Var	Obs	Mean	Std. dev.	Min	Max
PMR	3,228	6.340	2.148	0.790	23.100
Lnmedical	3,228	6.263	0.653	4.150	9.050
Lnurb	3,228	3.918	0.299	2.854	4.605
Lnedu	3,228	4.571	1.160	0.000	7.675
Lngov	3,,227	13.750	1.134	10.174	18.087
Lnfog	3,132	9.648	1.152	3.526	15.458
Lnfdi	3,131	9.950	1.883	1.099	14.941

5. Empirical analysis

5.1. Results of DID

In this study, we constructed an empirical model based on equation (1) and gradually added control variables for regression. Table 2 gives the regression results of the impact of the public hospital reform on public health. In column (1), the estimated coefficient of the reform indicated a significant negative relationship between public hospital reform and population mortality rate and based on the explanatory variable's meaning: the lower the population mortality rate is, the higher public health will be, which means that it can improve public health as well, hence verifying hypothesis 1. After gradually adding control variables, the significance of the coefficient did not change. Still, the net effect of the policy did alter, suggesting that the control variables did affect the population mortality rate. Overall, public hospital reform can significantly reduce the population mortality rate and promote public health.

Further, from Table 2, it can be found that the urbanization rate has the largest negative effect on population mortality, concluding that urbanization effectively improves public health. The possible reason is that urbanization can bring more medical sources and more income for residents and can exaggerate the scale effects of infrastructure, and with the improvement of these factors, resident health will also be promoted. The marginal impact of government scale and education level on population mortality is also statistically significant and negative, improving public health, validating the results of Grossman (5). While the coefficient of the openness and environmental pollution, although not statistically significant, has a positive effect on population mortality, the possible explanation is that due to the lack of environmental regulations in China, as the openness increases, it attracts low-quality foreign investment in pollution-intensive industries, which in turn exposes the regional

TABLE 2 DID regression results.

VAR	PMR (1)	PMR (2)	PMR (3)	PMR (4)	PMR (5)	PMR (6)
DID	−0.438*** (0.135)	−0.439*** (0.134)	−0.437*** (0.134)	−0.429*** (0.133)	−0.452*** (0.133)	−0.498*** (0.136)
Lnurb		−1.336*** (0.418)	−1.261*** (0.426)	−0.928** (0.416)	−0.972** (0.416)	−1.087** (0.426)
Lnedu			−0.152** (0.071)	−0.162** (0.072)	−0.166** (0.074)	−0.167** (0.075)
Lngov				−0.414** (0.166)	−0.464*** (0.173)	−0.534** (0.217)
Lnfog					−0.064 (0.046)	−0.062 (0.048)
Lnfdi						0.063 (0.061)
Con	5.724*** (0.070)	10.772*** (1.577)	11.133*** (1.575)	15.240*** (2.396)	16.699*** (2.553)	17.467*** (2.895)
Obs	3,228	3,228	3,228	3,227	3,132	3,042
R^2	0.205	0.207	0.208	0.209	0.212	0.219
Year-fix	YES	YES	YES	YES	YES	YES
City-fix	YES	YES	YES	YES	YES	YES

***, **, and * represent statistical significance at the 1%, 5%, and 10% levels, respectively. The values in parentheses are robust standard errors for clustering to the city level.

environment to a low level of equilibrium and creates a "pollution sanctuary." This leads to an increase in population mortality.

5.2. Robustness tests

5.2.1. Parallel trend test

According to the above study, the public hospital reform has effectively reduced the population mortality rate and thus improved public health. However, as a model for policy effect assessment, the unbiased estimation of time-varying DID results was needed to satisfy a prerequisite assumption that the treatment and control groups must have the same or similar development trend before the policy implementation so that the influence of other possible variables can be excluded. Otherwise, the estimation results were to be biased. To verify the feasibility of parallel trends and further observe the dynamic effects of the policy, this study referred to Jacobson et al. (33) and Guo et al. (34) and adopted the event analysis method to study the dynamic effects of the reform. The following regression model is based on Equation (1).

$$y_{ct} = \alpha + \sum_{j=-6}^{2} \beta_j D_{c,\,t-j} + \varphi X_{ct} + \gamma_t + \sigma_c + \varepsilon_{ct} \qquad (2)$$

In the equation, D is a dummy variable and takes the value of 1 if the city c implements the reform in year $t - j$; otherwise, it is 0. β_0 represents the policy effect in the current period of the reform, β_{-6} to β_{-1} represents the policy effect before the reform, and β_1 to β_2 represents the after.

Figure 1 demonstrates the coefficient of mortality rate. The dots represent the values of the coefficients, and the dashed lines represent their 95% confidence interval. As can be seen from Figure 1, the estimated coefficients basically fluctuated around zero

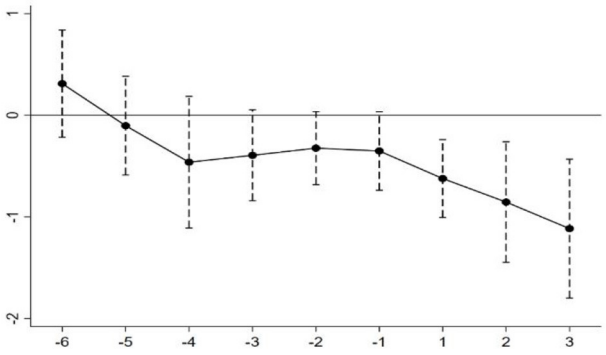

FIGURE 1
Parallel trend test.

before the policy shock, and none of them could pass the 95% confidence interval. It implies that the difference in development between treatment and control groups before the policy shock was not significant, validating the premise of a parallel trend.

It should also be noted that the estimated coefficients have a significant downward trend in the year of the reform implementation and have the momentum of decreasing annually, which indicates that the reform of public hospitals can effectively reduce the mortality rate, and the policy effect will increase with time.

5.2.2. Tailoring test

Considering that the estimation results may be affected by extreme values, which may generate estimation being biased, in this study, all the continuous variables were treated with bilateral tail

TABLE 3 Results of robustness tests.

VAR	(1) Pre 3	(2) Pre 1	(3) Tailoring
DID	0.127 (0.115)	0.074 (0.109)	−0.450*** (0.119)
Constant	17.817*** (2.896)	17.758*** (2.903)	14.144*** (2.662)
Observations	3,042	3,042	3,042
R^2	0.215	0.215	0.220
Controls	YES	YES	YES
Year-fix	YES	YES	YES
City-fix	YES	YES	YES

***, **, and * represent statistical significance at the 1%, 5%, and 10% levels respectively. The values in parentheses are robust standard errors for clustering to the city level.

reduction at 5% and 95%, respectively, and reoperated the model. The results are shown in Table 3. The results showed that there were no significant changes in the regression coefficient and remained negative even after excluding the extreme values, thus verifying the robustness of the above study.

5.2.3. Setting virtual time

To further avoid biased regression results, we referred to Fan and Tian (35) to construct a virtual policy implementation so that we could examine whether the changes in the explained variable are related to the implementation of the policy. In this study, we assumed that the implementing year of the reform is uniformly advanced by 1 year and 3 years and re-regressed to determine whether the coefficients of their explanatory variable are statistically significant. The results are listed in Table 3, which shows that the estimated coefficient of the explanatory variable is not significant in the DID model. Table 3 indicates that the difference in public health between the implemented and non-implemented cities is due to the "dividends" brought by the reform. The robustness of the baseline regression results was further verified.

5.2.4. Placebo test

In the meantime, this study referred to Guo et al. (36) to conduct placebo tests by constructing a fake treatment group. If the coefficient remained significantly negative, it indicated that the changes in population mortality rate were not driven by the reform but by other unobserved factors, and vice versa, supporting the robustness of the result. In this study, a random sample with put-back was conducted from the sample of 269 cities, keeping other control variables fixed, and then a DID regression was performed. To enhance the convincingness of the estimation results, this study repeated the sampling 500 times, and the estimated coefficients of the reform are shown in Figure 2.

Each black dot in Figure 2 represents the estimated coefficients of the explanatory variable in the false treatment group. The results showed that the estimated coefficients were mainly distributed around the value of 0 and were close to the normal distribution. The position of the vertical line in Figure 2 indicates the estimated coefficient of the baseline regression (i.e., −0.498), which falls

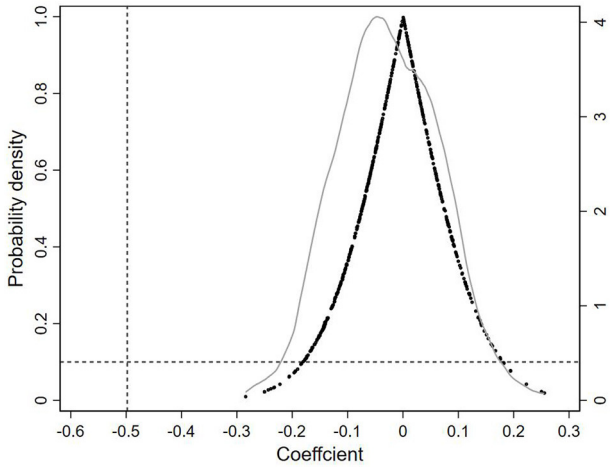

FIGURE 2
Results of the kernel density distribution of the DID of the placebo test.

at the end of the random sample distribution, is much smaller than the estimated coefficients of the placebo. It indicates that the population mortality rate is not significantly affected by the reform under the placebo treatment group, confirming that the reduction in mortality rate was indeed a result of the reform.

5.3. Results of the mediating effect

The empirical results from the benchmark regression indicated that public hospital reform improved public health by lowering the population mortality rate. However, the channels through which the reform goals are achieved need to be further analyzed. The construction of empirical models needs to be based on the reform programs. In the *Opinions,* it is clearly stated that the reform focuses on fundamental changes in the income-generating mechanism of doctors. The public hospitals should eliminate their profit-seeking character, highlight the "national welfare" orientation, and achieve the reform goals by increasing financial support and enhancing the government's responsibility in the healthcare department. Therefore, the support of the government's financial investment in health is an important path to achieving the goal. This study used the per capita medical fiscal expenditures as a proxy for the strength of financial investment to test the transmission path of the reform on public health.

Based on equation (1), this study first explored the effect of the mediating variable (*lnmedical*) on the explanatory variables to verify whether there was a significant linear relationship between them. Second, based on equation (1), the mediating variable was added to test the effect of financial expenditure on the results of the benchmark study. The model is as follows.

$$\text{lnmedical} = \alpha + \beta_2 DID_{ct} + \varphi X_{ct} + \gamma_t + \sigma_c + \varepsilon_{ct} \quad (3)$$

$$y_{ct} = \alpha + \beta_3 DID + \theta lnmedical + \varphi X_{ct} + \gamma_t + \sigma_c + \varepsilon_{ct} \quad (4)$$

The bootstrap method referred to Wen et al. (37) and Chen et al. (38) to test the mediation effect. First, there were 500 random

TABLE 4 Mediating test.

	Observed coef.	Std. err.	z	$p > \|z\|$	Normal-based [90% conf. interval]	
Indirect	−0.020	0.011	−1.768	0.078	−0.038	−0.001
Direct	−0.434	0.144	−3.014	0.003	−0.670	−0.197

TABLE 5 Regional heterogeneity test.

VAR	(1) Eastern	(2) Central	(3) Western
DID	−0.207 (0.213)	−0.603** (0.249)	−0.687*** (0.241)
Constant	32.939*** (5.548)	11.505* (5.842)	21.507*** (4.653)
Observations	1,093	1,069	880
R^2	0.332	0.204	0.163
Controls	YES	YES	YES
Year-fix	YES	YES	YES
City-fix	YES	YES	YES

***, **, and * represent statistical significance at the 1%, 5%, and 10% levels, respectively. The values in parentheses are robust standard errors for clustering to the city level.

replicates according to the samples that were put back, which were then used to estimate the mediation effects; if their confidence intervals of 90% or above did not include zero, it means that the original hypothesis $H_0 = \beta_2 \times \theta$ was rejected. If the coefficients were statistically significant, the mediation effect was valid.

