AGE-RELATED DISEASES THROUGH THE LENS OF HEALTH ECONOMICS

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AGE-RELATED DISEASES THROUGH THE LENS OF HEALTH ECONOMICS

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Physical Exercise, Social Interaction, Access to Care, and Community Service: Mediators in the Relationship Between Socioeconomic Status and Health Among Older Patients With Diabetes

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The differences in socioeconomic status (SES) will cause a disparity in the health of the elderly. Taking diabetes as an example, previous studies have focused on risk factors of diabetes, while the relationship and mechanism between SES, multi-faceted factors, and the health of older patients with diabetes are not well-understood. This study aims to investigate the association between SES and health in older patients with diabetes and the interrelated mediators between them. Based on the data of the Chinese Longitudinal Healthy Longevity Survey (CLHLS) in 2018, structural equation modeling (SEM) was used to test whether physical exercise, social interaction, access to care, and community service mediated the effect of SES on the health in older patients with diabetes. We found support for the model in which SES predicted the health in older patients with diabetes (comparative fit index = 0.910, incremental fit index = 0.911, goodness-of-fit index = 0.982, adjusted goodness-of-fit index = 0.959, standardized root mean square residual = 0.037, and root mean square error of approximation = 0.061). The total indirect effect of SES on the health accounted for 55.52% of the total effect. Results indicated that physical exercise ($\beta = 0.108$, $p < 0.01$), social interaction ($\beta = 0.253$, $p < 0.001$), and community service ($\beta = 0.111$, $p < 0.001$) had significant positive effects on the health of older patients with diabetes. SES was positively associated with physical exercise ($\beta = 0.417$, $p < 0.001$) and community service ($\beta = 0.126$, $p < 0.01$). Although no direct effect of SES on the health was found, SES mediated the positive effect in their relationship by physical exercise (indirect effect = 0.045, $p < 0.01$), and community service (indirect effect = 0.014, $p < 0.05$). This study showed the health disparities of older patients with diabetes were influenced by individual-level (physical exercise, social interaction) and environmental-level (community service). It suggests that a lack of physical exercise and health-related community service may impair the health of older patients with diabetes with low SES, which recommends individuals' positive actions and environmental supports for promoting health of regarding population.

Keywords: socioeconomic status, diabetes, health services research, quality of life, older patients, China

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INTRODUCTION

Socioeconomic status (SES) is an overall measure of an individual's position in society relative to others based on a combination of education, occupation and income (1, 2). As the health disparities between the socially advantaged and disadvantaged populations become much wider (3), the impact of SES on health has increasingly been explored. A positive association between SES and health among older adults has been reported in many previous studies, which revealed that the higher the SES the better the health (4–7). In addition to SES, a set of social determinants of health, which includes health behavior (e.g., lifestyle and behavioral risk factors) and environmental factors (e.g., neighborhood and health system factors), were also reported as having impact on health status.

These findings were in line with the Anderson's model (Behavioral Model of Health Services Use) (8), which includes four important components, namely, environment, population characteristics, health behavior, and outcomes. The Anderson's model preliminarily showed the relationship between SES and other elements while influencing the health, which provided theoretical clues for further clarifying the mechanism. For instance, in Kino's study, it demonstrated that SES (high education and income predict health) predict health, and it was also confirmed that SES were associated with the adoption of health behavior and the availability of health resources (9). However, the overall mechanism by which SES affects health remains largely unknown, especially for the population with certain age-related disease.

For instance, diabetes is a common chronic and age-related disease in older adults, which has become a leading challenge of global public health due to its high incidence, disability and mortality (10). As reported by the International Diabetes Federation, China is becoming the epicenter of the diabetes epidemic with 28% of the world's older patients with diabetes live in (11). The focus of previous studies in diabetes has largely lied in the risk of the disease (12), and the relationship between the increased prevalence of diabetes and some single factors, such as low SES (13, 14), unhealthy living habits (15), poor community conditions (16), and so on, have been confirmed. However, there was still very few studies have looked at the relationship between these factors mentioned above and the health of patients with diabetes. For example, a study conducted in Korea has indicated that unfavorable socioeconomic status and adverse lifestyle behaviors negatively predicted poor health status of Korean adults with diabetes (17). And another study has found that race or ethnicity was independent predictor of health decline among older patients with diabetes in the USA (5). To be more specific, the potential mediators or other relationships formed by the interaction of SES, other multiple factors and health are not well-understood. Therefore, this study aims to investigate the association between SES and the health in older patients with diabetes and the interrelated mediators between them.

MATERIALS AND METHODS

Theoretical Framework

The theoretical framework of this study was adapted from the Anderson's model. Among the four important components in the model, health behavior and environment were taken as mediating domains to investigate the relationship between population characteristics and health outcomes. Health behavior included physical exercise and social interaction, while environment included access to care and community service. Based on the above understanding, we proposed a theoretical framework (**Figure 1**) of this study.

Data Resource

This study used the data of the cross-sectional survey in 2018 from the Chinese Longitudinal Healthy Longevity Surveys (CLHLS), a nationally representative and public dataset basing on a selected sample of older adults from 22 out of the 31 provinces of mainland China. All these populations represent about 85% of the total population of China (18). The CLHLS has established the sampling frame with all centenarians from the sampled counties/cities. Each sampled centenarian was matched to one octogenarian and non-agenarian that were randomly selected based on their code; for every three sampled centenarians, four older adults aged 65–79 were randomly

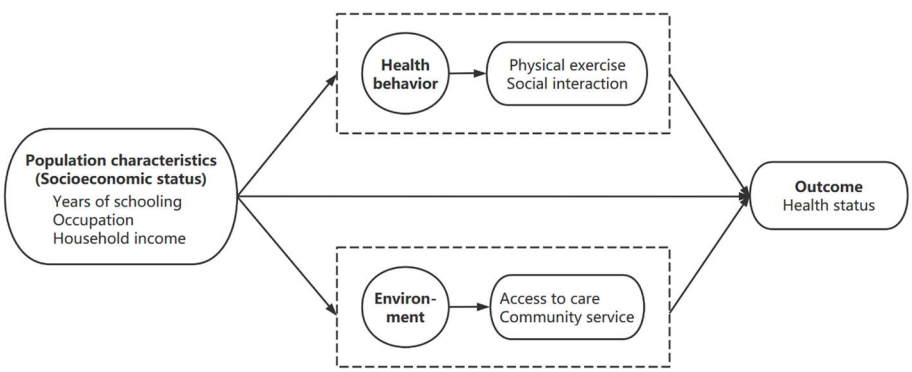

FIGURE 1 | Theoretical framework.

TABLE 1 | QWB's items, weights, calculation formula, and corresponding variables in the CLHLS data.

Step No.	Definition	Corresponding variables in the CLHLS data	Weight
	Mobility Scale (MOB)	e14, g131, g132	
5	No limitations for health reasons		0.000
4	Did not drive a car, health related; did not ride in a car as usual for age (younger than 15 year), health related, and/or did not use public transportation, health related; or had or would have used more help than usual for age to use public transportation, health related		−0.062
2	In hospital, health related		−0.090
	Physical Activity Scale (PAC)	e4, e11∼e13, g9, g131	
4	No limitations for health reasons		0.000
3	In wheelchair, moved or controlled movement of wheelchair without help from someone else; or had trouble or did not try to lift, stoop, bend over, or use stairs or inclines, health related; and/or limped, used a cane, crutches, or walker, health related; and/or had any other physical limitation in walking, or did not try to walk as far or as fast as others the same age are able, health related		−0.060
1	In wheelchair, did not move or control the movement of wheelchair without help from someone else, or in bed, chair, or couch for most or all of the day, health related		−0.077
	Social Activity Scale (SAC)	e0∼e10	
5	No limitations for health reasons		0.000
4	Limited in other (e.g., recreational) role activity, health related		−0.061
3	Limited in major (primary) role activity, health related		−0.061
2	Performed no major role activity, health related, but did perform, self-care activities		−0.061
1	Performed no major role activity, health related, and did not perform or had more help than usual in performance of one or more self-care activities, health related		−0.106
	Symptom/Problem Complexes (CPX) There are 23 categories in total. Detailed indicators and weights can be found in Table 2 in Kaplan and Anderson (19)	b34, b36, b38, e4, g106, g131, g15e∼h1, g15j∼k1, g15m∼q1, g15a∼y3, g22, g24, g181	

Formula: $W = 1 + (CPX\omega t) + (MOB\omega t) + (PAC\omega t) + (SAC\omega t)$.
where ωt is the preference-weighted measure for each indicator. For example, a person's MOB, PAC, SAC, and CPX, respectively corresponds to 4, 3, 3, and 11, the W score for he/she is $W = 1 + (-0.257) + (-0.062) + (-0.060) + (-0.061) = 0.56$.

chosen from a nearby geographical unit. The data were obtained through in-home interviews using internationally compatible questionnaire, and all investigators were trained in advance. To ensure the quality of data, the CLHLS has taken various measures in terms of proxy use, non-response rate, sample attrition, reliability and validity of major health measures, and rates of logically inconsistent answers. For example, when the interviewees are unable to answer the questions, a close family member or another proxy will provide the answers, but questions such as self-rated health, life satisfaction, and cognitive tests are answered by the interviewees only. The surveyed individuals over 65 years old with diabetes diagnosed by a physician will be included in this study, except for the samples with missing values in any variables of interest as mentioned below.

Measurements

Outcome Variable

The Quality of Well-being Scale (QWB) developed by Kaplan and Anderson (19) was used as the outcome variable in this study. QWB is a common indicator to measure health that reflects both the objective indicators and subjective evaluation of personal health status (20), which combines preference-weighted measures of symptoms and functions. The QWB is ranging from 0 (for death) to 1.0 (for asymptomatic full function). **Table 1** describes the items contained in QWB, the weight of relevant items, calculation formula (19), and corresponding variables in the CLHLS data.

Explanatory Variable

SES was the explanatory variable of this study, which was measured by asking three questions: "years of schooling," "main occupation before age 60," and "total income of your household last year." Years of schooling was classified into three categories: 0 years (1), 1∼5 years (2), and 6 years or more (3), respectively referred to uneducated, primary school, and middle school or more. The categories of occupation in the questionnaire included professional and technical personnel, governmental, institutional or managerial personnel, commercial, service or industrial worker, self-employed, agriculture, forestry, animal husbandry or fishery worker, house worker, and others. In this study, occupation was recoded into two categories according to occupational characteristics: manual worker (1), including commercial or industrial worker, farmer, self-employed, house

worker, and others; and non-manual worker (2), including professional, technical or managerial personnel; Household income was divided into four quartiles with quintile 1 (1) indicating the poorest and quintile 4 (4) indicating the richest.