The regression results of the mediating effect under the Bootstrap method are given in Table 4. The outcome showed that the mediating effect of expenditure holds significantly for the population mortality rate, and its direct and indirect effects did not include zero at the 90% confidence interval. Thus, hypothesis 2 was verified. However, the impact of reform on the population mortality rate through the mediating channel was much lower than its direct effect (indirect effect = −0.020; direct effect = −0.434), which may be explained by the imperfection of supporting policies such as management system, staff deployment, remuneration mechanism, and promotion mechanism during the reform process in cities. These issues were the result of the lack of clarity on the responsibility between the government departments and public hospitals and led to the inability to fully utilize the government's financial support for public hospitals.

5.4. Regional heterogeneity test

As a typical large economy, China has an obvious imbalance in regional development, such as the basic healthcare and urbanization ratio among regions. To analyze the regional differences in the impact of the reform on public health, the study divided China into three major regions: eastern, central, and western. Then, we estimated the impact of the reform separately. The results are shown in Table 5.

After the year-fix and time-fix effects were under-controlled, the estimated coefficient of the reform in the eastern region was not statistically significant (refer to Table 5). At the same time, the coefficient in the central and western regions were −0.603 and −0.687, respectively. The coefficients were not only significant at the 1% level but also much smaller than that of the eastern region. This indicates that the reform in the central and western regions could suppress mortality more significantly and promote public health, which is consistent with the benchmark estimation results at the national level, thus verifying hypothesis 3. The above comparison shows that the positive effect of public hospital reform on public health was significantly stronger in the central and western regions than in the eastern region. The probable reason is that the eastern region has more advantages than the other two regions. For instance, economic base, marketization, medical resource allocation, public health services, residents' human capital, government financial scale, and other health-influencing factors. At the same time, with the transformation and upgrading of the industrial structure in the eastern region, the tertiary industry has been increasing in proportion to the GDP, and the improvement of environment; therefore, the reform to break the profit-seeking layout, improve the management system, and a series of policies brought about by the eastern population has less impact. In contrast, urban medical resources in the central and western regions are relatively scarce, public infrastructure needs to be strengthened, and the supplement of education and medical resources is slower than the population growth rate. Moreover, the central and western regions have begun to gradually take over the role of manufacturing industries from the eastern coastal areas. With the secondary industries accounting for an increasingly high proportion and the ecological environment deteriorating, the positive effect of reform on the level of public health has been significant.

6. Conclusion and implications

Compared with the qualitative analysis of public hospital reform in previous literature, this study, using the panel data of 269 prefecture-level cities from 2008 to 2019, examined the net effect of public hospital reform on public health and conducted relevant robustness tests by applying the time-varying DID model. Further, we identified the mechanism of the impact and analyzed the heterogeneity of the policy effects of public hospital reform.

The following conclusions were obtained: first, at the national level, public hospital reform significantly contributed to public health. Specifically, compared with the non-implemented cities, the reform can effectively reduce the rate of mortality by 0.498 per thousand of the population. The result showed that the policy is an important driving strategy to improve public health and validates previous qualitative studies from the perspective of empirical models. Second, the mediating result showed that the reform can improve public health by increasing government medical expenditure. Still, the indirect effect was minimal compared with

the direct impact; in fact, the proportion of indirect effect was only 4.405%. It showed that the role of medical expenditure has not been fully utilized in the reform process. Third, there was heterogeneity in the impact of reform in different regions, it significantly promoted public health in the central and western regions, but not in the eastern regions. This indicated that the effect of reform policy on the progress of public health varied from region to region, and the impact of the reform policy was more significant in regions with weaker economic strength and poorer ecological environments.

Based on the above research findings, this study puts forward the following policy recommendations: first, public hospital reform is an important strategy to improve public health. Governments at all levels should ensure the orderly implementation of the reform and expedite the formation of medical service systems that guarantees the national welfare of public hospitals. The path of this policy can lay a solid foundation for further public hospital reform. Second, positive actions need to be taken to optimize the structure of financial expenditures, implement the responsibility of healthy financial investment, and accelerate local economic development to enrich the financial reservoir. The central government should increase its ability to make financial transfers to the provinces and improve the efficiency of health financial investment to establish a long-term health financial investment that is in line with people's health needs. Third, there are certain differences in the economic, social, and ecological conditions of different regions in China, and the "one-fits-all" approach cannot meet the needs for high-quality development of local health. The governments at various levels need to customize the policies according to local conditions to promote balanced development in each region, accelerate the process of building *Health China*, and continue to provide health protection for China's high-quality development.

There are still some limitations that could be studied further. On the one hand, due to data limitations, this study used the population mortality rate as a proxy for general health rather than directly measuring public health levels. On the other hand, we only used one of the measurements as a transmission mechanism to study. However, with a specific focus on public hospital reform, the research is still worthy of attention. We believe that further work will provide useful supplements in these aspects.

Data availability statement

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

Author contributions

BG and WF designed the study, performed the research, analyzed data, and wrote the paper. HC collected most of data. JL conducted empirical analysis.

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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.

Publisher's note

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Trends and disparities in disease burden of age-related macular degeneration from 1990 to 2019: Results from the global burden of disease study 2019

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Objectives: This study aims to estimate the trends and disparities in the worldwide burden for health of AMD, overall and by age, sex, socio-demographic index (SDI), region, and nation using prevalence and years lived with disability (YLDs) from Global Burden of Disease (GBD) study 2019.

Methods: This retrospective study presents the prevalent AMD cases and YLDs from 1990–2019, as well as the age-standardized prevalence rate (ASPR) and age-standardized YLD rate (ASYR) of AMD. To measure changes over time, estimated annual percentage changes (EAPCs) of the age-standardized rates (ASRs) were analyzed globally, then studied further by sex, SDI, region, and nation. We included data from the 2019 Global Burden of Disease (GBD) database to examine AMD prevalence and YLDs from 1990–2019 in 204 countries and territories, as well as demographic information such as age, sex, SDI, region, and nation.

Results: Globally, the number of prevalent AMD cases increased from 3,581,329.17 (95% uncertainty interval [UI], 3,025,619.4–4,188,835.7) in 1990 to 7,792,530 (95% UI, 6,526,081.5–9,159,394.9) in 2019, and the number of YLDs increased from 296,771.93 (95% uncertainty interval [UI], 205,462.8–418,699.82) in 1990 to 564,055.1 (95% UI, 392,930.7–789,194.64) in 2019. The ASPR of AMD had a decreased trend with an EAPC of −0.15 (95% confidence interval [CI], −0.2 to −0.11) from 1990 to 2019, and the ASYR of AMD showed a decreased trend with an EAPC of −0.71 (95% confidence interval [CI], −0.78 to −0.65) during this period. The prevalence and YLDs of AMD in adults over 50years of age showed a significant increase. The prevalence and YLDs of AMD were significantly higher in females than males, overall. The ASPRs and ASYRs in low SDI regions was greater than in high SDI regions from 1990 to 2019. In addition, increases in prevalence and YLDs differed by regions and nations, as well as level of socio-economic development.

Conclusion: The number of prevalent cases and YLDs due to AMD increased over 30 years and were directly linked to age, sex, socio-economic status, and geographic location. These findings can not only guide public health work but also provide an epidemiological basis for global strategy formulation regarding this global health challenge.

KEYWORDS

age-related macular degeneration, trends, disparities, global burden of disease study, prevalence

Introduction

Globally, age-related macular degeneration (AMD) is a leading cause of irreversible vision loss in many patients with posterior segment eye diseases (1, 2). AMD has imposed a heavy burden on these individuals and society: poor vision due to AMD can cause negative consequences, such as increased risk of falls, depression, lack of meaningful activities in daily life, and requirement of long-term care (3–5). More importantly, the overall aging of the population means that the cases of AMD have risen exponentially in recent years. The number of patients affected by AMD is expected to increase globally, from around 200 million in 2020 to nearly 300 million in 2040 (6, 7). Vision complications from AMD can significantly affect the quality of life in older adults and contribute to already-challenging health problems and comorbidities (8, 9). Understanding the AMD disease burden over time (and any influencing factors) may aid in formulating targeted public policies and reducing the public disease burden.

Many population-based AMD studies have been conducted worldwide. A cohort study reported that the incidence rate of early AMD was highest among White people (5.3%), medium among Chinese (4.5%) and Spanish people (3.3%), and the lowest among Black people (1.6%). The incidence rate of late AMD was similar; 4.1, 2.2, 0.8, and 0.4%, respectively (10). One meta-analysis of studies with European populations indicated that the prevalence of early or late AMD was lower in the group of 50–55 year old participants (0.08%) than in the group of 90+ year old participants (20.1%) (11). Another meta-analysis showed that in Asian participants aged 40–79 years, early AMD prevalence was 6.8% and late AMD prevalence was 0.56%; the corresponding prevalence in the White participants of the same age range were 8.8 and 0.59%, respectively (12). Although there have been several studies on the disease burden of AMD, few studies described the prevalence of the condition globally, across geographical regions, over time, and any overall influencing factors (13–15).

The 2019 Global Burden of Disease Study (GBD 2019) is the latest published data from 204 countries and territories, and it includes the most recent estimates of disease burden and data of influencing factors for researchers to study. The GBD database (GBDx) is essential for understanding the global burden of many diseases and Global Burden of Disease Study in 2019 (GBD 2019) is the most updated and comprehensive systematic study on the prevalence and years lived with disability (YLDs) of AMD. The purpose of this study is to understand the global, regional, and national prevalence and YLDs of AMD and influences on this prevalence and YLDs. In this study, we investigated the changes in the global prevalence and YLDs of AMD from 1990 to 2019 and assessed the global burden of AMD by age, sex, socio-demographic index (SDI), region, and nation. Our findings can not only guide public health work, but also provide an epidemiological basis for global strategy formulation regarding AMD burden.

Methods

Data

Our global burden data on AMD are from the GBD 2019 which is freely available; therefore, no ethical approval or informed consent was required. These data include the estimated number of prevalent AMD cases and YLDs each year, age-standardized prevalence rate (ASPR), age-standardized YLD rate (ASYR), and change over time by age, sex, SDI, region, and nation from 1990 to 2019. Results are presented as number of prevalent cases, ASPR, ASYR and the estimated annual percentage change (EAPC), using 95% uncertainty intervals (UI) and 95% confidence intervals (CI).

Factor calculations

The Disease Modeling-Meta Regression (DisMod-MR) version 2.1 was used to model the epidemiological outcomes of AMD, a Bayesian meta-regression framework widely used for GBD epidemiological modeling. The general methods and disease burden estimation methods of GBD 2019 have been previously reported (16). The prevalent cases, YLDs, prevalence and YLD rate of AMD were reported from the GBDx and stratified by age, sex, SDI, region, and nation.

SDI assignment is based on the country's *per capita* income distribution, average years of education and the fertility rate of women younger than 25 years old. The GBDx divided the countries and territories into five SDI levels (high, high-middle, middle, low-middle, and low). In this study, the SDI ranged from 0 to 1 (low to high) and was used to describe the development level of a country or geographical region. The GBDx also grouped the countries and territories into 21 regions, the details of which have been previously reported (16–18). The disability-adjusted life-years (DALYs) are the sum of YLDs and years of life lost (YLLs) due to premature death. As for AMD, DALYs generally mean YLDs. Trends of AMD were quantified using ASPR, ASYR and EAPC. When considering variations in the age structure, it was necessary to standardize the ASR calculation (18). The ASR was obtained by the formula:

$$ASR\left(\text{per } 100{,}000 \text{ population}\right) = \frac{\sum_{i=1}^{A} aiwi}{\sum_{i=1}^{A} wi} \times 100{,}000$$

The EAPC was used to explain the ASR change trend over time. A linear relationship between ASR and time can be seen in its natural logarithm. The natural logarithm rate that a regression line fit is given by the equation $y = \alpha + \beta x + \varepsilon$, where $y = \ln(\text{ASR})$, and x = calendar year. The EAPC was calculated as $100 \times (\exp(\beta) - 1)$. The linear regression model was used to obtain the EAPC's 95% CI (17). All data visualization was completed using the R program (version 4.2.2) and GraphPad Prism 9.0 statistics software.