TABLE 2 | Characteristics of the sample ($N = 1030$).

Characteristic	*N* or mean	% or SD
Sex		
female	588	57.1
male	442	42.9
Age (years old)		
90 and above	186	18.1
75∼89	502	48.7
65∼74	342	33.2
Marital status		
Other	443	43.0
Married and living with spouse	587	57.0
Residential area		
Rural	283	27.5
Urban	747	72.5
Years of schooling (years)		
0	333	32.3
1∼5	234	22.7
≥6	463	45.0
Occupation		
Manual worker	809	78.5
Non-manual worker	221	21.5
Household income		
Q1	221	21.5
Q2	248	24.1
Q3	239	23.2
Q4	322	31.3
Regularly exercised in the past		
No	579	56.2
Yes	451	43.8
Frequency of social interaction		
Never	318	30.9
Not monthly, but sometimes	95	9.2
At least once for a month	87	8.4
Once for a week	192	18.6
Almost everyday	338	32.8
Can you get medical service in time		
No	17	1.7
Yes	1013	98.3
Are healthcare or psychological comfort services available in your community		
Neither	316	30.7
The former	320	31.1
The latter	54	5.2
Both	340	33.0
QWB	0.6	0.1

Mediating Variables

To evaluate the pathways through which SES affected the health of older patients with diabetes, physical exercise and social interaction at the individual level, as well as access to care and community service at the environmental level, were all considered as potential mediators. The question "Do you regularly exercise in the past, such as playing ball, running and Qigong?" was used to collect information on physical exercise, and the responses to this question were dichotomized into no (1) or yes (2). Given the social background and feature of times for the social interaction of Chinese older adults, the measurement of social interaction included three indicators: the frequencies of participation in group leisure activities (i.e., square dancing, playing cards/mah-jongg), informal interaction (series, interact with friends), and organized social activities. A score was given to each indicator based on five responses: almost every day (5), not daily, but once for a week (4), not weekly, but at least once for a month (3), not monthly, but sometimes (2), and never (1). And the highest frequency of the three kinds of indicators was deemed as the frequency of an individual's social interaction. Access to care was assessed by one question "Can you get medical service in time?" Responses to this question were dichotomized into no (1) or yes (2). Community service was measured with two indicators: the availability of healthcare (i.e., home visit services, healthcare education) and psychological comfort services (i.e., psychological consulting services, social and recreation services) in your community. Options for both questions include no (1) and yes (2). The score for community service was recoded after merging options of the two questions as four classes: both (4), the former (3), the latter (2), and neither (1).

Covariates

The respondents' sex and age were the covariates in this study. Females and males were coded as 1 and 2. Ages were classified into three groups: 65∼74 years old (3), 75∼89 years old (2), 90 years old and above (1).

Statistical Analysis

Frequency and percentage were used to describe sample characteristics. Structural equation modeling (SEM) method was applied to test the relationship between SES and health condition of older patients with diabetes as well as the mediating effect of physical exercise, social interaction, access to care, and community service. Following fit indices were used to evaluate the model fit: comparative fit index (CFI), incremental fit index (IFI), the goodness-of-fit index (GFI), the adjusted goodness-of-fit index (AGFI), standardized root mean square residual (SRMR), and the root mean square error of approximation (RMSEA). We aimed at an adequate fit: CFI $\geq$ 0.90, IFI $\geq$ 0.90, GFI $\geq$ 0.90, AGFI $\geq$ 0.90, SRMR $\leq$ 0.08, RMSEA $\leq$ 0.08. The parameters were estimated by the maximum likelihood method. All the analyses were performed with M*plus* 8.0 software.

RESULTS

Of the 15,874 individuals aged 65 and over based on the 2018 CLHLS survey, 1,423 had diabetes. After excluding the sample

TABLE 3 | Model fit indices of potential models.

Model	Fit indices							
	χ^2	df	GFI	AGFI	CFI	IFI	SRMR	RMSEA
Model 0	22.370	2	0.978	0.889	0.884	0.885	0.044	0.144
Model 1	48.083	4	0.981	0.930	0.911	0.912	0.038	0.103
Model 2	58.991	7	0.981	0.943	0.920	0.921	0.041	0.085
Model 3	74.697	11	0.980	0.949	0.907	0.908	0.040	0.075
Model 4	77.537	16	0.982	0.959	0.910	0.911	0.037	0.061

with missing values in any variables of interest, a total of 1,030 respondents (older patients with diabetes) were included in the final analyses.

Table 2 shows the individual characteristics and the QWB scores of these 1,030 respondents. The respondents comprised of 57.1% ($n = 588$) females, 81.9% ($n = 844$) were under 90 years old, 57.0% ($n = 587$) were married and lived with their spouse, and 72.5% ($n = 747$) lived in the urban area. Among the respondents, 45.0% ($n = 463$) had more than 6 years of schooling, 78.5% ($n = 809$) mainly engaged in manual labor before 60 years old, and 31.3% ($n = 322$) were in the highest quartile of household income, i.e., the total household income of more than 100,000 yuan. The prevalence of past exercising was estimated to be 43.8% ($n = 451$). Of social interaction, 32.8% ($n = 338$) participated almost daily, whereas 30.9% ($n = 318$) never participated. Nearly all the respondents (98.3%, $n = 1013$) reported that they could get adequate medical service in time. About one third (33.0%, $n = 340$) of the respondents had both healthcare and psychological comfort services available in the community, while another one third (30.7%, $n = 316$) had neither of these two services. The average value of the QWB scores was 0.6.

In order to test the proposed framework, we constructed several models. Model fit indices for all models are summarized in **Table 3**. Model 0 was the base model that no mediations involved, which showed poor model fit. Model 1 posited physical exercise as a mediator of the effect of SES on the health of older patients with diabetes, which still fitted poorly. Model 2 added social interaction as the second mediator to Model 1. Model 3 set physical exercise, social interaction, and community service as mediators. Model 4 allowed the effect of SES to be mediated via variables of Model 3 plus additional access to care. The fitting statistics of Model 2 to Model 4 met the criteria, among which, model 4 incorporated all the mediator hypotheses and generated the best fit statistics.

Model 4, namely the final model, was illustrated in **Figure 2**. **Table 4** displays a decomposition of the direct and total effect of SES on the QWB among older patients with diabetes, the specific indirect effect through four mediations, and the ratio of indirect effect to total indirect effect. In the final Model, after controlling for respondents' sex and age, the total effect of SES on the QWB of older patients with diabetes was 0.125 ($p < 0.01$). SES positively predicted physical exercise ($\beta = 0.417$, $p < 0.001$) and community service ($\beta = 0.126$, $p < 0.01$). Social interaction ($\beta = 0.253$, $p < 0.001$) had the largest direct effect on the QWB of older patients with diabetes, followed by community service ($\beta = 0.111$, $p < 0.001$), and physical exercise ($\beta = 0.108$, $p < 0.01$). Additionally, although the model did not show a direct effect of SES on the QWB for older adults with diabetes ($p > 0.05$), SES mediated the effect in their relationship through physical exercise (indirect effect = 0.045, $p < 0.01$) and community service (indirect effect = 0.014, $p < 0.05$).

DISCUSSION

To the best of our knowledge, there was a dearth of studies on the relationship between SES and health among older patients with diabetes. This study not only examined this relationship, but also determined whether SES mediated the health of older patients with diabetes through four latent variables: physical exercise, social interaction, access to care, and community service. Although the direct influence of SES on the health status of older patients with diabetes was not found in the final model, mediation roles of physical exercise and community service in their relationship were observed in this study. Additionally, physical exercise, social interaction, and community service showed significant effects on the health of older patients with diabetes.

At the individual level, the findings showed that the SES of older patients with diabetes positively predicted their physical exercise, while its impact on social interaction was not significant. Meanwhile, both physical exercise and social interaction have a positive effect on the health of older patients with diabetes. As a result, SES mediated health through physical exercise rather than social interaction. On the one hand, higher SES tended to have a better sense of control over their life outcomes (21), which associated with good adherence to health behavior and regular physical exercises (22). And the regular physical exercise has been shown to be an outstanding way to improve physical and mental health (23–25), for example, controlling blood glucose, preventing and treating depression and reducing the risk of cardiovascular disease (26). These would explain the significant association between SES and physical exercise, as well as between physical exercise and health of older patients with diabetes. On the other hand, among the three categories of social interaction, namely group leisure activities, informal interaction and organized social activities, participating in group leisure activities (square dancing and playing mah-jongg/cards are the most common forms) and informal social interaction

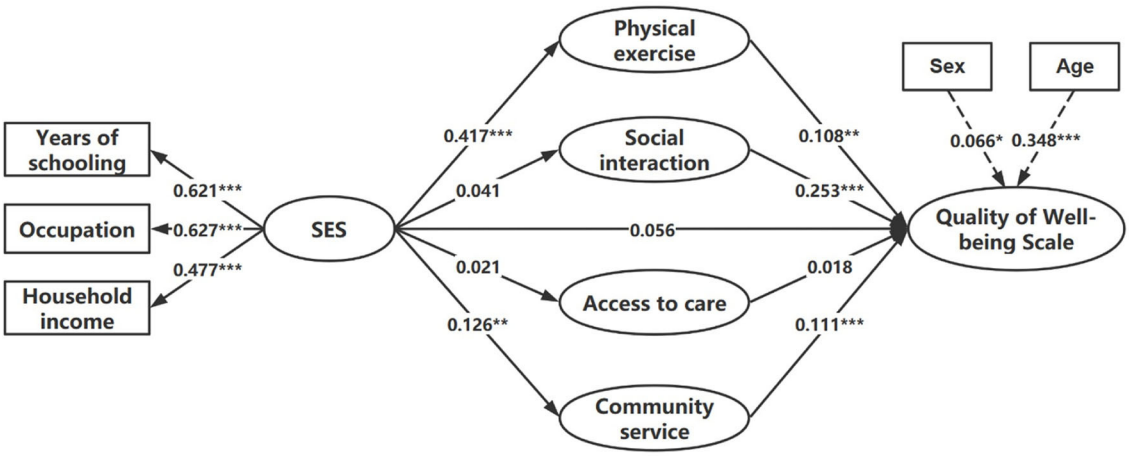

FIGURE 2 | Final model of the association between SES and the QWB of older patients with diabetes (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$).