Results

Global AMD burden

The number of prevalent AMD cases increased from 3,581,329.17 (95% uncertainty interval [UI], 3,025,619.4–4,188,835.7) in 1990 to 7,792,530 (95% UI, 6,526,081.5–9,159,394.9) in 2019, and the number of YLDs increased from 296,771.93 (95% uncertainty interval [UI], 205,462.8–418,699.82) in 1990 to 564,055.1 (95% UI, 392,930.7–789,194.64) in 2019

(Tables 1, 2). However, the ASPR of AMD dropped from 98.8 (95% UI, 83.7–114.6) per 100,000 people in 1990 to 96.8 (95% UI, 81.3–113.2) per 100,000 people in 2019, with an EAPC of −0.15 (95% CI, −0.2 to −0.11), and the ASYR of AMD dropped from 8.29 (95% UI, 5.8–11.58) per 100,000 people in 1990 to 7.05 (95% UI, 4.92–9.84) per 100,000 people in 2019, with an EAPC of −0.71 (95% CI, −0.78 to −0.65). Despite the decrease in overall ASPR and ASYR, the number of cases and YLDs due to AMD revealed increasing trends that changed between 1990 and 2019 (Figures 1A,B).

AMD burden by age

With age increasing, the global number of cases and YLDs due to AMD gradually increased when age was 50 years old in 1990, reaching the peak at age of 65–69, after that it decreased with age increasing (Figures 2A,C). It has the similar trend in 2019 (Figures 2B,D). The crude prevalence rates and YLD rates of AMD increased with age, the fastest increasing speed is the age over 80 years old in 1990. In 2019, the general trend of the crude prevalence rates and YLD rates is similar to the trend in 1990. Additionally, the rate of increasing of the curves after age of 90 years old showed a significantly increasing in both 1990 and 2019.

AMD burden by sex

Between 1990 and 2019, the number of AMD cases and YLDs, and ASPRs and ASYRs in females was significantly higher than in males (Tables 1, 2; Figure 1). The female number of AMD cases and YLDs due to AMD were all significantly larger than males in 1990 and 2019, and the difference in crude rates was obviously, especially the age after 80 years old in 1990 and 2019 (Figure 2).

AMD burden by SDI

In 2019, the number of AMD cases and YLDs were the highest in middle SDI regions and the lowest in low SDI regions. Meanwhile, the ASPRs and ASYRs of AMD were highest in the low SDI regions and lowest in the high SDI regions (Tables 1, 2). The relationship between ASPR and ASYR and SDI in 204 countries and territories in 2019 are shown in Figure 3. The relationship between ASPR and ASYR and SDI in 21 regions between 1990 and 2019 are shown in Supplementary Figure S1. ASPRs and ASYRs in developing countries and regions were significantly higher than those in developed countries and regions.

Regional AMD burden

At the regional level in 1990 and 2019, the number of AMD cases and YLDs were highest in East Asia, followed by South Asia, and lowest in Oceania (Tables 1, 2). The ASPR and ASYR were highest in Western Sub-Saharan Africa, followed by North Africa and Middle East, and lowest in High-income Asia Pacific. From 1990 to 2019, the EAPCs of ASPR and ASYR in South Asia were lowest at −1.41 (95% CI, −1.55 to −1.27) and − 1.75 (95% CI, −1.87 to −1.62), followed by Southeast Asia at −0.75 (95% CI, −0.82 to −0.68) and − 1.09 (95% CI, −1.18 to −1). In contrast, the EAPC of ASPR and ASYR in Southern Sub-Saharan Africa was highest at 0.37 (95% CI, 0.29–0.45) and 0.37 (95% CI, 0.22–0.51), followed by Central Sub-Saharan Africa were 0.26 (95% CI, 0.23–0.29) and 0.2 (95% CI, 0.14–0.26).

National AMD burden

The growth rates of cases and YLDs in Burkina Faso, Benin, and Niger were more than 300% increase from 1990 to 2019. While Ukraine, Belarus, Latvia, and Georgia were less than 20% increase during this period (Figures 4A,B). In addition, China and India demonstrated the largest cases and YLDs of AMD in 2019, while Tokelau, Niue and Nauru demonstrated the lowest (Supplementary Tables S1, S2). The ASPRs of AMD in 2019 ranged from 19.1 to 390.9 per 100,000 people in 204 countries and territories, Nepal demonstrated the highest ASPR of AMD, while Barbados demonstrated the lowest (Figure 4C; Supplementary Table S1). The ASYRs in 2019 ranged from 0.51 to 21.6 per 100,000 people in 204 countries and territories, Iran demonstrated the highest ASYR of AMD, while Barbados demonstrated the lowest (Figure 4D; Supplementary Table S2). In addition, Malaysia saw the largest decline in ASPR (EAPC, −1.97; 95% CI, −2.16 to −1.78) and ASYR (EAPC, −2.62; 95% CI, −2.87 to −2.37), followed by Thailand, Iceland, and India. Only a few countries or territories (such as Burkina Faso, Gambia, Chad, Benin, and Côte d'Ivoire) reported an increasing ASPR and ASYR of AMD between 1990 and 2019 (Figures 4E,F; Supplementary Tables S1, S2).

Discussion

This study reported on the cases and YLDs, and ASPRs and ASYRs of AMD from 1990 to 2019 in 204 countries and territories around the world and revealed disparities by age, sex, socio-economic level, region, and nation. Although the ASPR and ASYR decreased overall from 1990 to 2019 (with a global EAPC of −0.15 and − 0.71), the overall cases and YLDs due to AMD still increased. Furthermore, compared with other age groups, the ASPRs and ASYRs in older adults increased significantly. Globally, aging population is the most important medical and social demographic issue. The global population aged 65 and over in 2000 was 18 percent, while by 2050 it will reach 38 percent (19). The aging population and high prevalence and YLDs of AMD in people over 60 may be the main reasons for the near doubling of overall cases between 1990 and 2019. Due to the age of the global population is increasing, AMD cases will continue to rise.

Global policy making and economic restructuring can guide the prevention and treatment of AMD. Initially, for the purpose of eliminating preventable blindness by 2020, the WHO and the International Agency for the Prevention of Blindness (IAPB) started the VISION 2020 global initiative in 1999 to prevent, control, and eliminate avoidable blindness at the national level

TABLE 1 Estimated number and age-standardized rate (per 100,000 persons) of prevalence and temporal trends for AMD from 1990 to 2019 by sex, SDI, and GBD regions.

Characteristics	1990		2019		1990–2019
	Number (95% UI)	ASR (95% UI)	Number (95% UI)	ASR (95% UI)	EAPC (95% CI)
Global	3,581,329.17 (3,025,619.44–4,188,835.66)	98.78 (83.72–114.63)	7,792,530.04 (6,526,081.5–9,159,394.94)	96.76 (81.32–113.2)	−0.15 (−0.2—0.11)
Sex					
Female	2,118,523.4 (1,791,457–2,473,214.1)	103.97 (88.4–121)	4,506,554.63 (3,789,113.1–5,266,137.2)	102.42 (86.1–119.7)	−0.15 (−0.2—0.11)
Male	1,462,805.76 (1,221,218.7–1,724,282.3)	90.94 (76.8–106.1)	3,285,975.41 (2,715,084.1–3,893,320)	89.55 (74.5–105.3)	−0.1 (−0.15—0.06)
SDI region					
High SDI	5,89,371.09 (4,95,590.14–6,87,094.36)	55.48 (47.03–64.67)	1,016,422.12 (8,57,435.16–1,185,659.08)	48.37 (40.74–56.29)	−0.53 (−0.59—0.46)
High-middle SDI	9,74,824.6 (8,22,768.73–1,140,725.42)	99.43 (84.57–115.34)	2,170,539.67 (1,834,349.22–2,543,933.37)	106.02 (89.95–123.71)	0.21 (0.15–0.28)
Middle SDI	1,033,914.12 (8,53,461.05–1,226,652.56)	115.34 (96.54–135.56)	2,612,130.53 (2,156,473.44–3,116,298.3)	111.12 (92.18–131.19)	−0.25 (−0.32—0.18)
Low-middle SDI	6,94,714.54 (5,70,668.71–8,22,902.11)	132.95 (111.23–156.27)	1,362,695.17 (1,122,775.79–1,621,775.89)	107.55 (89.44–127.05)	−0.9 (−0.97—0.83)
Low SDI	2,87,161.52 (2,39,354.86–3,39,032.18)	141.57 (119.62–165.63)	6,28,003.99 (5,21,118.82–7,47,865.96)	139.46 (116.25–164.76)	−0.14 (−0.19—0.09)
South–East Asia, East Asia, and Oceania					
East Asia	8,99,060.25 (7,31,153.2–1,079,383.03)	118.47 (98.5–140.87)	2,633,284.4 (2,160,679.12–3,154,893.43)	128.83 (106.73–153.26)	0.21 (0.06–0.36)
Southeast Asia	2,21,497.53 (1,83,008.36–2,64,015.65)	100.04 (83.5–117.72)	4,69,432.79 (3,90,412.44–5,57,154.75)	84.69 (70.55–99.84)	−0.75 (−0.82—0.68)
Oceania	855.47 (675.02–1,054.89)	35.46 (28.73–42.89)	1,857.22 (1,453.94–2,300.81)	32.74 (26.39–39.96)	−0.18 (−0.21—0.16)
Sub-Saharan Africa					
Eastern Sub-Saharan Africa	86,940.82 (72,271.67–1,02,765.09)	136.98 (114.83–161.38)	1,66,809.58 (1,36,759.2–1,99,384.13)	121.92 (101.38–144.97)	−0.22 (−0.29—0.16)
Central Sub-Saharan Africa	4,916.47 (3,827.5–6,163.78)	29.31 (23.31–35.76)	12,022.37 (9,520.59–14,777.57)	30.94 (24.56–37.73)	0.26 (0.23–0.29)
Southern Sub-Saharan Africa	10,093.32 (8,289.38–12,031.54)	42.05 (34.77–49.95)	22,310.37 (18,139.13–26,708.64)	45.6 (37.46–54.38)	0.37 (0.29–0.45)
Western Sub-Saharan Africa	1,66,710.92 (1,37,627.01–1,98,928.82)	210 (174.12–247.64)	3,59,408.81 (2,92,801.3–4,36,020.69)	219.31 (179.65–262.11)	0.03 (−0.06—0.13)
South Asia					
South Asia	7,46,805.46 (6,10,989.39–8,94,878.54)	154.5 (128.24–182.79)	1,499,084.21 (1,227,077.74–1,798,350.9)	114.72 (94.59–136.68)	−1.41 (−1.55—1.27)
Latin America and Caribbean					
Caribbean	6,064.03 (4,840.04–7,421.13)	24.31 (19.47–29.6)	11,526.89 (9,272.32–14,073.93)	22.29 (17.9–27.25)	−0.24 (−0.27—0.21)
Central Latin America	44,019.28 (35,831.2–52,938.98)	60.08 (49.01–71.73)	1,20,607.08 (98,249.09–1,44,367.12)	53.36 (43.57–63.61)	−0.32 (−0.35—0.29)
Tropical Latin America	68,381.04 (56,261.86–82,040.25)	83.77 (69.15–99.38)	1,93,602.3 (1,61,055.55–2,30,808.98)	82.06 (68.01–97.85)	0.18 (0.01–0.34)
Andean Latin America	21,698.24 (17,766.47–26,067.51)	116.27 (95.42–139.18)	61,461.71 (50,861.49–73,157.27)	113.58 (94.1–135.01)	−0.09 (−0.2—0.02)
North Africa and Middle East					
North Africa and Middle East	184.2 (153.9–217.8)	184.2 (153.9–217.8)	6,41,221.43 (5,28,275–7,62,563.1)	168.45 (139.4–199.2)	−0.21 (−0.27—0.16)

(Continued)

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TABLE 1 (Continued)

Characteristics	1990		2019		1990–2019
	Number (95% UI)	ASR (95% UI)	Number (95% UI)	ASR (95% UI)	EAPC (95% CI)
Central Europe, Eastern Europe, and Central Asia					
Central Asia	32,302.84 (26,043.92–39,734.46)	75.27 (60.84–92.16)	46,946.53 (37,395.69–57,823.12)	73.9 (59.71–90.29)	−0.12 (−0.16—0.08)
Eastern Europe	74,578.23 (60,736.8–89,143.14)	27.83 (22.8–33.02)	92,659.99 (76,042.2–1,09,661.05)	25.9 (21.29–30.65)	−0.33 (−0.37—0.29)
Central Europe	95,775.52 (78,777.33–1,13,942.37)	66.62 (55.04–79)	1,43,534.34 (1,16,963.63–1,72,033.35)	63.26 (51.59–75.97)	−0.21 (−0.24—0.18)
High-income regions					
Southern Latin America	15,307.08 (12,211.59–18,588.54)	35.63 (28.85–43.12)	26,823.92 (21,547.5–32,523.97)	31.2 (25.06–37.81)	−0.42 (−0.44—0.4)
Western Europe	6,48,357.13 (5,46,249.76–7,59,665.06)	107.85 (91.59–125.39)	9,76,388.69 (8,25,781.49–1,138,807.18)	93.13 (78.71–108.25)	−0.54 (−0.56—0.52)
North America					
Australasia	9,754.96 (8,011.3–11,565.82)	42.92 (35.44–50.82)	20,593.54 (17,012.15–24,503.01)	37.96 (31.26–45.24)	−0.4 (−0.47—0.32)
Asia Pacific	40,983.6 (33,396.48–49,283.4)	22.22 (18.27–26.57)	1,05,854.63 (87,551.31–1,25,058.63)	19.69 (16.3–23.36)	−0.43 (−0.54—0.32)

AMD, age-related macular degeneration; SDI, socio-demographic index; UI, uncertainty interval; CI, confidence interval; ASR, age-standardized rate; EAPC, estimated annual percentage change; GBD, global burden of disease.