TABLE 4 | Mediators in the association between SES and the QWB of older patients with diabetes.

Variable	Model 0	Model 1	Model 2	Model 3	Model 4
Socioeconomic status					
Direct effect on the QWB	0.111**	0.059	0.075	0.056	0.056
Total effect	0.111**	0.112**	0.127**	0.125**	0.125**
Physical exercise					
Direct effect on the QWB	-	0.126***	0.100**	0.108**	0.108**
Indirect effect (SES × physical exercise)	-	0.053**	0.042**	0.045**	0.045**
The ratio of indirect effect to total indirect effect (%)	-	1	80.77	65.22	65.22
Social interaction					
Direct effect on the QWB	-	–	0.258***	0.253**	0.253***
Indirect effect (SES × social interaction)	-	–	0.010	0.010	0.010
The ratio of indirect effect to total indirect effect (%)	-	–	19.23	14.49	14.49
Community service					
Direct effect on the QWB	-	–	–	0.111***	0.111***
Indirect effect (SES × community service)	-	–	–	0.014*	0.014*
The ratio of indirect effect to total indirect effect (%)	-	–	–	20.29	20.29
Access to care					
Direct effect on the QWB	-	–	–	–	0.018
Indirect effect (SES × access to care)	-	–	–	–	0.000
The ratio of indirect effect to total indirect effect (%)	-	–	–	–	0.00

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

among relatives and friends were the most leading aspects of social relationships for the elderly in China, regardless of social class (27). This may explain why SES did not have a significant impact on social interaction. However, the positive effects of social interaction on health have been confirmed by many studies (28, 29). Psychologically, social interaction can help older patients with diabetes find emotional support, enhance self-efficacy and reduce psychological problems, as older patients with diabetes report more depression (30, 31). Physically, social interaction benefits the health of older patients with diabetes by keeping them physically active. Thus, significant relationship was found between social interaction and health, rather than between SES and social interaction.

From the environmental perspective, the results indicated that richer community service was predicted by higher SES. Community service significantly affected the health of older patients with diabetes, while access to care did not. SES affected the health with mediation through community service rather than access to care. Benefiting from the health reform initiated in 2009, the coverage of primary care service institutions has been greatly expanded (32). According to the respondents included in this study, almost all of them (98.3%) were able to reach the nearest health facility in time when needed, which may result in the failure to detect significance. With respect to the relationship among the SES, community service and the health of older patients with diabetes, it may be explained that people

with higher SES have higher health awareness and tend to actively seek and use relevant health services, which was also demonstrated in previous research that people with higher SES were more likely to be aware of their diabetes status and to take measures to keep healthy (13). With a wider social network and information resource, as well as better economic affordability, such people will have greater access to various services resources in the community, which would benefit disease control and health maintenance.

It is also noteworthy that no significant impact of SES was shown on the health of older patients with diabetes in this study, which was inconsistent with the results of Nicklett (5) and Lee (17) studies that low SES leads to poor health among patients with diabetes. One plausible reason may be national differences. Both Nicklett (5) and Lee (17) studies were conducted in developed countries, where negative association between SES and prevalence of diabetes have been confirmed (33). People with low SES tended to be associated with chronic stress and negative life events. They also had less access to resources and were more vulnerable to behavioral risks, which would affect health status in the long term (34). However, for the developing countries, there may be some non-negligible differences in change of behavioral lifestyle between lower and higher SES. Taking China for example, during the past four decades of rapid economic growth from a state of poverty and backwardness, the consumption of high energy diets occurs broader and faster in the lower SES than in the higher SES (13), while higher SES generally increases the adoption of sedentary habits, excessive calorie intake (35). In other words, some behavioral lifestyle risk of diabetes generally increased both in the lower and higher SES. Since there were not merely positive or negative effects, the impact of SES on the health of older patients with diabetes was not significant.

Some limitations of this study should be recognized. First, all of the data in this study were obtained from self-reported, which may result in information bias. Second, considering the limitation of a cross-sectional study in causal inferences, it may be more prudent to investigate the causality by panel session data or so on in future research. Third, since the possibility cannot be ruled out that some potential mediators between SES and the health of older patients with diabetes not included in this study, more comprehensive models should be studied in the future.

CONCLUSION

In this study, we evaluated the relationship between SES and the health of older patients with diabetes, as well as the mediating roles of physical exercise, social interaction, access to care, and community service. The findings showed SES probably enhanced health by increasing regular exercise and providing more community service, which indicated that health-related individual behaviors and environmental supports can mediate the relationship between SES and the health of older patients with diabetes, and relieve the health disadvantages cumulated by SES in old age. To improve the health of older patients with diabetes and create healthier aging, it requires not only the individuals' initiatives and positive actions, such as keeping physical and mental health through exercising and socializing, but also the support of the environment, such as making health-related resources and services available in the community and residence.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: http://162.105.138.117/dataset.xhtml?persistentId=doi:10.18170/DVN/WBO7LK.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Research Ethics Committees of Peking University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WL and QD contributed to the conception and design of the study. QD conducted the data reduction, analyses, and wrote the manuscript. WL guided the whole process and reviewed the manuscript. All authors read and approved the manuscript before submission.

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Health-Related Quality of Life and Its Correlation With Depression Among Chinese Centenarians

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Background: As evidence on depression and health-related quality of life (HRQoL) among the oldest-old is currently limited, this study aimed to re-examine the association between depression and HRQoL among centenarians.

Methods: We analyzed cross-sectional data from the China Hainan Centenarian Cohort Study (CHCCS). The 15-item Geriatric Depression Scale (GDS-15) and three-level EuroQol five-dimensions (EQ-5D-3L) were used to evaluate depression and HRQoL, respectively. Poor health states were defined as EQ-5D index <0.665. Based on their GDS-15 score, individuals were categorized into three stages of depression: major depressive disorder (MDD; score ≥10), minor depressive disorder (MnDD; score between 6 and 9), and normal (score ≤5). Based on sex and comorbidity stratification, multivariable logistic regression was used to calculate the risk of poor health state in different levels of depression. We also used restricted cubic splines with a knot at 5 points (GDS-15) to flexibly model the association of GDS-15 scores with poor health states.

Results: Totally, 1,002 participants were included in this study for analysis. Participants' median age was 102 years, and 82.04% were female. The median EQ-5D index was 0.68 (range: −0.149–1), and the mean VAS and GDS-15 scores were 61.60 (range: 0–100), and 5.23 (range: 0–15), respectively. Centenarians with MnDD and MDD accounted for 38.12 and 9.98%, respectively. While those with poor health states accounted for 45.11%. For every 1-point increase in GDS-15, the risk of poor health state increased by 20% ($P < 0.001$) after an adjustment for age, gender, ethnicity, marital status, education, residence type, smoking, drinking, weekly exercise, body mass index category, serum albumin, 25-hydroxyvitamin D, C-reactive protein, and comorbidities. MnDD and MDD were independent risk factors for poor health state (MnDD, OR = 2.76, $P < 0.001$; MDD, OR = 3.14, $P < 0.001$). The association was more prominent in centenarians without comorbidity.

Conclusions: This study demonstrated a negative association between depression and HRQoL in Chinese centenarians, especially in centenarians without comorbidity. Large-scale prospective studies are needed to corroborate our findings and provide more information about the causal inference and internal mechanisms of this association.

Keywords: centenarians, depression, comorbidity, chronic disease, health-related quality of life

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INTRODUCTION

The global population is aging. Worldwide, the proportion of the population aged 60 years and older increased from 9.2% in 1990 to 11.7% in 2013, and will continue to increase and account for 21.1% of the world's population by 2050 (1). Due to dramatic changes in population structure, aging-related problems have significantly impacted social and economic development, health and disease prevalence patterns, and individuals' lifestyles.

In recent years, there has been an increased emphasis on promoting healthy aging. Health-related quality of life (HRQoL) is a widely used instrument to evaluate individuals' daily activities, physiological functions, and subjective satisfaction in their emotional and social life (2). HRQoL comprehensively reflects the health-related factors of older adults, covering all aspects of the biopsychosocial model; it is considered an important indicator of healthy aging (3). As centenarians are considered an ideal template for healthy aging (4–6), research on this population may contribute to an enhanced understanding of the mechanisms and determinants of healthy aging.

Depression is the most common mental disorder in older adults (7). Especially in the oldest-old age group, depression is more prevalent and complicated due to age-related risk factors such as disease and functional decline (8–10). In a study of older adults over 90 years of age, the prevalence of depression was related to an overall decreased health status and quality of life and with increased mortality (11). The relationship between depression and HRQoL has been demonstrated in the general older population (10, 12) and people with certain diseases such as diabetes (13), breast cancer (14), sensory disabilities (15), and HIV (13–16). However, no previous study has investigated the association in centenarians. In consideration of the age-related vulnerabilities and potential unique patterns related to longevity (17, 18), there is a need to examine the association between depression and HRQoL in the oldest-old.

Therefore, we assessed the baseline characteristics of HRQoL and investigated the association with the levels of depressive disorder, especially the difference in sex and comorbidities, using cross-sectional data obtained from a complete sample of a centenarian cohort from regions in China with the oldest population.

METHODS

Study Population

This study derived information from the baseline data of China Hainan Centenarian Cohort Study (CHCCS). Hainan Province has the highest percentage of centenarians (18.75/100,000) and average life expectancy (76.3 years) in China (19, 20). Furthermore, as a relatively closed island area, the low proportion of immigrants ensured a high homogeneity of centenarians. We adopted a longitudinal observational design based on a complete sample of both community-dwelling and institutionalized population in Hainan, China. CHCCS is a complete sample study involving all centenarians in Hainan Province. The sampling frame and investigation methods of CHCCS are outlined in previous reports (21). This study was approved by the Ethics Review Committee of the People Liberation Army General Hospital in Beijing, China, and written informed consent was obtained from all participants.

A baseline survey was conducted from June 2014 to December 2016. In 2014, there were 1,811 living centenarians in total, according to the household register. After a rigorous validation, we excluded the people with wrong registration information ($n = 18$), residential address mismatches ($n = 55$), age mismatches ($n = 58$), and who had died ($n = 207$). Totally, 1,473 eligible centenarians were identified from the Civil Affairs Bureau of Hainan Province in 2014. Excluding lost interviews due to inability to complete the investigation ($n = 124$), death before interview ($n = 268$), and refusal to participate ($n = 79$), 1,002 centenarians were included for analysis.