(20). In line with earlier studies, the fact that the AMD cases presented a growing tendency globally in the last 30 years, nevertheless, the age-standardized prevalence rates showed a descending trend during this period (13, 21). It indicates that we have made some progress in the fight against AMD, but preventing vision loss caused by AMD remains a major challenge due to population growth and aging.

Although previous studies have implicated many risk factors related to AMD progression, age is uniquely important (22–25). A meta-analysis in 2020, combining data of 26 studies, showed an overall increase in prevalence of AMD in people aged 60^+ years; the prevalence of early or intermediate AMD increased by 25.3%, and the prevalence of late AMD increased by 2.4%. The combined annual incidence rate of late AMD in all age groups was 1.4/1000 people (26). Another meta-analysis showed that for late AMD, the prevalence rates of people aged 55–59 and 85^+ years were 0.1 and 9.8%, respectively. For early AMD, the prevalence rates of the two groups were 3.5% and 17.6%, respectively (27). Our study found similar results. The prevalence and YLDs of AMD in the older groups was significantly higher than that of the young group. Aging is the most significant risk factor for AMD because changes in retinal structure and function can promote the development of AMD (28). In time, this may cause other pathological risk factors to have a cumulatively detrimental effect.

The number of AMD cases and YLDs, and the ASPRs and ASYRs were significantly higher in females than in males overall from 1990 to 2019. AMD and its subtypes are equally prevalent in both males and females, and while some studies have shown that females have a faster progression rate than males, this difference was not observed in the more recent 2005–2008 NHANES study (29–31). Sex is often regarded as an independent risk factor, with some studies reporting higher risk in females, while other studies report the opposite (32–35). Possible explanations for the conflicting results include differences in follow-up time points and longer life expectancy in women (36). However, some studies suggested that the progression of AMD may be related to the difference of sex hormones in the body, such as estrogen (37). Another hypothesis is that the difference in AMD progression is related to the number of X-linked genes, which may be associated with the pathogenesis of AMD (38). Further studies may be needed to explore the possible mechanisms between sex and AMD.

Between 1990 and 2019, the ASPRs and ASYRs of low SDI regions were higher than those of high SDI regions. There is no doubt those a higher socio-economic level reduces the burden of disease because in more developed countries, health care systems are better equipped to provide access to preventative medicine, including services for early detection, early diagnosis, and early treatment of diseases (14). In this study, the burden of AMD was significantly different in regions with different socioeconomic statuses. SDI is a summary index that can be used to represent the position of a nation on the spectrum of economic development, and different regions in each nation can have significantly different SDI levels (39). A previous study has reported the AMD burden to be higher in low SDI regions (40). However, this study showed that the middle SDI regions demonstrated the highest number of AMD cases and YLDs, and the low SDI region

TABLE 2 Estimated number and age-standardized rate (per 100,000 persons) of YLDs and temporal trends for AMD from 1990 to 2019 by sex, SDI, and GBD regions.

Characteristics	1990		2019		1990–2019
	Number (95% UI)	ASR (95% UI)	Number (95% UI)	ASR (95% UI)	EAPC (95% CI)
Global	2,96,771.93 (2,05,462.8–4,18,699.82)	8.29 (5.8–11.58)	5,64,055.1 (3,92,930.7–7,89,194.64)	7.05 (4.92–9.84)	−0.71 (−0.78—0.65)
Sex					
Female	1,81,276.1 (1,25,519.65–2,54,378.31)	8.98 (6.29–12.52)	3,36,957.39 (2,35,303.4–4,68,589.1)	7.66 (5.35–10.66)	−0.72 (−0.78—0.65)
Male	1,15,495.83 (79,647.83–1,62,540.46)	7.22 (5.03–10.12)	2,27,097.7 (1,57,225.88–3,18,773.44)	6.24 (4.33–8.7)	−0.64 (−0.69—0.58)
SDI region					
High SDI	56,549.62 (38,698.89–79,752.38)	5.36 (3.65–7.52)	89,186.24 (61,512.91–1,25,367.71)	4.23 (2.91–5.94)	−0.86 (−0.93—0.79)
High-middle SDI	80,577.72 (55,730.14–1,12,856.78)	8.42 (5.92–11.74)	1,51,425.15 (1,05,795.89–2,10,706.32)	7.47 (5.24–10.37)	−0.51 (−0.6—0.43)
Middle SDI	80,168.16 (54,566.35–1,13,955.76)	8.93 (6.14–12.58)	1,78,884.37 (1,23,116.19–2,52,644.56)	7.62 (5.26–10.74)	−0.83 (−0.96—0.7)
Low-middle SDI	56,343.01 (38,634.82–79,390.34)	10.71 (7.4–15.07)	98,275.14 (67,790.85–1,36,494.68)	7.78 (5.42–10.82)	−1.31 (−1.38—1.24)
Low SDI	23,002.94 (16,015.48–32,345.57)	11.38 (7.98–15.91)	46,042.97 (31,703.49–64,125.98)	10.29 (7.06–14.36)	−0.45 (−0.5—0.41)
South–East Asia, East Asia, and Oceania					
East Asia	55,353.98 (37,834.15–78,429.21)	7.28 (5.02–10.25)	1,43,162.91 (97,844.99–1,98,785.38)	7.01 (4.77–9.78)	−0.53 (−0.8—0.26)
Southeast Asia	20,462.27 (13,700.6–29,390.74)	9.28 (6.26–13.31)	39,747.55 (26,951.3–56,339.11)	7.18 (4.9–10.22)	−1.09 (−1.18—1)
Oceania	86.03 (56.26–125.09)	3.46 (2.33–4.94)	172.19 (113.34–250)	2.95 (1.99–4.26)	−0.4 (−0.44—0.35)
Sub-Saharan Africa					
Eastern Sub-Saharan Africa	9,525.57 (6,372.84–13,595.76)	15.01 (10.11–21.38)	16,275.43 (10,767.18–23,258.98)	11.89 (7.89–16.94)	−0.54 (−0.66—0.42)
Central Sub-Saharan Africa	328.39 (218.34–473.88)	1.94 (1.32–2.79)	780.39 (511.67–1,120.21)	1.99 (1.32–2.85)	0.2 (0.14–0.26)
Southern Sub-Saharan Africa	749.07 (507.68–1,070.84)	3.08 (2.11–4.34)	1,625.79 (1,109.26–2,325.68)	3.29 (2.26–4.7)	0.37 (0.22–0.51)
Western Sub-Saharan Africa	11,611.15 (8,105.96–15,995.84)	14.82 (10.31–20.34)	23,623.94 (16,146.99–32,542.97)	14.57 (10.11–20.1)	−0.35 (−0.48—0.22)
South Asia					
South Asia	61,518.15 (42,096.2–86,249.88)	12.59 (8.75–17.7)	1,10,817.8 (76,989.61–1,54,669.96)	8.54 (5.96–11.93)	−1.75 (−1.87—1.62)
Latin America and Caribbean					
Caribbean	504.5 (337.94–729.04)	2.03 (1.36–2.9)	886.71 (590.77–1,280.88)	1.71 (1.14–2.46)	−0.52 (−0.58—0.45)
Central Latin America	3,855.6 (2,640.4–5,531.32)	5.25 (3.6–7.51)	9,524.43 (6,524.96–13,529.82)	4.21 (2.89–5.97)	−0.71 (−0.77—0.65)
Tropical Latin America	4,137.05 (2,878.72–5,695.31)	5.12 (3.56–7.04)	11,324.86 (7,848.25–15,618.62)	4.82 (3.34–6.68)	−0.09 (−0.25—0.06)
Andean Latin America	1,709.42 (1,157.77–2,427.37)	9.18 (6.25–13.14)	4,391.82 (3,022.64–6,180.43)	8.12 (5.58–11.41)	−0.42 (−0.5—0.34)

(Continued)

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TABLE 2 (Continued)

Characteristics	1990		2019		1990–2019
	Number (95% UI)	ASR (95% UI)	Number (95% UI)	ASR (95% UI)	EAPC (95% CI)
North Africa and Middle East					
North Africa and Middle East	25,151.77 (16,785.47–35,942.95)	16.5 (10.96–23.58)	51,536.01 (34,297.27–73,195.78)	13.57 (9.12–19.3)	−0.63 (−0.66—0.6)
Central Europe, Eastern Europe, and Central Asia					
Central Asia	2,186.86 (1,488.98–3,099.7)	5.1 (3.49–7.24)	2,989.07 (2,031.26–4,199.87)	4.73 (3.23–6.57)	−0.31 (−0.41—0.21)
Eastern Europe	6,188.36 (4,124.41–8,842.04)	2.31 (1.56–3.27)	7,150.62 (4,794.29–10,139.43)	2.01 (1.36–2.84)	−0.67 (−0.74—0.61)
Central Europe	6,758.13 (4,613.22–9,511.59)	4.74 (3.24–6.63)	9,434.8 (6,450.88–13,175.46)	4.19 (2.87–5.85)	−0.41 (−0.46—0.37)
High–income regions					
Southern Latin America	1,460.83 (966.34–2,107.65)	3.42 (2.3–4.89)	2,371.84 (1,606.53–3,410.71)	2.76 (1.87–3.95)	−0.68 (−0.7—0.67)
Western Europe	68,785.27 (47,042.98–97,198.86)	11.52 (7.89–16.29)	97,364.81 (67,087.7–1,37,766.58)	9.31 (6.39–13.09)	−0.76 (−0.79—0.73)
North America	10,796.58 (7,397.68–15,397.11)	2.91 (2–4.14)	18,170.68 (12,528.56–25,673.35)	2.64 (1.81–3.75)	−0.45 (−0.6—0.31)
Australasia	1,055.49 (707.49–1,520.13)	4.66 (3.15–6.69)	2,080.78 (1,405.74–2,989.83)	3.86 (2.59–5.58)	−0.63 (−0.69—0.58)
Asia Pacific	4,547.43 (3,014.94–6,477.05)	2.44 (1.63–3.44)	10,622.68 (7,186.98–15,401.48)	2.01 (1.36–2.9)	−0.7 (−0.84—0.55)

AMD, age-related macular degeneration; SDI, socio-demographic index; UI, uncertainty interval; CI, confidence interval; ASR, age-standardized rate; EAPC, estimated annual percentage change; GBD, global burden of disease; YLDs, years lived with disability.

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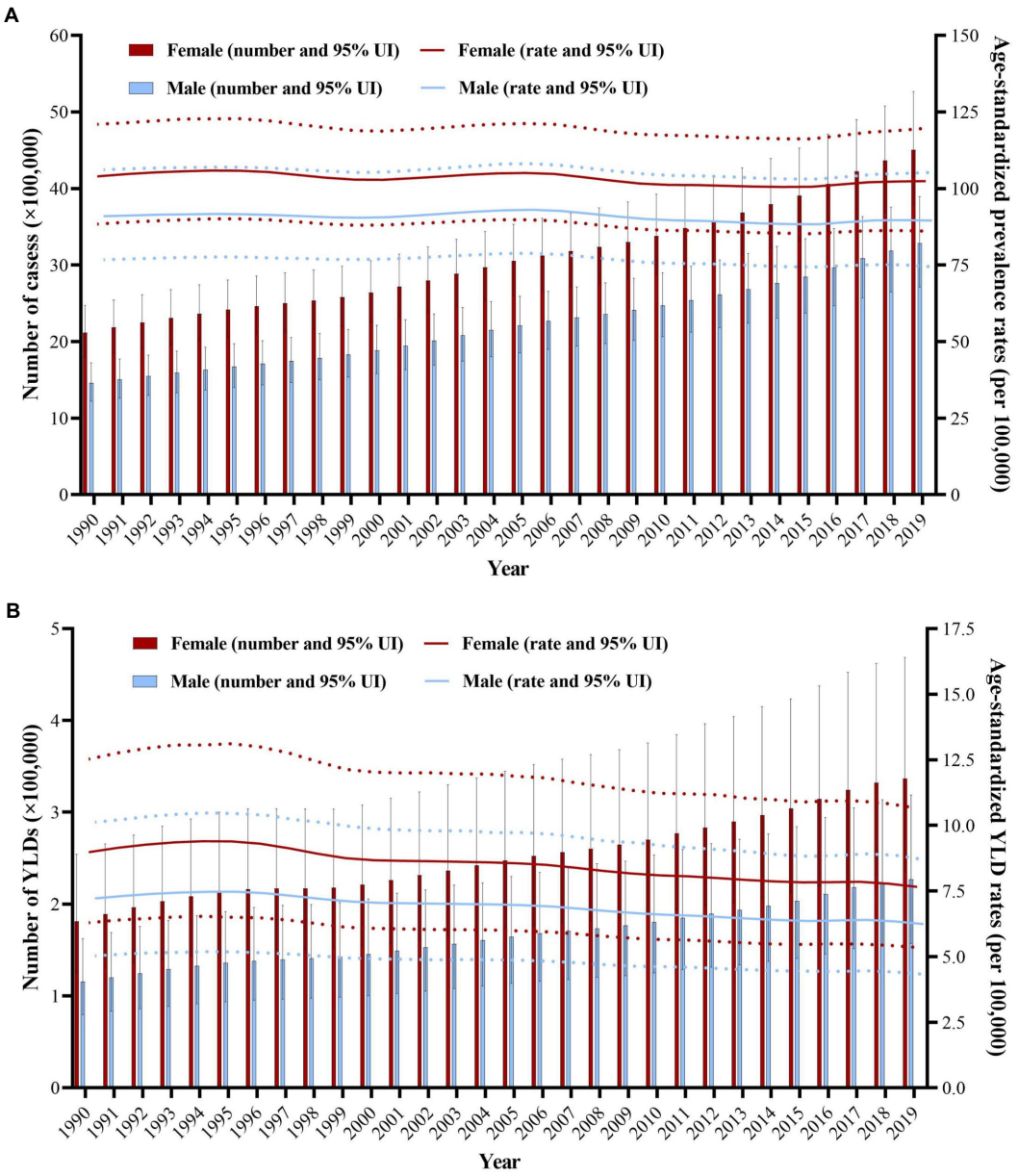

FIGURE 1
Changes in global burden of the prevalence and YLDs of AMD from 1990 to 2019. **(A)** The number of cases and age-standardized prevalence rates of AMD from 1990 to 2019. **(B)** The number of YLDs and age-standardized YLD rates of AMD from 1990 to 2019. Red and blue dashed line indicates the upper and lower limits of the 95% uncertainty intervals (95% UIs) for females and males, respectively. AMD, age-related macular degeneration; UI, uncertainty interval; YLDs, years lived with disability.

demonstrated the lowest. The main reason may be that China and India are considered middle SDI regions. In addition, the ASPRs and ASYRs in developing countries and regions were higher than those in developed countries and regions. The burden of AMD in developing countries were higher than those of developed countries. Possible explanations for this phenomenon that the increased levels of ultraviolet radiation in the countries of the South, the prevalence of arterial hypertension, diabetes, et al. maybe contribute to the spread of this pathology (41, 42). Moreover, in response to the VISION 2020, the developed countries funded for various programs to reduce levels of low vision and blindness. Along with more active diagnosis, early detection and treatment could positively influence the performance of the developed countries. More attention and further studies are supposed to be paid to this phenomenon, to explore the possible mechanisms of the disparities.

The prevalence and YLDs of AMD also varied significantly in different regions and nations. From 1990 to 2019, the number of AMD cases and YLDs increased by 117.59 and 90.06%, and the disease burden more than doubled. The ASPR and ASYR of AMD decreased by an EAPC, which may indicate that the increase in overall AMD cases and YLDs are related to the increasing age of

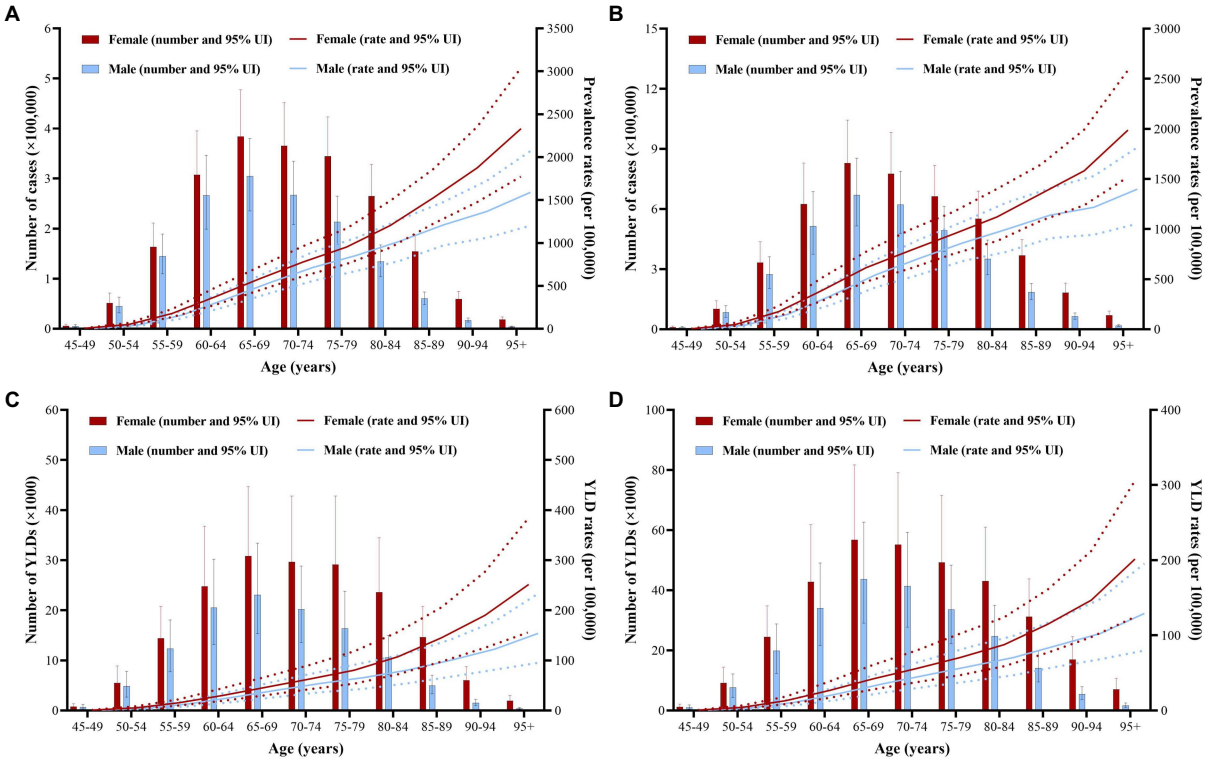

FIGURE 2
Global burden of the prevalence and YLDs of AMD by age and sex in 1990 and 2019. **(A)** The number of cases and crude prevalence rates of AMD in 1990. **(B)** The number of cases and crude prevalence rates of AMD in 2019. **(C)** The number of YLDs and crude YLD rates of AMD in 1990. **(D)** The number of YLDs and crude YLD rates of AMD in 2019. Red and blue dashed line indicates the upper and lower limits of the 95% uncertainty intervals (95% UIs) for females and males, respectively. AMD, age-related macular degeneration; UI, uncertainty interval; YLDs, years lived with disability.

the global population, as well as the increasing population. The number of AMD cases and YLDs in East Asia remained highest, followed by South Asia, while the number of AMD cases and YLDs in Oceania remained lowest in 2019. In the past 30 years, East Asia and South Asia have demonstrated increasing cases and YLDs of AMD, primarily because of the population sizes and land area of China and India. However, the ASPR and ASYR in East Asia demonstrated an increasing trend, while the ASPR and ASYR in South Asia demonstrated a decreasing trend. This discrepancy may be due to the different population structures and average ages of the major countries in the two regions. The population of India is also growing much faster than the population of China; however, the proportion of older adults (older than 65 years) in China is far higher than in India because China experienced population aging earlier than India (43–45). One meta-analysis of Chinese populations has indicated that, as a result of the rapid population aging, the total prevalent AMD cases and its subtypes has increased dramatically: from 1990 to 2015, cases of AMD had increased by 121.80% in China (46). The social security system of China and India should be improved so that older adults have the basic financial security they need to reduce the burden of AMD.

Between 1990 and 2019, the EAPCs of ASPR and ASYR in Southern Sub-Saharan Africa were 0.37 (the highest among all regions), and the number of cases and YLDs in this region increased significantly in the past 30 years. This region has unique characteristics, including the highest population growth rate and high rates of poor living conditions and poor health; the average life expectancy of people born in this region is only 54 years (47). Compared with other regions of the world, the burden of non-communicable and communicable diseases in this region is significantly heavier (48). The overall level of social, economic, and educational development in this region is low, which represents a microcosm of many low and low-middle SDI regions. Additionally, because many people still live in tribal societies, most countries of Southern Sub-Saharan Africa are highly underdeveloped (49). Thus, in developing countries, it is as important as developed counties to emphasize the priority of reducing AMD burden when making health policy.

Limitations

Although the 2019 GBD study enables us to study the global AMD burden with high confidence, some limitations should be noted. First, as noted by other research reports of the GBD study, actual data on disease burden cannot be obtained, only estimated. Second, the nature of the database makes differences inevitable in data collection methods and data source quality between studies. Thirdly, because of the lack of relevant data in the GBD database,