Data Collection

The baseline survey mainly included a questionnaire interview, physical examination, biological specimen collection, and laboratory examination. All the questionnaires were conducted through face-to-face interviews by the systematically trained nurses in the Hainan dialect. The content of the questionnaire survey included general demographic characteristics, lifestyles, personal, and family disease history, cognitive and mental health status, and functional status. Questionnaire items that participants were unable to answer or self-assessed were answered by their closest caregivers. Epidata 3.1 software was used for data entry, and all data were cross-checked by two researchers.

Depression and Depressive Disorders

We used the 15-item Geriatric Depression Scale (GDS-15) to measure depression in centenarians (22). The scale assesses the depression status of participants since the last week, mainly testing older adults' feelings of depression, reduced activity, irritability, withdrawal and pain, and negative views of the past, present, and future. There are 15 items on this scale, and each item requires the participants to answer "yes" or "no." Each answer indicating depression counts 1 point, with a maximum score of 15 points. The higher the score, the more obvious the symptoms of depression. Depressive disorders were defined using the cutoff points for community-dwelling elders (23): $\leq$ 5, normal; 6–9, minor depressive disorder (MnDD); $\geq$10, major depressive disorder (MDD).

Health-Related Quality of Life

HRQoL was measured using the three-level EuroQol five-dimensions (EQ-5D-3L), which is a general tool for describing and evaluating health states (24, 25). The EQ-5D-3L covers three levels of the five dimensions: mobility, self-care, daily activities, pain/discomfort, and anxiety/depression. To quantify participants' preferences, a time trade-off (TTO) model based on a specific population was used to calculate the EQ-5D index. The EQ-5D index was derived from the Chinese EQ-5D-3L value set (26), and it ranged from −0.149 to 1. An EQ-5D index of 1 indicated full health in all 5 dimensions. Under this TTO value set, mild states were health states in which dimensions were either in level 1 (no problems) or in level 2 (some/moderate problems)

and with a maximum of 3 dimensions impaired, which means that EQ-5D index ≥0.665 (excluding "full health"). Therefore, we defined poor health states as EQ-5D index<0.665, and normal health states as EQ-5D index ≥0.665 in this study. The Visual Analog Scale (VAS) is a self-assessment tool for participants to assess their health status on a 20 cm vertical visual scale with a grade ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).

Covariates

Socio-demographic characteristics assessed included age, sex, education, ethnicity, marital status, education, and residence type at the time of face-to-face interviews. We also considered lifestyle characteristics such as smoking status, alcohol drinking status, and weekly exercise. Some important indicators including body mass index (BMI), serum albumin (Alb), 25-hydroxyvitamin D[25 (OH)D], and C-reactive protein (CRP) were also considered for analysis. Participants were asked to report whether they had been diagnosed and treated by a doctor for any specific medical conditions. The presence of heart disease, stroke, chronic obstructive pulmonary disease, and cancer were self-reported. The presence of hypertension was defined by a self-report of high blood pressure, and/or sitting systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg (27). Similarly, diabetes was defined by a self-report and/or a fasting blood glucose concentration of ≥7.0 mmol/L (28). Chronic renal dysfunction was defined by a self-report and/or a glomerular filtration rate <60 ml·min-1/1.73 m^2 (29). In this study, comorbidities were defined as two simultaneously occurring chronic diseases in addition to depression and poor health states. The process of clinical examination and biological specimen collection were outlined in previous reports (21).

Statistical Analyses

All continuous variables were assessed by QQ plot and Shapiro–Wilk normality test. Normally distributed continuous variables were expressed as mean ± standard deviation (SD); non-normal continuous variables were expressed as median (interquartile range [IQR]); and categorical variables were presented by counts and percentages. The differences between the means (medians) and proportions of the two groups were compared by Student's *t*-test (Wilcoxon rank-sum test) and chi-square test. We applied logistic regression analysis to calculate the odds ratios (ORs) of poor health states, using the continuous and categorical forms of GDS-15 as independent variables. Due to the uneven distribution and different vulnerabilities of depression and impaired health status between men and women, we conducted a stratification analysis on gender. In addition, we observed the association between depression and HRQoL according to the comorbidity category. Further, we tested the interactions of comorbidities and GDS-15 categories on HRQoL in different models. In order to avoid the influence of subjectivity and information loss for the number of categories and node positions in the classification, we also used restricted cubic splines with five knots at the 5th, 35th, 50th, 65th, and 95th centiles to flexibly model the association of GDS-15 scores with poor health states and examine their non-linear associations. In multivariable analyses, model 1 were adjusted for age, gender, ethnicity, marital status, education, and residence type, and model 2 were additionally adjusted for smoking, drinking, weekly exercise, BMI category, serum albumin, 25-hydroxyvitamin D, C-reactive protein, and comorbidities. Demographic characteristics and lifestyle-related variables were directly included into the models, and covariates that met any of the following criteria were included in the fully adjusted model: (1) the inclusion of covariates in the basic model or the elimination of covariates from the complete model has an impact on the regression coefficient of >10%; (2) *p*-value of the regression coefficient between the covariate (X) and dependent variable (Y) was <0.1. All statistical analyses were performed using SPSS Statistics version 24.0 (IBM Corporation, Armonk, NY, United States) and Empower Stats (X&Y Solutions, Inc., Boston, MA). A $p < 0.05$ (2-tailed) was considered statistically significant.

RESULTS

Baseline Characteristics

Table 1 summarizes the general characteristics of the 1,002 participants (180 men and 822 women) by the categories of HRQoL. Participants' ages ranged from 100 to 116 years, with a median age of 102 years (IQR, 101–104). The median EQ-5D index was 0.68 (IQR, 0.55–0.79; range: −0.149–1.000) and the average VAS score was 61.60 ± 15.56 (range: 0–100). Among the 1,002 participants, 452 centenarians (66 men and 386 women) reported a poor health state, accounting for 45.11%. Totally, 38.12% of participants had MnDD and 9.98% of participants had MDD. Compared with participants in normal health states, participants in poor health states had a significantly lower GDS-15, VAS, and EQ-5D index, and a higher proportion of depressive disorders. Significant differences were also found between the two groups in terms of sex, residence type, alcohol drinking, weekly exercise, Alb, 25(OH)D, CRP, and BMI categories.

Association of GDS-15 and Depressive Disorders With Poor Health States

As shown in **Table 2**, continuous and categorical forms of GDS-15 were used as independent variables and the dichotomous EQ-5D index as the dependent variable. The demographic characteristics, lifestyle, and other covariates [BMI category, Alb, 25(OH)D, CRP, and comorbidities] were gradually adjusted, and multiple logistic regression analyses were performed. In the total study population, for every 1-point increase in GDS-15, the risk of poor health state increased by 24, 25, and 20% in each model ($P < 0.001$). Similar results were found in men and women.

Compared with the normal group of depression, the multivariable logistic analysis revealed a significant association between depressive disorders and poor health states in total population (Model 2: MnDD, OR = 2.76, $P < 0.001$; MDD, OR = 3.14, $P < 0.001$). The risk of MnDD in male centenarians [Model 2, OR = 3.62, 95% confidence interval (CI):1.59–8.25, $P = 0.002$] was higher than in female centenarians (Model 2, OR = 2.61, 95% CI: 1.85–3.68, $P < 0.001$). The risk of MDD was 2.47 times higher than the normal group of depression in female

TABLE 1 | General characteristics of 1,002 centenarians according to the HRQoL categories[a,b].

Characteristics	Total(n = 1,002)	Normal HRQoL (n = 550)	Poor health state (n = 452)	P-value
Age, year	102.00 (101.00–104.00)	102.00 (101.00–104.00)	102.00 (101.00–104.00)	0.224*
GDS-15	5.23 ± 3.05	4.42 ± 2.86	6.23 ± 2.97	<0.001
VAS	61.60 ± 15.56	66.35 ± 13.78	55.82 ± 15.67	<0.001
EQ-5D index score	0.68 (0.55–0.79)	0.79 (0.68–0.89)	0.50 (0.30–0.59)	<0.001*
Alb, g/L	38.43 ± 3.99	39.42 ± 3.49	37.22 ± 4.23	<0.001
CRP, mg/dl	0.21 (0.08–0.58)	0.17 (0.07–0.49)	0.29 (0.09–0.58)	<0.001*
25(OH)D, ng/mL	22.74 ± 9.24	24.00 ± 9.06	21.22 ± 9.24	<0.001
Depression				<0.001
Normal	520 (51.90%)	353 (64.18%)	167 (36.95%)	
MnDD	382 (38.12%)	163 (29.64%)	219 (48.45%)	
MDD	100 (9.98%)	34 (6.18%)	66 (14.60%)	
Gender				0.012
Male	180 (17.96%)	114 (20.73%)	66 (14.60%)	
Female	822 (82.04%)	436 (79.27%)	386 (85.40%)	
Ethnicity				0.796
Han	883 (88.12%)	486 (88.36%)	397 (87.83%)	
Others	119 (11.88%)	64 (11.64%)	55 (12.17%)	
Education				0.071
Illiterate	915 (91.32%)	493 (89.64%)	422 (93.36%)	
Primary school	67 (6.69%)	42 (7.64%)	25 (5.53%)	
Middle school or higher	20 (2.00%)	15 (2.73%)	5 (1.11%)	
Marital status				0.384
Married	100 (9.98%)	59 (10.73%)	41 (9.07%)	
Widowed/ divorced/ never married	902 (90.02%)	491 (89.27%)	411 (90.93%)	
Residential type				0.002
Living together with families	863 (86.13%)	457 (83.09%)	406 (89.82%)	
Living alone at home	139 (13.87%)	93 (16.91%)	46 (10.18%)	
BMI categories				<0.001
BMI<18.5kg/m^2	575 (57.39%)	286 (52.00%)	289 (63.94%)	
18.5≤BMI<24 kg/m^2	393 (39.22%)	242 (44.00%)	151 (33.41%)	
BMI≥24kg/m^2	34 (3.39%)	22 (4.00%)	12 (2.65%)	
Smoking status				0.794
Non-smoker	893 (89.12%)	492 (89.45%)	401 (88.72%)	
Former	74 (7.39%)	38 (6.91%)	36 (7.96%)	
Current	35 (3.49%)	20 (3.64%)	15 (3.32%)	
Alcohol drinking				0.02
Non-drinker	824 (82.24%)	444 (80.73%)	380 (84.07%)	
Former	79 (7.88%)	39 (7.09%)	40 (8.85%)	
Current	99 (9.88%)	67 (12.18%)	32 (7.08%)	
Weekly exercise				<0.001
Yes	129 (12.87%)	119 (21.64%)	10 (2.21%)	
No	873 (87.13%)	431 (78.36%)	442 (97.79%)	
Comorbidity				0.755
Yes	331 (33.03%)	184 (33.45%)	147 (32.52%)	
No	671 (66.97%)	366 (66.55%)	305 (67.48%)	

HRQoL, health-related quality of life; EQ-5D, EuroQol five dimensions questionnaire; GDS-15, 15-item Geriatric Depression Scale; VAS, Visual Analog Scale; Alb, serum albumin; 25(OH)D, 25-hydroxyvitamin D; CRP, C-reactive protein; MnDD, minor depressive disorder; MDD, major depressive disorder; BMI, body mass index.