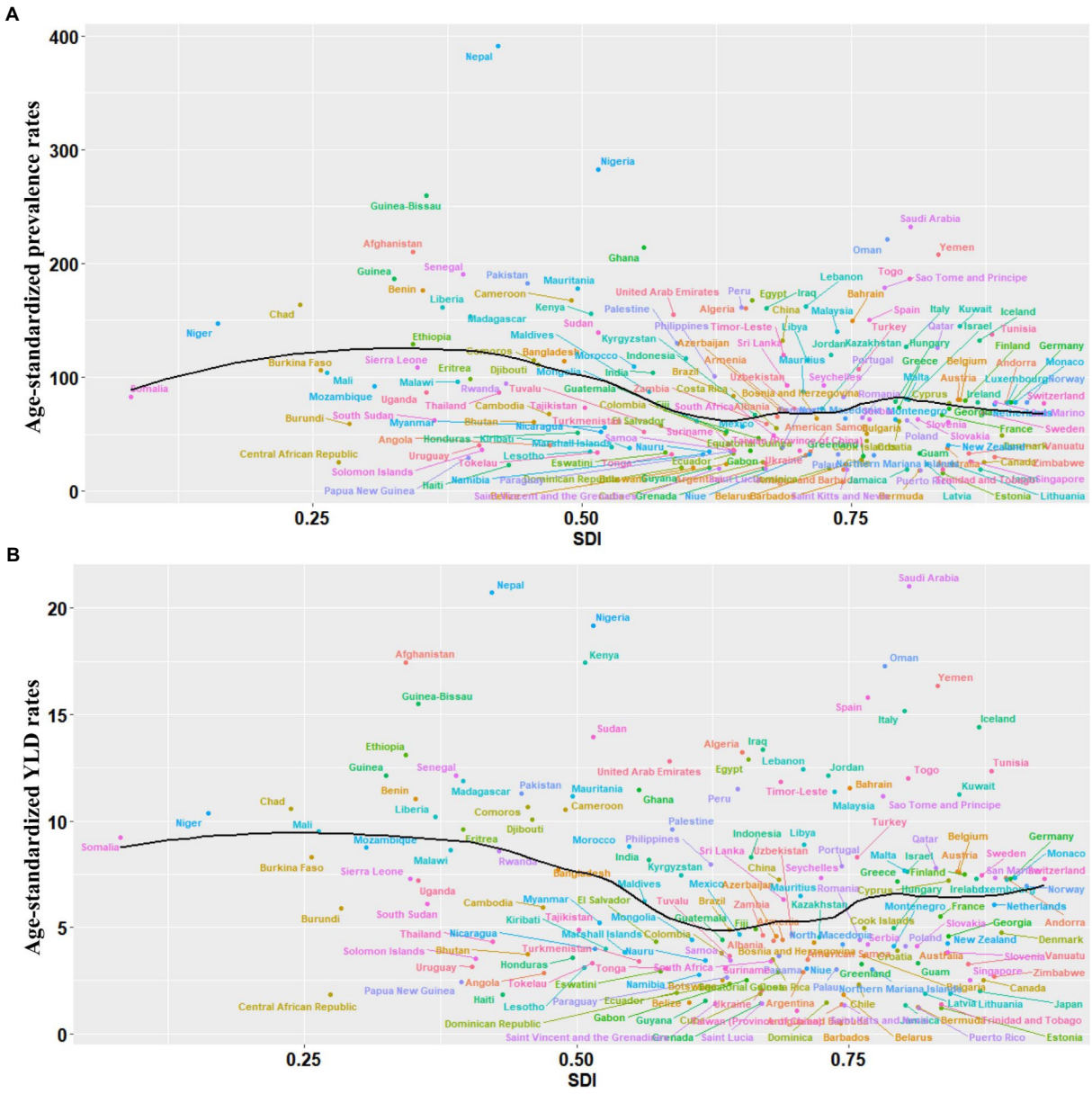

FIGURE 3
Global burden of the prevalence and YLDs of AMD by SDI. **(A)** The black line represents the average expected relationship between SDIs and age-standardized prevalence rates for AMD based on values from 204 countries and territories in 2019. **(B)** The black line represents the average expected relationship between SDIs and age-standardized YLD rates for AMD based on values from 204 countries and territories in 2019. AMD, age-related macular degeneration; SDI, socio-demographic index; YLDs, years lived with disability.

prevalence over time based on specific characteristics of AMD, such as dry (non-neovascular) versus wet (neovascular), could not be assessed in this study. Moreover, the incidence of AMD was not examined in this study.

Conclusion

Overall, despite reductions in ASPR and ASYR, with the global aged population increasing, AMD remains a major cause of irreversible vision loss and burden across the world. The prevalent AMD cases and YLDs, and the ASPR and ASYR due to AMD were higher in females than in males. The prevalence and YLDs of AMD were also closely related to socio-economic status, and they varied geographically, especially people in less developed countries seemed to be more likely to bear heavier burden of AMD. Knowledge of differences in development levels of countries and how these differences affect the prevalence and YLDs of AMD could help policy-makers and public health specialists formulate better approaches to treatment and prevention. These findings can help us better understand the global disease burden of AMD, and the influences of the included factors may provide a theoretical

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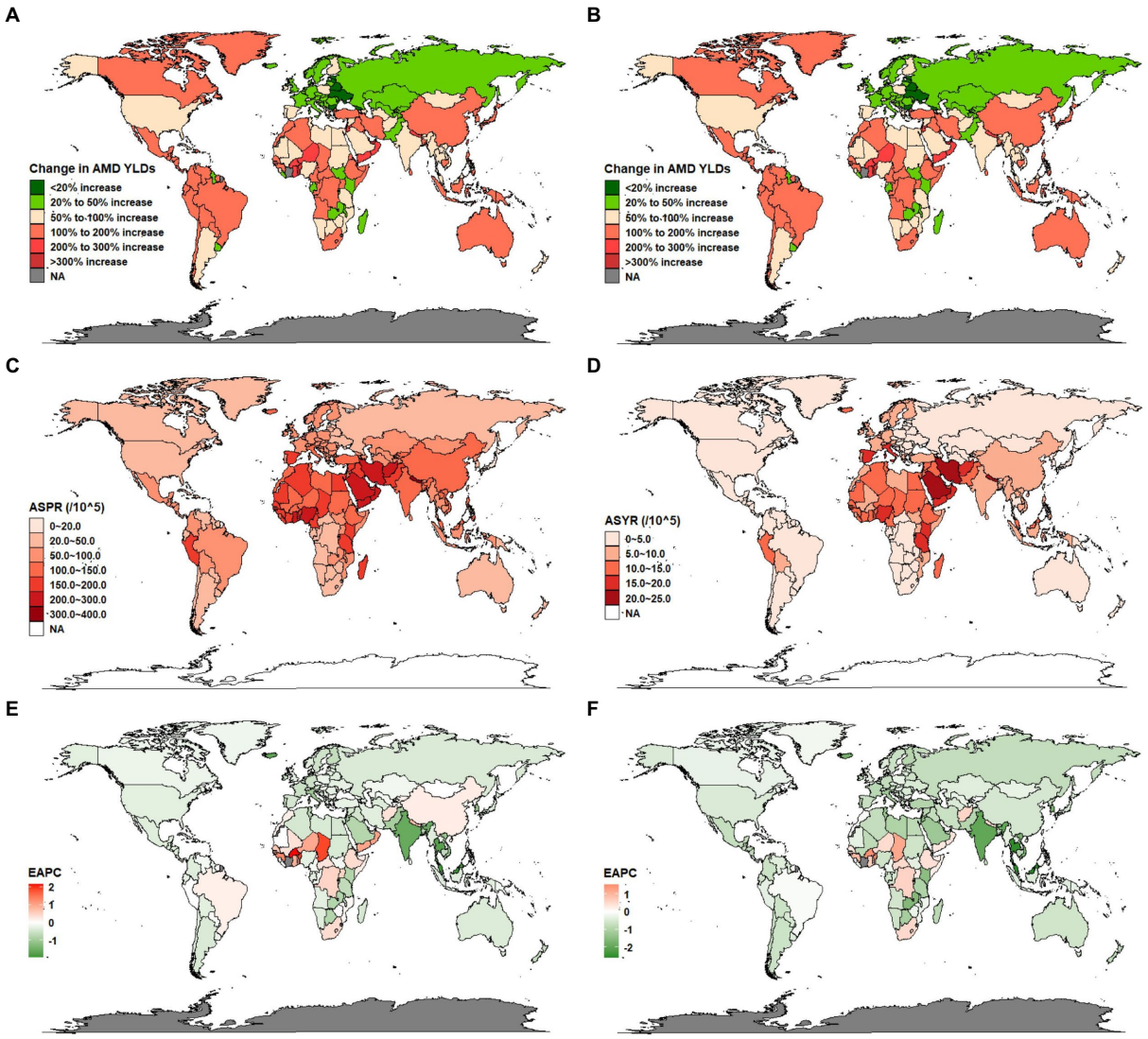

FIGURE 4
Global burden of the prevalence and YLDs of AMD in 204 countries and territories. **(A)** The growth rates of AMD cases from 1990 to 2019. **(B)** The growth rates of AMD YLDs from 1990 to 2019. **(C)** The ASPR of AMD in 2019. **(D)** The ASYR of AMD in 2019. **(E)** The EAPC of ASPR for AMD from 1990 to 2019. **(F)** The EAPC of ASYR for AMD from 1990 to 2019. AMD, age-related macular degeneration; ASR, age-standardized rate; EAPC, estimated annual percentage change; YLDs, years lived with disability.

basis for governments and health care planners to establish more effective and targeted AMD prevention strategies.

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

PL made contributions to the conception and design of the work, provided administrative support, and analyzed the data in our study. BJ collected and organized the data, made contributions to the acquisition, analysis and interpretation of data, and was a major contributor in writing the manuscript. JL made contributions to the critical revision of the manuscript for important intellectual content. CJ made contributions to writing the manuscript. All authors read and approved the final manuscript.

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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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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1138428/full#supplementary-material

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Association between individual, household, and area-level socioeconomic status indicators and sensorineural hearing loss in adults in southwest Iran: a population-based study

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Introduction: Hearing loss is the fourth most common chronic disease, but studies on the relationship between hearing loss and socioeconomic factors are limited. We aimed to examine the association between hearing loss and socioeconomic factors among 35–70 year adults in southwest Iran.

Materials and methods: This population-based cross-sectional study was conducted in the baseline of Hoveyzeh cohort study in adults aged 35–70 in southwest Iran between 2017 and 2021. Information on socioeconomic factors, demographic characteristics, comorbidities, family history of hearing loss, and noise exposure was collected. We assessed the relationship between three levels of socioeconomic factors (individual, household, and area level) with sensorineural hearing loss (SNHL). Multiple logistic regression was used to adjust the potential confounders.

Results: Among a total of 1,365 assessed participants, 485 patients were diagnosed as having hearing loss, and the other 880 individuals were diagnosed without hearing loss, which is considered the case and the control group, respectively. At the individual level of socioeconomic, the odds of having hearing loss in the participants with high school education and diploma, [OR = 0.51 (95%CI:0.28–0.92)], and the individuals with university education [OR = 0.44 (95%CI:0.22–0.87)] were significantly lower than the illiterate participants. At the household socioeconomic level, the odds of having hearing loss were lower for those with poor [OR = 0.63 (95%CI:0.41–0.97)] and moderate [OR = 0.62 (95%CI:0.41–0.94)] wealth status vs. those with the poorest wealth status. In the area level socioeconomic, although the odds of hearing loss in the residents of affluent areas were slightly lower than the residents of deprived areas, there was no significant difference among the groups.

Conclusion: The individuals with hearing loss may have insufficient education and income.

KEYWORDS

socioeconomic status, hearing loss, sensorineural, education, Iran

Introduction

Hearing loss is the most prevalent sensory disorder in the human population (1), which has received much attention in recent years. In 2019, it was reported that 1.57 billion (∼20%) people worldwide suffer from hearing loss. Globally, YLDs attributable to hearing loss increased by 73.6% from 25.02 million to 43.45 million between 1990 and 2019 (2). A study in Iran showed that the most common types of disability were "Hearing loss" (68.3%) and "Hearing impairment" (10.4%) (3). Hearing loss can annually impose an economic burden of about $1 trillion (4), and 80% of the global burden of hearing loss is in low- and middle-income countries (LMICs) (5).

Previous research has established health disparities in health outcomes based on socioeconomic status (SES) (6, 7). Despite advances in medicine and technology that have significantly improved human health outcomes, health, and healthcare disparities still exist among communities of different SES (8). However, the exact association mechanism between poor health, socioeconomic burden, and low economic status remains unclear (9).

Otologic problems, including hearing loss, have a direct negative effect on people's daily life, and therefore access to care and treatment services is very important. However, in some countries, including Iran, these services are not evenly distributed and are mostly concentrated in large medical centers. In addition, the provision of screening, treatment, rehabilitation, and rehabilitation services for hearing loss is expensive. Therefore, the frequency of hearing loss is expected to differ in various socioeconomic statuses.

So far, evidence to evaluate the association of hearing loss with socioeconomic factors has been limited. No research has so far been designed to examine the relationship between sensorineural hearing loss (SNHL) and socioeconomic factors in adults in Iran. At the same time, there is an urgent public health need, and understanding this relationship can effectively provide more appropriate recommendations for hearing loss prevention strategies. Therefore, we designed a cross-sectional study to identify the relationship between hearing loss and the socioeconomic factors at the three levels of individual, household, and area socioeconomic status in 35–70 years adults.

Materials and methods

Study design and participants

This study was a population-based cross-sectional study conducted in the Hoveyzeh Ear Cohort Study (HECS). HECS is Iran's first cohort study to assess ear health and audiology. It was designed in the context of the Hoveyzeh cohort study (HCS) in southwest Iran, which focused on non-communicable diseases. In the HCS enrollment phase, all eligible people aged 35 to 70 in the region were invited, and 85.16% (1,009 people) accepted the invitation and entered the study (10). We invited the participant from the list of 10,009 individuals who had registered to the Hoveyzeh cohort study according to the order of recruitment date, to perform hearing examinations and fill in the questionnaire. In this study, we recruited 1,872 participants 35–70 years who participated in HECS from Nov 2017 until now. The participants with chronic neurological disorders, inner ear diseases, otosclerosis, taking ototoxic drugs, and mixed hearing loss were excluded from the study. Also, we excluded people with conductive hearing loss (CHL) from the study because conductive hearing loss results from disruption of the transmission of sound through the outer and middle ear and is more common in infants. It can be congenital as a result of an anatomical abnormality, but can also be acquired after an inflammatory disease of the middle ear such as otitis media (11). Finally, 1,365 participants were considered in this analysis. We diagnosed 485 participants with SNHL and 880 individuals without SNHL.

The Ethics Research Committee approved this study of Iran University of Medical Sciences with a code of ethics I.R.IUMS.REC.1399.1441. This study was conducted based on the Helsinki Declaration. Participants signed a written informed consent form for the interview and audiometric evaluation.

Definition of socioeconomic variables

In this study, we assessed participants' socioeconomic status at three levels. Educational levels, resident type, and employment were individual-level socioeconomic indices. Participants' educational levels were categorized as illiterate, primary school, secondary school, high school diploma, and university levels. Residential type is categorized into two groups, rural and urban. Also, the employment variable was defined in the category "Yes" if the participant is employed and "No" if the individual were a housekeeper, retried, or unemployed.

The Wealth score was an indicator of SES at the household level. This index was calculated based on the information on household assets, such as motorcycle, car, TV, cell phone, internet access, vacuum cleaner, freezer, washing machine, computer, and household utilities consisting of house ownership and the number of rooms per capita. A principal component analysis (PCA) was performed to assign a coefficient to each asset. Finally, The wealth scores were recorded into quintiles of poorest, poor, moderate, rich, and richest (12).

The Townsend deprivation index is an area-level SES indicator. This index was calculated using four components in each area: the proportion of households without a car, the proportion of non-homeowner households, the percentage of unemployed residents, and the proportion of overcrowded households. Finally, the computed scores were categorized based on the quintiles as five ordered categories; most affluent, affluent, moderate, deprived, and most deprived (13).

Other possible confounding factors

We assessed the association between SNHL and demographic variables [sex (male/female)], age groups (35–44, 45–54, 55–64, and ≥65 years), and having comorbidity [hypertension (Yes/No), diabetes (Yes/No)]. Diabetes is defined as a fasting blood glucose level of 126 mg/dl or higher or using glucose-lowering medications or a self-reported diagnosis of diabetes. Hypertension is defined

as having systolic blood pressure above 140 mmHg or diastolic blood pressure above 90 mmHg, using blood pressure-lowering medications, or a self-reported diagnosis of hypertension. Also, hearing risk factors were [a family history of hearing loss (Yes/No) and noise exposure (Yes/No)].

Hearing assessment

A hearing questionnaire was completed for all participants. The information included auditory-vestibular symptoms, noise exposure, and a family history of hearing loss. An experienced audiologist examined the subjects using pure tone audiometry (PTA). Conventional pure tone air conduction (AC) and bone conduction (BC) thresholds are set at octave periods from 250 Hz to 8,000 Hz and 250 Hz to 4,000 Hz, respectively. Normal hearing was determined as the perception of sound stimuli with an intensity of 20 dB HL or less (14) at all frequencies. People with hearing thresholds higher than 20 dB HL in one or more pure tone sounds in both ears were considered having hearing loss. Finally, all diagnoses were confirmed by an otologist.

Statistical analysis

Descriptive statistics were performed for quantitative variables by mean, standard deviation, and categorical variables by frequency and percentage. The Chi-square test evaluated the association between hearing loss and demographic variables, socioeconomic status, comorbidity, and hearing factors. We examined the independent associations of demographic, clinic, individual, household, and area-level SES with SNHL using multi-level logistic regression, controlling for confounding factors. In the univariate analysis, the criterion for the initial entry of variables into multiple regression models was $P < 0.25$. All reported p-values were based on two-tailed tests and considered to have a significance level of 0.05. Stata software version 14.0 was utilized for the statistical analysis.

Results

In this cross-sectional study, a total of 1,365 participants [Individuals with hearing loss were in the case group ($n = 485$), and those with normal hearing were in the control group ($n = 880$)] were assessed.

Most of the demographic characteristics were significantly different between the two groups. The participants with hearing loss were older ($P < 0.001$) and tended to be male ($P < 0.001$). The family history of hearing loss and noise exposure in the cases group was more reported ($P < 0.001$). Besides, diabetes ($P < 0.001$) and hypertension ($P < 0.001$) were more common in people with hearing loss. Literacy was different between the two groups ($P = 0.023$), so the illiterate participants were more frequent in the case group. A statistically significant difference was seen between the Townsend index and hearing loss ($P = 0.002$), living in the most deprived areas was more prevalent among the cases compared to the controls. On the other hand, there was no

TABLE 1 Demographic, socioeconomic, and comorbidity characteristics by hearing status of the participants.

	Case	Control	*P*-value*
	N = 485, *n* (%)	*N* = 880, *n* (%)	
Age category			
35–44	72 (14.85)	455 (51.70)	<0.001
45–54	162 (33.40)	290 (32.95)	
55–64	185 (38.14)	116 (13.19)	
≥65	66 (13.61)	19 (2.16)	
Sex			<0.001
Male	263 (54.23)	261 (29.66)	
Female	222 (45.77)	619 (70.34)	
Diabetes			<0.001
Yes	153 (31.55)	149 (16.93)	
No	332 (68.45)	731 (83.07)	
Hypertension			<0.001
Yes	182 (37.53)	194 (22.05)	
No	303 (62.47)	686 (77.95)	
Family history of hearing loss			<0.001
Yes	51 (10.52)	45 (5.11)	
No	434 (89.48)	835 (94.89)	
Noise exposure			<0.001
Yes	141 (29.07)	76 (8.64)	
No	344 (70.93)	804 (91.36)	
Employment			0.401
Yes	146 (30.10)	246 (27.95)	
No	339 (69.90)	634 (72.05)	
Residence type			0.519
Urban	309 (63.71)	576 (65.45)	
Rural	176 (36.29)	304 (34.55)	
Education levels			0.023
Illiteracy	323 (66.60)	508 (57.73)	
Primary school	77 (15.88)	161 (18.30)	
Secondary school	32 (6.60)	73 (8.30)	
High school and Diploma	29 (5.98)	74 (8.41)	
University	24 (4.95)	64 (7.27)	
Wealth score			0.230
Poorest	104 (21.44)	145 (16.48)	
Poor	91 (18.76)	177 (20.11)	
Moderate	100 (20.62)	205 (23.30)	
Rich	105 (21.65)	193 (21.93)	
Richest	85 (17.53)	160 (18.18)	

(Continued)

TABLE 1 (Continued)

	Case	Control	*P*-value*
	N = 485, *n* (%)	*N* = 880, *n* (%)	
Townsend index			0.002
Most affluent	111 (22.89)	256 (29.09)	
Affluent	82 (16.91)	152 (17.27)	
Moderate	93 (19.18)	194 (22.05)	
Deprived	51 (10.52)	92 (10.45)	
Most deprived	148 (30.52)	186 (21.14)	

*Chi-square test.

significant association between employment, residence type, and wealth score with hearing loss ($P > 0.05$) (Table 1).

The Logistic Regression Model was used to estimate crude and adjusted odds ratios. In univariate Logistic Regression analysis, most of the assessed factors, including age, sex, education, Townsend index, Diabetes, Hypertension, Family history of hearing loss, and noise exposure, were significantly associated with hearing loss ($P < 0.05$), while no association found between wealth, employment and type of residence with the disorder ($p > 0.05$). In the next step, all variables with a p-value < 0.25 were simultaneously included in the multiple logistic regression model. The findings of the multiple logistic regression analysis showed that the odds of having hearing loss enhanced with increasing the age of participants so that the people in the age group ≥65 years had almost 17 folds more odds of hearing loss in comparison to the participant in the age group 35–44 years [OR =17.93 (95% CI; 9.51–33.82)]. The odds of hearing loss in men were 2.7 times great than in women [OR = 2.70 (95% CI; 1.91–3.83)] (Table 2).

Among the three assessed socioeconomic factors, education level had an inverse and significant association with hearing loss ($P = 0.004$), so the odds of hearing loss continuously decreased with education levels (Figure 1).

This result indicated that the odds of having hearing loss in the participants with university education was about two times less than illiterate participants (reference group) [OR = 0.44 (95% CI; 0.22–0.87)]. Overall, the odds of having hearing loss decreased with increasing the wealth status of the participants; so it was statistically lower in participants in the poor and moderate quintiles in comparison to the poorest (Figure 2).

Although the odds of having hearing loss in the residents of affluent areas were lower than in those living in the deprived areas, after adjusting for confounding factors, this association was not statistically significant (Figure 3).

Moreover, the results showed a significant association between diabetes and hearing loss ($P = 0.006$). The diabetic participants had 56 percent more hearing loss than the non-diabetic people [OR = 1.56 (95% CI; 1.14–2.14)]. The participants with a family history of hearing loss were 2.5 times more likely to have hearing loss than those without a family history [OR =2.66 (95% CI; 1.62–4.38)] and this association was statistically significant ($P < 0.001$). Also, a statistically significant association was found between exposure to noise and hearing loss ($P < 0.001$), so the individual with noise exposure had threefold more odds of hearing loss than the unexposed group [OR =3.09 (95% CI; 2.12–4.52)]. However, there was no significant association between hypertension and hearing loss ($P = 0.295$).

Discussion

Summary of main findings

We found that education level as an individual socioeconomic level was statistically associated with SNHL, which is an important determinant of hearing loss. At the household level, hearing loss was more prevalent in the poorest households. Besides, at the area level, hearing loss was more prevalent in the most deprived areas, although, there was no statistically significant relationship between SNHL and Townsend Deprived Index. Our findings demonstrated strong associations between hearing loss and sex, age, diabetes, noise exposure, and family history of hearing loss.

Comparison of our findings with previous studies

This study showed a direct relationship between age and hearing loss. Most studies mentioned that age was significantly associated with hearing loss, indicating that older adults were at higher risk than younger adults (15–20). Some believe that progressive hearing loss occurs as a normal outcome of aging (21) due to a slow progressive decline in the ability to perceive high-frequency tones, caused by the degeneration of the hair cells in the ear (22). Also, aging may lead to the accumulation of oxidative stress damage, mitochondrial DNA damage, and the induction of cochlear cell apoptosis and, eventually, hearing loss (23, 24). Another explanation may be due to the exposure accumulation of the risk factor of deleterious auditory the during the aging process (25).

In our study, hearing loss was more common in men, even after adjustment for the effects of other variables. Most studies reported men had higher odds of hearing loss (18–21, 26, 27). It might reflect gender differences in exposure to other hearing loss risk factors such as lifestyle and CVD.

Our result showed that education level was inversely associated with hearing loss. The results of some studies were also in line with our findings (26, 28–30). A low level of education may be related to an unhealthy lifestyle (31), such as smoking and noise exposure, which may lead to a higher risk of hearing loss. Individuals with higher education levels may have better nutrition, access to health care, fewer ear infections, or more usage of hearing protection devices. However, the relationship between hearing loss and fewer years of formal schooling may be subject to reverse causality bias. Hearing loss can provide some limitations for people that prevent continuing education and lead to low educational levels (21).

We observed an inverse gradient between hearing loss and the wealth index. Participants in lower wealth quintiles experienced significantly high occurrence of hearing loss compared to those in the highest wealth quintile. Perhaps the reason is that in the poorest households, most of their income is spent on daily expenses,

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TABLE 2 Crude and adjusted odds ratios of hearing loss using the logistic regression model.