[a]Normally distributed continuous variables were expressed as mean ± standard deviation (SD); non-normal continuous variables were expressed as median (interquartile range); categorical variables were presented by the percentage.

[b]Differences between two groups were evaluated by t-test or chi-square test.

**Differences between two groups were evaluated by Wilcoxon rank-sum test or Fisher's exact chi-square test.*

TABLE 2 | Odds ratios for poor health states among centenarians with different levels of depression[a,b].

	GDS-15 score	Categorized variables of GDS-15 score			*P* for trend
		Normal	MnDD	MDD	
Total					
Crude model	1.24 (1.18, 1.29) <0.001	Ref.	2.84 (2.16, 3.73) <0.001	4.10 (2.61, 6.45) <0.001	<0.001
Model 1	1.25 (1.19, 1.31) <0.001	Ref.	2.84 (2.14, 3.76) <0.001	4.42 (2.76, 7.07) <0.001	<0.001
Model 2	1.20 (1.14, 1.27) <0.001	Ref.	2.76 (2.03, 3.76) <0.001	3.14 (1.90, 5.20) <0.001	<0.001
Male					
Crude model	1.27 (1.12, 1.44) 0.001	Ref.	3.91 (1.98, 7.72) <0.001	3.62 (0.91, 14.39) 0.067	0.001
Model 1	1.27 (1.11, 1.45) <0.001	Ref.	3.79 (1.83, 7.87) <0.001	2.90 (0.67, 12.46) 0.152	0.005
Model 2	1.23 (1.06, 1.42) 0.008	Ref.	3.62 (1.59, 8.25) 0.002	1.83 (0.36, 9.27) 0.464	0.044
Female					
Crude model	1.22 (1.16, 1.29) <0.001	Ref.	2.61 (1.93, 3.52) <0.001	3.95 (2.44, 6.40) <0.001	<0.001
Model 1	1.25 (1.18, 1.31) <0.001	Ref.	2.64 (1.93, 3.60) <0.001	4.47 (2.70, 7.38) <0.001	<0.001
Model 2	1.21 (1.14, 1.28) <0.001	Ref.	2.61 (1.85, 3.68) <0.001	3.47 (2.01, 6.00) <0.001	<0.001

[a]*Model 1: Adjusted for age, gender, ethnicity, marital status, education, and residence type. Model 2: Adjusted for age, gender, ethnicity, marital status, education, and residence type, smoking, drinking, weekly exercise, BMI category, serum albumin, 25-hydroxyvitamin D, C-reactive protein, and comorbidities.*
[b]*Data are represented as OR (95% CI) P-value.*

centenarians (Model 2, OR = 3.47, 95% CI: 2.01–6.00, $P < 0.001$), but not significant in male centenarians (Model 2, OR = 1.83, 95% CI: 0.36–9.27, $P = 0.464$). Furthermore, it was observed in all models that the health states deteriorated with the severity of depression (P for trend <0.05).

In **Figure 1**, we used restricted cubic splines to flexibly model and visualize the relation of GDS-15 scores with poor health states. We have observed that there is a non-linear relationship between the GDS scores and poor health states of male centenarians, female centenarians, and all participants ($P = 0.010$, 0.014, and <0.001, respectively). We have observed an S-type association of GDS-15 scores with poor health states that among female centenarians, the risk of poor health states increased as the GDS-15 score increases, but the higher the score, the increase gradually slowed compared to the reference point (GDS-15 = 5). However, it has not been observed that the growth in GDS scores was related to the improvement of HRQoL at high levels of GDS scores.

Comorbidity-Stratified Analyses

The associations of GDS-15 and depressive disorders with poor health states in centenarians with and without comorbidities were explored (**Table 3**). In all models, we found that in the group with comorbidities, the increased risk of poor health states due to an increase in GDS-15 was lower than that in the group without comorbidities. In centenarians with comorbidities, compared with normal group, participants with MnDD, and MDD had a 1.88- and 0.56-fold increased risk of poor health state in the fully adjusted model, but this association was not statistically significant in MDD (MnDD: OR = 2.88, 95% CI: 1.61–5.14, $P < 0.001$; MDD: OR = 1.56, 95% CI: 0.63–3.86, $P = 0.340$). Interestingly, among centenarians who did not suffer from comorbidities, the association between depressive disorders and poor health states risk was more prominent (MnDD: OR = 2.98, 95% CI: 2.03–4.37, $P < 0.001$; MDD: OR = 5.09, 95% CI: 2.66–9.72, $P < 0.001$). The p-values of the interaction test of comorbidities and depression on HRQoL in the crude model, Models 1 and 2 were 0.026, 0.017, and 0.059, respectively.

DISCUSSION

To the best of our knowledge, this is the first study focused on the association between depression and HRQoL in a population-based sample of centenarians in China. We found that the elevated depression levels and the presence of depressive disorders were associated with the decrease in HRQoL, and this association was more prominent in centenarians without comorbidity. Therefore, this study provides evidence of the relationship between depression and HRQoL in the oldest-old and new information about comorbidities.

A study about EQ-5D-5L norms for the urban Chinese population in China has reported that 54% of the sample reported their health as "perfect health," and the average EQ-5D scores of men and women in the age group older than 70 years were 0.932 (SD: 0.034) and 0.912 (SD: 0.031), respectively (30). A Hong Kong survey of adults with an average age of 72.74 years showed that the participants' average EQ-5D index was 0.83 (31). Another longitudinal study reported that 17% of the older adults in northern Italy was perfectly health in HRQoL (32). The HRQoL level of centenarians in the CHCCS was worse than these studies. This may be due to the differences in age groups and the representativeness of the participants. A study based on the Spanish population showed that the norms for the EQ-5D index and VAS in the age group of 85 years and higher were 0.622 (95% CI, 0.591–0.652) and 54.6 (95% CI, 52.4–56.7) (33), which is lower than those in our study. This may indicate that the self-reported health status of the centenarians in this study was better than the reported population.

In this study, both depression levels and depressive disorders were found to have a negative correlation with HRQoL. These results are in line with previous studies conducted on the

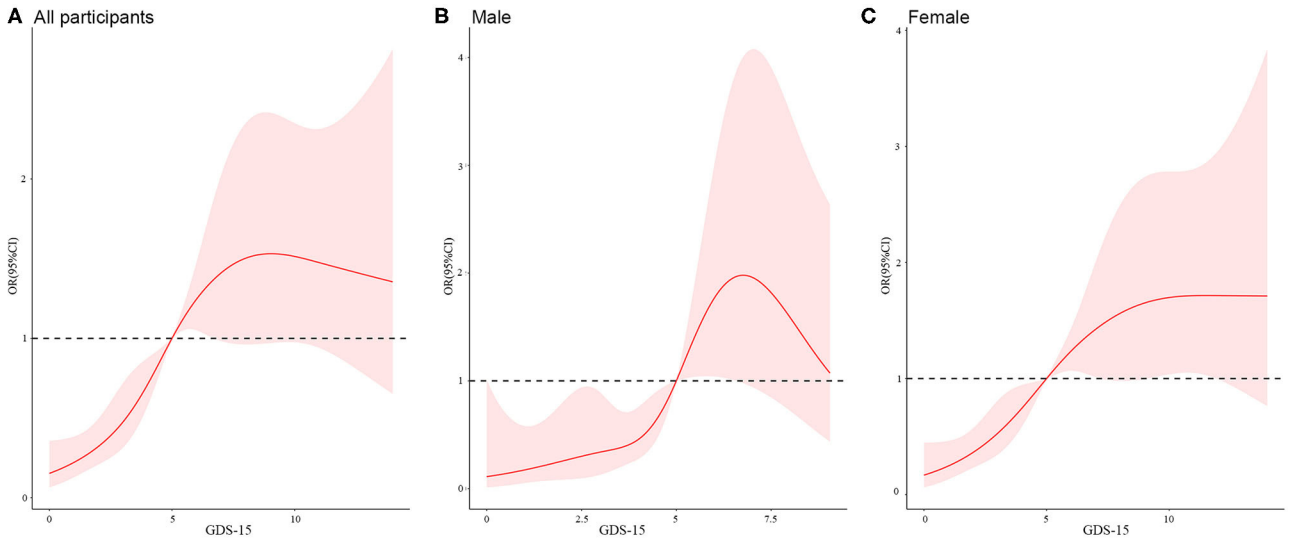

FIGURE 1 | Restricted cubic splines of the relationship between poor health states and GDS-15 score[a,b] in the total study population **(A)**, male population **(B)**, and female population **(C)**.
[a]Adjusted for age, gender, ethnicity, marital status, education, and residence type, smoking, drinking, weekly exercise, BMI category, serum albumin, 25-hydroxyvitamin D, C-reactive protein, and comorbidities.
[b]The GDS-15 score of 5 was set as the reference point (OR = 1).

TABLE 3 | Odds ratios for poor health states among centenarians with different levels of depression with or without comorbidities[a,b].

	Continuous variable of GDS-15 score	Categorized variables of GDS-15 score			*P* for trend	*P* for interaction c
		Normal	MnDD	MDD		
With comorbidity						
Crude model	1.15 (1.07, 1.25) <0.001	Ref.	2.73 (1.69, 4.43) <0.001	1.75 (0.81, 3.76) 0.153	0.01	0.026
Model 1	1.17 (1.08, 1.28) <0.001	Ref.	2.92 (1.73, 4.93) <0.001	1.93 (0.85, 4.38) 0.118	0.009	0.017
Model 2	1.16 (1.06, 1.27) 0.002	Ref.	2.88 (1.61, 5.14) <0.001	1.56 (0.63, 3.86) 0.340	0.05	0.059
Without comorbidity						
Crude model	1.28 (1.21, 1.36) <0.001	Ref.	2.95 (2.11, 4.13) <0.001	6.45 (3.59, 11.59) <0.001	<0.001	
Model 1	1.30 (1.22, 1.38) <0.001	Ref.	2.95 (2.09, 4.16) <0.001	7.00 (3.83, 12.80) <0.001	<0.001	
Model 2	1.25 (1.17, 1.33) <0.001	Ref.	2.98 (2.03, 4.37) <0.001	5.09 (2.66, 9.72) <0.001	<0.001	

[a]Model 1: Adjusted for age, gender, ethnicity, marital status, education, and residence type. Model 2: Adjusted for age, gender, ethnicity, marital status, education, and residence type, smoking, drinking, weekly exercise, BMI category, serum albumin, 25-hydroxyvitamin D, C-reactive protein, and comorbidities.
[b]Data are represented as OR (95% CI) P-value.
[c]The interactions of comorbidities and GDS-15 categories on HRQoL were tested in different models.

general older adult population (10). A cohort study that included individuals over 90 reported that the presence of depression was associated with a decline in overall functional status, a decline in HRQoL, and increased mortality (11). In addition, in studies of people with certain diseases such as diabetes (34), breast cancer (14), and HIV (16), depression was negatively associated with HRQoL. Our findings contribute new evidence in centenarians and may contribute to a better understanding of the determinants of improving the HRQoL. However, the causality between depression and HRQoL remains uncertain. In a representative survey of the German general population aged 75 years and over (12), it was found that there was a significant negative correlation between the initial changes in HRQoL and the subsequent changes in GDS-15, and not conversely. This conflicts with the findings of Van der Weele (11). Thus, this study is insufficient to solve the above controversy, and follow-up cohort studies are needed to explore the direction of development between depression and HRQoL.

In the fully adjusted model, MDD in male centenarians was not significantly associated with poor health states ($P = 0.464$). Considering the direction of association (OR = 1.83, 95% CI: 0.36, 9.27) and results of continuous variables of GDS-15 (Model 2, OR = 1.23, 95% CI: 1.06, 1.42, $P = 0.008$), this may be due to the insufficient sample size of the male centenarians, and may not be a reflection of the actual correlation between depression and poor health states in this population. However,

we have not found any other research evidence to prove our results. A previous meta-analysis using nationally representative samples demonstrated that gender differences exist in depression symptoms throughout life (35). As for the prevalence of depression, women are almost twice as likely to experience depression than men across the lifespan (36). On the other hand, older men and women may have different perceptions of HRQoL, and women are more likely to report worse HRQoL (37). The susceptibility of biological and psychological aspects between different sexes and the influence of environmental factors at the macro and micro levels make the association complicated. But even among centenarians of different genders, we should pay more attention to the oldest-old with severe depressive disorder, because they are more likely to be accompanied by a low level of the HRQoL.

It is somewhat surprising that in centenarians with comorbidities, the increased risk of poor health state due to elevated GDS-15 was lower than those without comorbidities. It is generally considered that multimorbidity aggravates both depression (7) and HRQoL (38) in older individuals. Studies based on the Chinese population found that participants with chronic diseases had a significantly lower EQ-5D index than participants without diseases (39), and the impact of comorbidities on HRQoL changed due to different disease combinations (40). There may be two explanations for our results. With aging, the older may gradually accept the decline in physical function and the deterioration in health due to changes in biology and social psychology, which may change their internal standards of health and reduce expectations (10). Therefore, HRQoL of centenarians may score higher even if the health status is not significantly improved. Moreover, survivor bias should also be taken into consideration. The centenarians are a relatively healthy group of the older population (41). Centenarians with comorbidities are more tolerant of the adverse effects of diseases than others so that they can age well. Further studies are needed to validate our findings and better understand the mechanisms involved in this survival effect.

Several limitations need to be noted. First, this study is limited by its cross-sectional design, and no causal inference can be drawn. Longitudinal studies on depression and HRQoL will further clarify the predictive factors of HRQoL decline and provide potential targets for future interventions. Second, the depressive disorders were evaluated by GDS-15, not the clinical diagnosis. However, GDS-15 has been proven to be a stable assessment of depression and is commonly used for measuring depression in older people (42). Third, the results of self-reported questionnaires may be biased when the respondents are older adults with cognitive impairment. However, the same questions were asked to caregivers to ensure the authenticity of the information.

CONCLUSION

This study demonstrated that depression is negatively related to HRQoL in Chinese centenarians. Elevated levels of GDS-15 score and depressive disorders are independent determinants of poor health states in the oldest-old. Especially, in centenarians without comorbidities, this association becomes more remarkable. However, large-scale prospective studies are needed to prove our findings and provide more information about the causal inference and internal mechanisms of this association.

DATA AVAILABILITY STATEMENT

The dataset used in this study can be obtained from the corresponding authors by a reasonable requests.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Hainan branch of the Chinese People's Liberation Army General Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WJ, WC, ML, and YH contributed to the conception and design of the study. SW, YS, and JW managed the data and provided help in the data analysis. KH and SY performed the statistical analysis and wrote the first draft of the manuscript. All authors contributed to the study design, critically reviewed draft versions and provided important intellectual content during revisions, and accept accountability for the overall work.

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Cost of Illness, Quality of Life, and Work Outcomes in Active Ankylosing Spondylitis Patients Treated With Adalimumab in China

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Objectives: To access the cost of illness, quality of life and work limitation in active ankylosing spondylitis (AS) patients using adalimumab in China.

Methods: A prospective study was performed in 91 patients with active AS in China. Adult patients (aged ≥ 18 years) fulfilled the 1984 New York modified criteria of AS with the Bath Ankylosing Spondylitis Disease Activity Index ≥ 4 were enrolled. All participants received adalimumab (40 mg per 2 weeks) therapy and completed questionnaires about disease characteristics, quality of life and cost. Only patients with pay-work completed the Work Limitation Questionnaire and Work productivity and activity impairment questionnaire in AS. Factors associated with work outcomes were evaluated.

Results: A total of 91 patients with mean age of 30 years old (87.8% males) and mean disease duration of 10 years received adalimumab treatment for 24 weeks. The annual estimated cost of each patient was $37581.41 while the direct cost accounted for 84.6%. Seventy-eight percent of patients have a paid job with average work productivity loss of 0.28 measured by work limitation questionnaire, absenteeism and presenteeism were 10.22 and 43.86%, respectively, with a mean work productivity loss of 47.92% measured by Work productivity and activity impairment questionnaire in AS. Patients experienced significantly greater improvements after adalimumab treatment in presenteeism, absenteeism, work productivity, and quality of life.

Conclusions: The cost of AS patients with adalimumab therapy was high in China. Disease activity, physical function, quality of life, and work outcomes improved significantly after therapy.

Keywords: ankylosing spondylitis, work outcomes, cost of illness, quality of life, adalimumab

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INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disease characterized with low back pain, morning stiffness, peripheral joints and extra-articular manifestations. With a prevalence of 0.3% (1) and young age onset in China, AS may lead to limited physical function, impaired quality of life and increased economic

burden for society. Besides, more attention of the person's career, family and social life have been rose from both patients and doctors' perspective (2).

Work ability plays an important role in people's daily life and is a core component of family income. International guidelines from the Canadian Rheumatology Association and the Spondyloarthritis Research Consortium of Canada recommended that work activities should be included as part of disease monitoring (3). It has been reported that withdrawal from work and work instability were more common in AS patients than general population (4), even non-radiographic spondyloarthritis (SpA) patients experienced similar disease burden as (5). In China, spark researches focus on the work ability and indirect cost of AS (6), although many studies indicated that indirect cost including cost caused by work inability may contribute to a large scale of total cost (7).

The 2013 China Health Insurance Research Association (CHIRA) database including 1,299 patients with AS reported that only 4.5% received biologic agents with a mean direct medical cost of 14539RMB (8), indicating significant barrier for patients access to biologic agents because of higher cost and hospital-based reimbursement policy in China. Treatment with adalimumab in AS patients has been proved to be effective in symptom release, disease activity and functional remission in several studies (9, 10). Meanwhile, the improvements of quality of life and work outcomes (11, 12) have been observed after treated with adalimumab. However, the impact of adalimumab treatment on disease burden and work outcomes is rarely reported in Chinese AS patients. In this study, we aim to estimate the cost of illness, work ability, quality of life and related factors among AS patients treated with adalimumab in China.

METHODS

Study Design and Patients

This study is a prospective, open-label, post-authorization, observational study in AS patients, focusing on the effects of adalimumab on work productivity, and quality of life. Consecutive patients with active AS were enrolled between July 2017 and Jan 2018 at the Rheumatology clinic of third affiliated hospital of Sun Yat-sen University of China. Inclusion criteria includes fulfilling the 1984 modified New York criteria for AS, disease activity measured by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) $\geq$4 after treated with at least 4 weeks' full dose of non-steroidal anti-inflammatory drugs (NSAIDs). Exclusion criteria includes tumor, other rheumatic diseases and serious infections. This study was approved by the ethics board of third affiliated hospital of Sun Yat-sen University and all patients provided written informed consent before participation in this study. Patients received adalimumab 40 mg per 2 weeks for 24 weeks. Assessments including disease activity, physical function, work productivity and quality of life were performed at baseline, week 12 and 24.

Socio-Demographic and Clinical Characteristics

Socio-demographic characteristics including age, sex, marital status, household monthly income, employment, and education were collected. Clinical features such as disease duration, delayed diagnosis time, family history, BASDAI, Ankylosing Spondylitis Disease Activity Score (ASDAS), use of medications, Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Metrology Index (BASMI), lab examinations including C reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were recorded through face-to-face interview surveys and medical charts.

Cost of Illness (COI)

Direct cost and indirect cost were calculated to evaluate the COI of AS patients from societal perspective. Direct medical cost included inpatient cost, outpatient attendance, medication usage, examinations and physiotherapy while direct non-medical cost included transportation fees and paid helper for household. Indirect cost included unemployment, productivity loss from work, sick leave and early retirement due to disease. All cost in this study were presented with 2017 Chinese currency Renminbi (RMB) and exchanged for US dollar at the rate of 1: 0.15.