	Crude odds ratio	(CI 95%)	*P*-value	Adjusted odds ratio	(CI 95%)	*P*-value
Age groups						
35–44 y	1			1		
45–54 y	3.53	2.58–4.83	<0.001	3.22	2.26–4.58	<0.001
55–64 y	10.08	7.17–14.16	<0.001	9.03	6.07–13.43	<0.001
≥65 y	17.93	12.44–38.72	<0.001	17.93	9.51–33.82	<0.001
Sex						
Male	2.80	2.23–3.53	<0.001	2.70	1.91–3.83	<0.001
Female	1			1		
Education levels						
Illiteracy	1			1		
Primary school	0.75	0.55–1.02	0.068	0.77	0.51–1.15	0.198
Secondary school	0.69	0.44–0.1.07	0.096	0.60	0.34–1.08	0.092
High school and Diploma	0.62	0.39–0.97	0.036	0.51	0.28–0.92	0.024
University	0.59	0.36–0.96	0.034	0.44	0.22–0.87	0.019
Wealth index						
Poorest	1			1		
Poor	0.72	0.50–1.02	0.07	0.63	0.41–0.97	0.034
Moderate	0.68	0.48–0.96	0.03	0.62	0.41–0.94	0.025
Rich	0.75	0.54–1.07	0.118	0.84	0.54–1.28	0.413
Richest	0.74	0.51–1.1	0.106	0.79	0.49–1.27	0.330
Townsend index						
Most deprived	1			1		
Deprived	0.70	0.46–1.04	0.080	0.82	0.50–1.32	0.417
Moderate	0.60	0.43–0.84	0.002	0.87	0.58–1.30	0.490
Affluent	0.68	0.48–0.96	0.027	0.89	0.58–1.37	0.604
Most affluent	0.54	0.40–0.74	<0.001	0.75	0.50–1.14	0.176
Employment						
Yes	1.11	0.87–1.42	0.401	-	-	-
No	1			-	-	
Type of residence						
Urban	1.07	0.86–1.36	0.519	-	-	-
Rural	1			-	-	
Diabetes						
Yes	2.26	1.74–2.93	<0.001	1.56	1.14–2.14	0.006
No	1			1		
Hypertension						
Yes	2.12	1.66–2.71	<0.001	1.18	0.87–1.60	0.295
No	1			1		
Family history of hearing loss						
Yes	2.18	1.44–3.31	<0.001	2.66	1.62–4.38	<0.001
No	1			1		
Exposure to noise						
Yes	4.34	3.19–5.89	<0.001	3.09	2.11–4.52	<0.001
No	1			1		

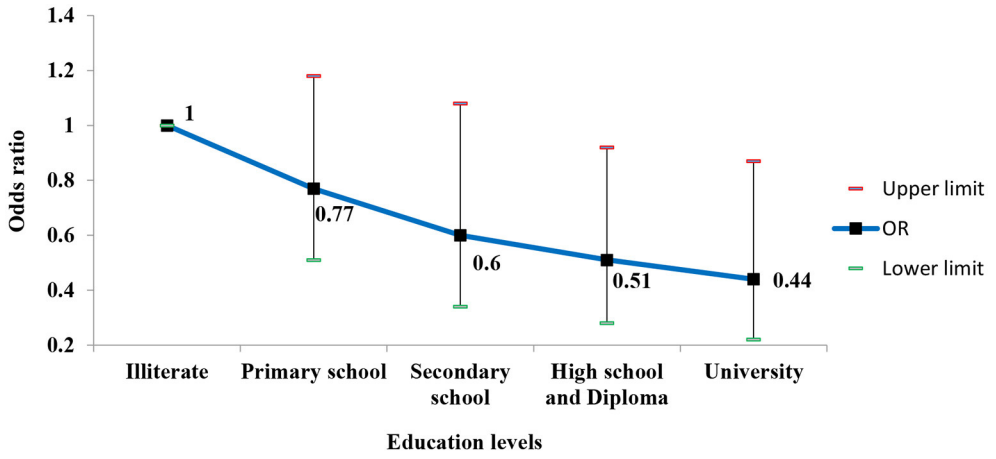

FIGURE 1
Adjusted odds ratios (95% CI) of hearing loss according to levels of education.

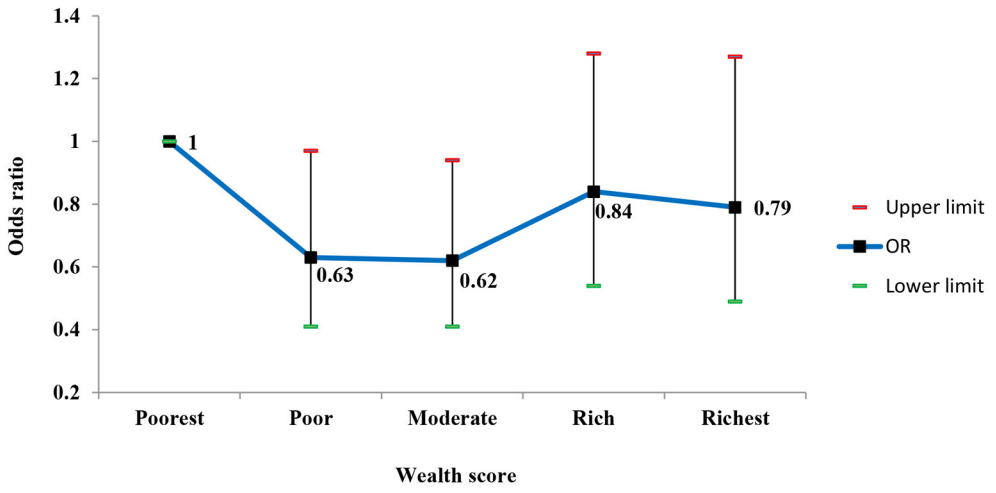

FIGURE 2
Adjusted odds ratios (95% CI) of hearing loss according to wealth status.

including the purchase of food, and the share of income that can be spent on health care is limited.

Studies on the relationship between area-level socioeconomic indicators and hearing loss are scarce. Our results demonstrated an inverse but non-significant relationship between the Townsend deprivation index as an area-level socioeconomic indicator and hearing loss so that people who lived in the most deprived areas experienced hearing loss more than those living in the most affluent areas. This finding was consistent with the previous results on the relationship between regional SES and chronic disease (6). The association of regional SES and multiple health outcomes is mediated or influenced by several factors: disparities in access to social and health resources, to the detriment of environmental exposure (e.g., noise and overcrowding), difficult living conditions, cost of available resources, etc. On the contrary, a Chinese study showed that people living in affluent areas had more hearing impairment than those in deprived areas and reported loud noise above 80 dB caused by heavy traffic in affluent areas of China (25).

Most previous studies have shown that hearing impairment is associated with lower income (9, 32). Low income might be related to various causes of hearing impairment, including ear infections, lifestyle factors such as smoking (33), lax enforcement of noise exposure regulations, and a lack of access to preventive hearing care and health services (34). Some studies reported that lack of health insurance was the main reason for the lack of access to health care services (9). Because hearing screening and audiology evaluation services are expensive, access to these services is difficult for low-income people. In addition, we found that unemployment was higher in people with hearing loss, which agrees with the previous reports (29, 30). Unemployment can affect poor hearing knowledge and less access to health care for hearing impairments (29, 35).

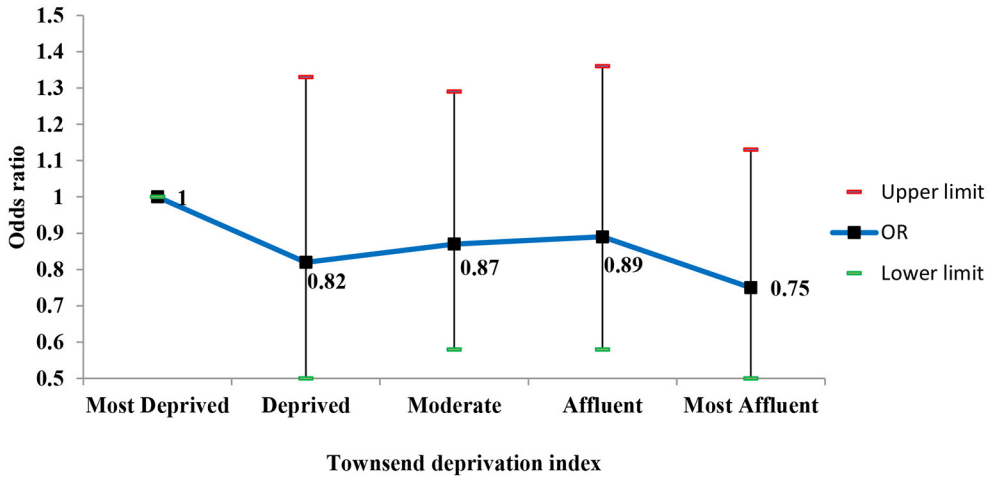

FIGURE 3
Adjusted odds ratios (95% CI) of hearing loss according to the Townsend deprivation index.

According to several studies, hearing loss in people with type 2 diabetes was more prevalent (19, 36–38), which was in line with the results of our research. Some mechanisms of hearing loss in diabetic patients include microangiopathy of the inner ear, neuropathy of the cochlear nerve, outer hair dysfunction, and disruption of the endolymphatic potential (39). The mechanisms of the effect of hypertension on hearing loss are not yet clear (40). It has been hypothesized that common cardiovascular risk factors, such as hypertension through damage to the cochlear microvasculature, may play an essential role in the etiology of hearing loss (31). However, in our study, after adjustment for demographic and socioeconomic factors, comorbidities, history of noise exposure, and history of hearing loss in the family, there was no statistically significant association between hypertension and hearing loss; similar results were reported from the other studies (31, 41).

We showed a statistically significant relationship between hearing loss and a family history of hearing loss. Recently, evidence of gene-environment interactions in adult hearing loss has accumulated (42). Several studies have shown a strong relationship between hereditary hearing loss and being siblings, cousins, or common family ancestry (43–45). The pairing of hearing loss genes is more common in relatives. Besides, a positive family history of hearing loss can result from common cultural and lifestyle characteristics for family members. We suggest a direct relationship between noise exposure and hearing loss. Previous evidence confirmed the role of noise exposure in the onset or progression of hearing impairment (27, 46) through neuropathy of the end of the cochlea auditory nerve (47).

Strengths and limitations

Our study has several strengths, including conducting this study in the context of a population-based cohort study using a representative sample of the population that can reduce selection bias; examining the relationship of SES at three individual, household, and regional levels separately; applying valid instruments and measure audiometric tests according to the definition of the world health organization.

There were some limitations in our study. First, the relationship between hearing loss and noise exposure may be susceptible to recall bias. Hence, the patients with hearing loss are more likely to recall and report a history of noise exposure than the control group. This can overestimate the reported odds ratios. Second, considering the study design, exposure-outcome temporality cannot be demonstrated. Hence, the relationship between hearing loss and literacy may be subject to reverse causality bias.

Conclusion

Our findings revealed that SNHL was inversely related to SES. Among the three assessed socioeconomic indicators, education level and wealth index had the association with hearing loss. This shows that individual and household socioeconomic indicators are more associated with hearing loss. Understanding the socioeconomic impact of hearing loss can help health policymakers in planning health improvement programs, including screening and educational interventions. Besides, early diagnosis of hearing loss in high-risk people, treatment and rehabilitation measures were performed earlier and more effectively. The relationship between socioeconomic status and hearing loss is complex, likely involving multiple simultaneous pathways. Therefore, future longitudinal studies will be necessary to better understand the mechanisms behind these associations.

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.

Ethics statement

The studies involving human participants were reviewed and approved by the Vice-Chancellor provided financial support for Research at Iran University of Medical Sciences, Tehran, Iran. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MS, NS, BC, PA, and ZR contributed to the design and preparation of the manuscript and its interpretation. ZR was involved in the data collection and perforation. PA, BC, and ZR performed the statistical analysis. All authors have reviewed and approved the manuscript.

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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.

Publisher's note

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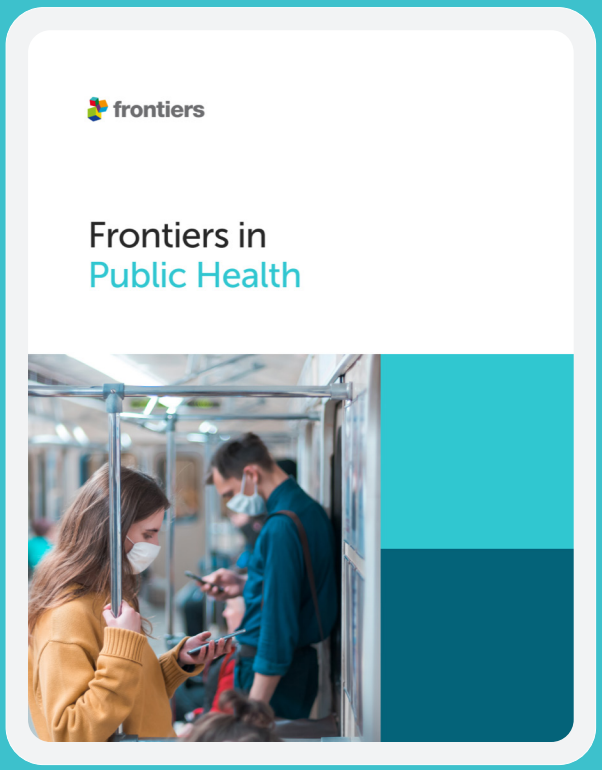

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