Work Outcomes

The Work limitation questionnaire (WLQ) (13) is a 25-items questionnaire exploring the degree of limitations experienced due to chronic health problems. Four scales including time management, physical demands, mental-interpersonal and output demands scales are calculated, and each range from 0 (limited none of the time)-100 (limited all of the time). Besides, a total WLQ index score can be calculated and converted into an estimate of productivity loss.

Work productivity and activity impairment questionnaire in AS (WPAI:SpA) (14) is a self-administered questionnaire for assessing the impact of disease on productivity during the previous 7 days. Four scores are derived including percentage of absenteeism (percentage work time missed because of problem), percentage of presenteeism (percentage impairment while working because of problem), an overall work impairment score (percentage overall work impairment because of problem), and percentage of impairment in activities performed outside of work. Higher scores indicate poorer work productivity and greater activity impairment due to AS.

Health-Related Quality of Life (QOL)

EuroQol-5D (EQ-5D) and Ankylosing Spondylitis Quality of Life (ASQoL) were used to measure QOL of patients based on face-to-face interview. The EQ-5D (15) comprises of five dimensions including mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and a visual analog scale (VAS) ranging from 0 (worst imaginable health) to 100 (best imaginable health) was used to rate health status that day. A health-state utility is calculated using the Chinese-specific values set and ranged from −0.39 (the worst health state) to 1 (full health) (16). The mean minimally important difference (MID) for the EQ-5D was reported to be 0.074 (17). ASQoL is an 18-items disease specific

TABLE 1 | Baseline socio-demographic and clinical characteristics of active ankylosing spondylitis patients treated with adalimumab ($n = 91$).

Characteristics	Mean (SD)
Age (year)	30.58 (7.76)
Sex (male), n (%)	79 (87.78%)
Marital status, n (%)	
Single	44 (48.35%)
Married	46 (50.55%)
Divorced	1 (1.1%)
Education, n (%)	
Middle school or less	25 (27.47%)
High school	36 (39.56%)
College or more	30 (32.97%)
Employment, n (%)	71 (78.02%)
Work productivity loss (0–1)	0.28 (0.28)
WAPI:SpA	
Absenteeism	10.22% (19.44%)
Presenteeism	43.86% (22.48%)
Work productivity loss	47.92% (25.81%)
Activity impairment	48.57% (22.02%)
Disease duration (year)	9.99 (6.93)
Delayed diagnosis time (year)	3.62 (4.69)
HLA-B27 positive, n (%)	78 (85.71%)
Positive family history, n (%)	33 (36.26%)
BASDAI (0–10)	5.31 (1.02)
BASFI (0–10)	4.23 (1.92)
BASMI (0–10)	2.98 (2.47)
ASDAS-CRP	3.54 (0.80)
ASQoL	9.1 (3.81)
EQ-5D	0.58 (0.22)
CRP	23.89 (19.82)
ESR	29.08 (21.90)
Biologic agents used before, n (%)	56 (61.54%)

SD, Standard Deviation; WPAI:SpA, Work productivity and activity impairment questionnaire in AS; HLA-B27, Human leukocyte antigen-B27; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; ASDAS, Ankylosing Spondylitis Disease Activity Score; ASQoL, Ankylosing Spondylitis Quality of Life; EQ-5D, EuroQol-5 Dimensions; CRP, C-Reactive Protein; ESR, Erythrocyte Sedimentation Rate.

questionnaire related to symptoms, functions and disease-related concerns in AS patients (18). A total score was calculated and ranged from 0 to 18, which higher score indicates poor QOL.

Statistical Analysis

Quantitative data were summarized as mean and SD for normal distributions. Summary statistics such as frequency and percentage were used for categorical variables. *T*-test was used to evaluate the change of costs and QOL between baseline and treatment. Regression analysis including univariable and multivariable generalized linear regressions was used to test the effect of related factors on presenteeism, absenteeism, and work productivity loss. Variables with $P < 0.1$ in the univariable linear regressions were included in the subsequent multivariable regression analyses. Factors with $P < 0.05$ in the multivariable regression were considered statistically significant. Results were reported as regression coefficients with 95% confidence interval. All tests were two-sided and $P < 0.05$ was considered statistically significant. Stata version 12.0 was used to perform statistical analyses.

TABLE 2 | Direct and indirect cost of AS patients using adalimumab in China (dollar).

	Mean (SD)	% of total cost
Direct cost	31794.57 (2396.79)	84.60%
Inpatient cost	22.79 (166.62)	0.06%
Outpatient attendance	4.57 (17.69)	0.01%
Medications	27685.39 (304.84)	73.67%
Examinations	991.86 (339.87)	2.64%
Physiotherapy	10.59 (30.09)	0.03%
Non-medical cost	3079.37 (2300.89)	8.19%
Indirect cost	5786.84 (7005.23)	15.39%
Productivity loss	3049.64 (3065.87)	8.11%
Sick leave	2737.19 (6429.79)	7.28%
Total cost per year	37581.41 (8276.86)	100%

SD, Standard Deviation.

RESULTS

Baseline Characteristics

A total of 91 patients were included during Jan 2017 to Jun 2018 in third affiliated hospital of Sun Yat-sen University. The average age of patients was 30.6 years with a mean disease duration of 10 years, and 87.8% of them were male. The mean BASDAI and BASFI score were 5.31 ± 1.02 and 4.23 ± 1.92, respectively. Quality of life (QOL) measured with EQ-5D and ASQoL was 0.58 and 9.1, respectively (demographics of this sample are presented in **Table 1**). The mean (SD) activity impairment of all patients due to ill-health was 48.57% (22.02%).

Cost of Illness

The mean COI per patient per year was 37581.41 dollars. Of the total, the percentage of direct cost was 84.6% and most of them amounted to adalimumab treatment. Of the indirect cost, productivity loss accounts for 52.7% (**Table 2**). The mean COI per patient per year to improve one unit of QOL/BASDAI/ASDAS is 42835/16753.68/4742.59 dollars, respectively.

Improvements in Disease Activity, Quality of Life, and Work Status After Adalimumab Treatment

The improvements in BASDAI and ASDAS from baseline to week 24 were from 5.31 to 2.21 and from 3.54 to 1.53, respectively, in AS patients treated with adalimumab. Reduction of activity impairment was observed by study end in all patients. There were significant differences in change of ASQoL (change, 3.89 [95%CI, 3.06 to 4.71]; $P < 0.0001$) and EQ-5D (change, −0.19 [95%CI,

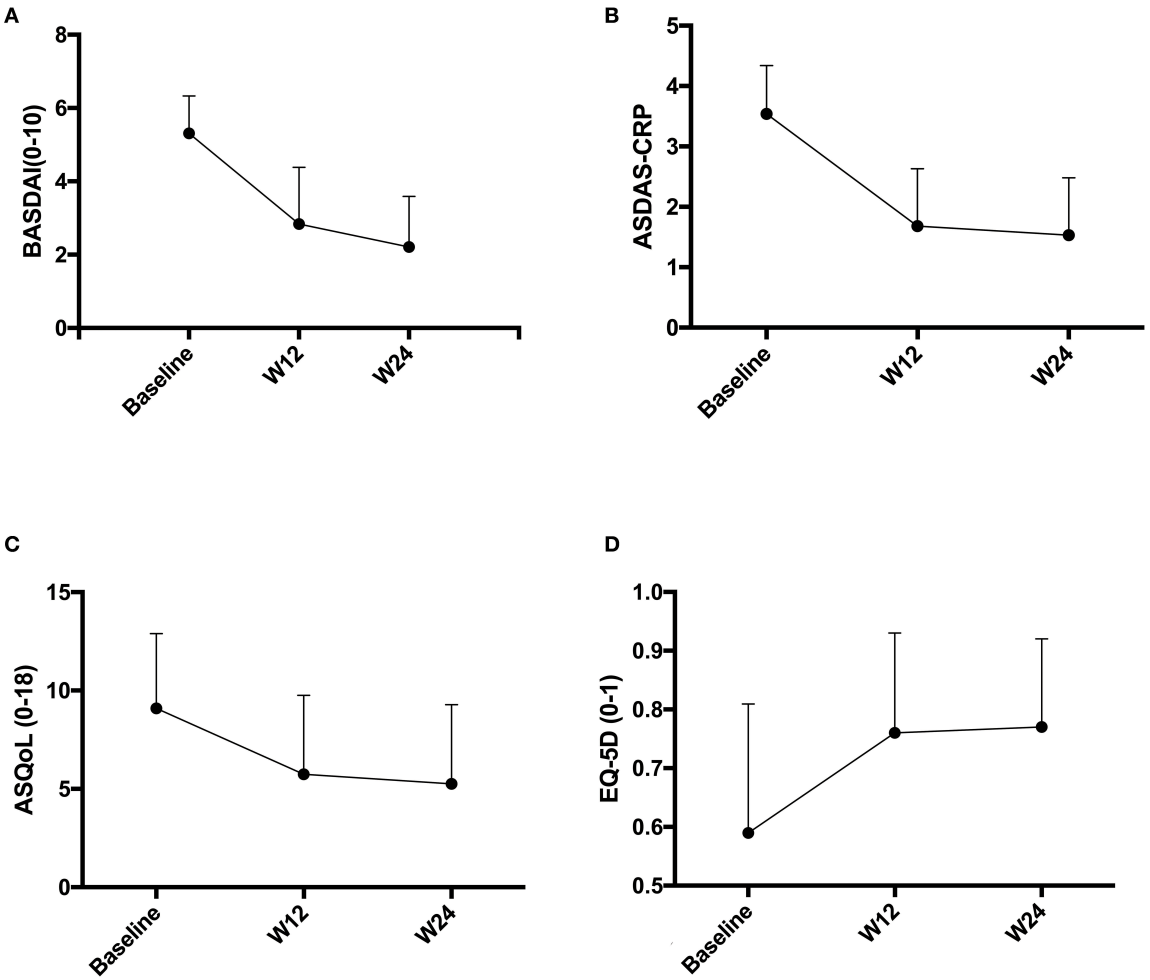

FIGURE 1 | (A–D) Disease activity and quality of life change before and after adalimumab treatment. BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ASDAS, Ankylosing Spondylitis Disease Activity Score; ASQoL, Ankylosing Spondylitis Quality of Life; EQ-5D, EuroQol-5 Dimensions.

−0.24 to −0.31]; $P < 0.0001$) scores from baseline and 24 weeks (**Figure 1**). Significant differences were found in work outcomes including absenteeism, presenteeism and work productivity loss at week 24 when compared with baseline (**Figure 2**).

Work Outcomes and Related Factors at Baseline

Of the total 91 patients, 78.02% ($n = 71$) of patients were employed, mean (SD) work productivity loss measured by WLQ was 0.28 (0.28) due to disease. By using WAPI:SpA, mean (SD) absenteeism, presenteeism and work productivity loss were 10.22% (19.44%), 43.86% (22.48%), and 47.92% (25.81%), respectively.

In univariable analysis, age, marriage, education, ASDAS, QOL, CRP and ESR were associated with work productivity loss measured by WLQ at baseline. While only age (β: −0.01, $P = 0.049$) and education (β: −0.1, $P = 0.03$) remained significant in multivariable analysis. **Table 3** show factors associated with WPAI scores at baseline. Disease duration was negatively associated with absenteeism (β: −0.71, $P = 0.03$), presenteeism (β: −0.77, P =0.04) and work productivity loss (β: −0.77, $P = 0.02$) in univariable analysis. These associations with absenteeism (β: −0.72, $P = 0.03$), presenteeism (β: −0.92, $P = 0.04$) were significant in multivariable analysis. BASFI was positively associated with activity impairment (β: 7.68, $P < 0.01$), presenteeism (β: 6.28, $P < 0.01$) and work productivity loss (β: 6.28, $P < 0.01$) in univariable analysis. In multivariable analysis, the associations with activity impairment (β: 4.94, $P < 0.01$), presenteeism (β: 4.63, $P < 0.01$), and work productivity loss (β: 5.35, $P < 0.01$) remained statistically significant. ASQoL was positively associated with activity impairment (β: 3.06, $P < 0.01$; β: 1.77, $P < 0.01$), presenteeism (β: 2.83, $P < 0.01$; β: 2.0, $P < 0.01$), and work productivity loss (β: 3.19, $P < 0.01$; β: 2.33, $P < 0.01$) in both univariable and multivariable analysis, respectively.

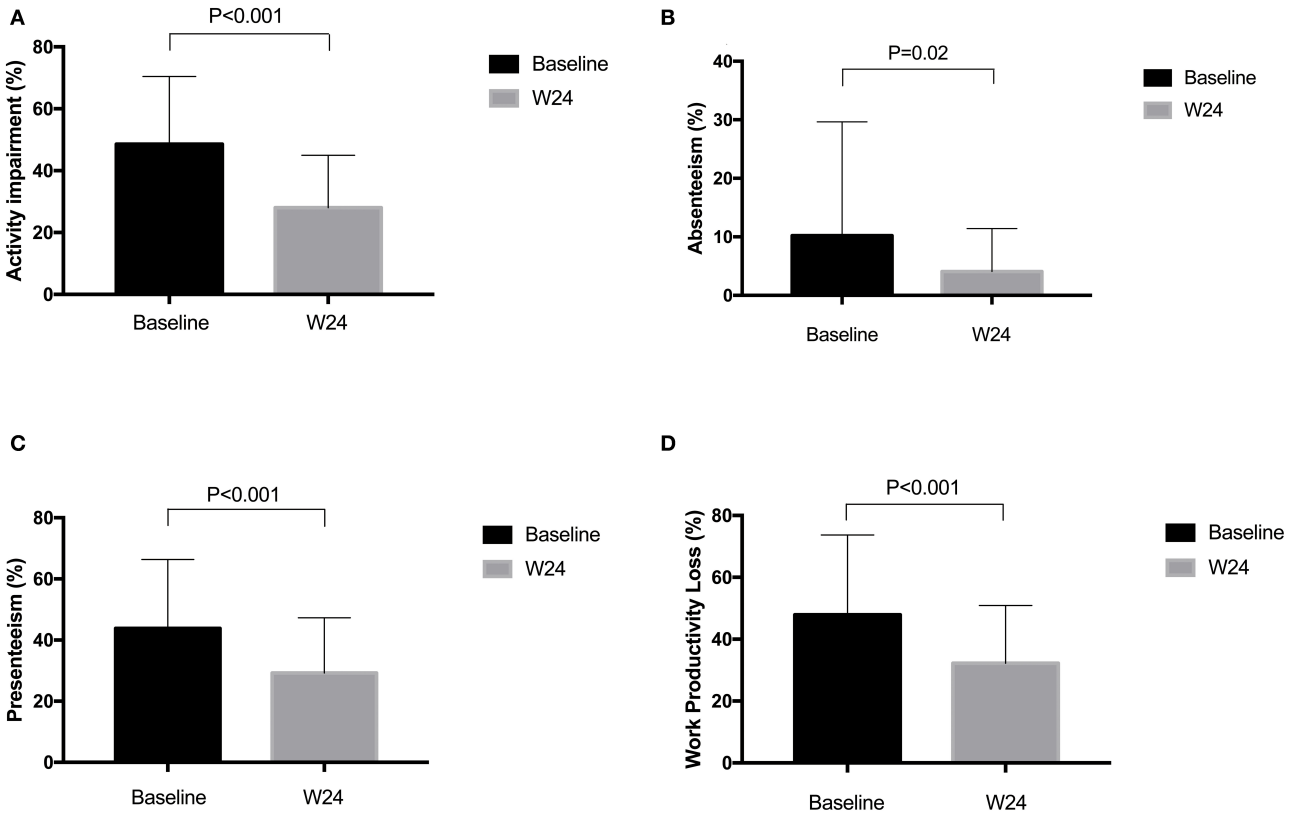

FIGURE 2 | (A–D) Change of WPAI:SpA scores before and after adalimumab treatment. WPAI:SpA, Work productivity and activity impairment questionnaire in AS.

DISCUSSION

In this study, marked improvements were observed in symptoms and physical function after adalimumab therapy, as well as QOL and work outcomes. These findings are consistent with other studies reporting improvement on QOL and work outcomes in AS patients treated with biological therapy (12, 19, 20). Besides, we found that disease duration, BASFI and ASQoL were associated with presenteeism. Disease duration was associated with absenteeism. Work productivity loss was related to age, education, BASFI and ASQoL. The strength of current study includes being a prospective study to evaluate cost of illness and work outcomes after adalimumab treatment of AS patients in China. Besides, this is the first study to explore factors associated with work outcomes in Chinese AS patients.

AS-related healthcare cost varied in different countries and it is difficult to compare work-related cost beyond the country of origin. In Brazil, a population-based cohort study reported 78% of AS patients initiating treatment with anti-TNF drugs (free of charge) with a median monthly cost per capita of $1650 (21). An UK research reported that the total cost of AS was estimated at €19016 per patient per year and the majority of the cost was a result of work-related costs (7). In this study, a mean COI per patient per year of $37581.41 were estimated with most of it accounted to adalimumab treatment, which may be because patients enrolled in this study had high disease activity and the fee of adalimumab was not covered by government insurance. When compared with a GDP per capita of $8800 in 2017 of China, the annual total cost of Chinese AS patients treated with adalimumab was still huge. Effective treatment can reduce disease severity, increase physical function and quality of life, improve work capacity and productivity, thus in return alleviating economic burden in the long term. Previous studies conducted in Europe (12) and Australia (22) showed decreased healthcare resource utilization and increased labor force participation rate after adalimumab therapy. In this study, improvement of work outcomes was observed after adalimumab treatment while no significant difference was found in total cost and indirect cost, indicating that it may take time to observe the long-term benefit.

Impact on work productivity in AS patients has drawn attention of researchers and doctors all around the world. A three-times more likelihood to withdraw from work and an employment rates varying from 55 to 89% in different countries in AS patients had been reported in several studies (23, 24). Positive effect of biological therapy on work outcomes have been proven in AS and axial SpA patients (11, 12, 19, 20). Study conducted in Europe reported that presenteeism decreased from

TABLE 3 | Clinical characteristics associated with WPAI:SpA scores in AS patients at baseline.

	Activity impairment		Absenteeism		Presenteeism		work productivity loss	
	Univariable β (95% CI)	**Multivariable β (95% CI)**	**Univariable β (95% CI)**	**Multivariable β (95% CI)**	**Univariable β (95% CI)**	**Multivariable β (95% CI)**	**Univariable β (95% CI)**	**Multivariable β (95% CI)**
Age	−0.11 (−0.82, 0.59)	NA	−0.48 (−1.1, 0.15)	NA	−0.69 (−1.40, 0.01)	−0.27 (−1.07, 0.53)	−0.69 (−1.40, 0.01)	−0.58 (−1.54, 0.37)
Marriage	−2.65 (−12.67, 7.36)	NA	−6.26 (−15.14, 2.61)	NA	−3.73 (−13.98, 6.51)	NA	−3.74 (−13.98, 6.51)	NA
Education	−0.41 (−7.2, 6.37)	NA	3.5 (−2.6, 9.61)	NA	−0.88 (−7.83, 6.07)	NA	−0.88 (−7.83, 6.07)	NA
Disease duration	−0.002 (−0.71, 0.70)	NA	−0.71 (−1.35, −0.07)	**−0.72 (−1.37, −0.08)**	−0.77 (−1.49, −0.04)	**−0.92 (−1.77, −0.06)**	−0.77 (−1.49, −0.04)	−0.90 (−1.93, 0.12)
BASDAI	8.98 (4.19, 13.78)	2.08 (−4.12, 8.28)	3.56 (−1.04, 8.17)	NA	5.68 (0.47, 10.88)	−2.90 (−9.29, 3.48)	5.68 (0.47, 10.88)	−1.18 (−8.70, 6.33)
BASFI	7.68 (5.49, 9.87)	**4.94 (1.69, 8.19)**	1.49 (−1.06, 4.06)	NA	6.28 (3.76, 8.79)	**4.63 (1.28, 7.98)**	6.28 (3.76, 8.79)	**5.35 (1.48, 9.22)**
BASMI	3.30 (1.31, 5.28)	−0.52 (−2.72, 1.68)	−0.29 (−2.22, 1.64)	NA	1.22 (−0.95, 3.39)	NA	1.21 (−0.95, 3.38)	NA
ASDAS	13.45 (7.49, 19.41)	0.25 (−9.52, 10.01)	1.28 (−4.81, 7.36)	NA	8.94 (2.33, 15.54)	1.70 (−6.67, 10.08)	8.94 (2.33, 15.55)	−3.09 (−13.29, 7.10)
ASQOL	3.05 (1.87, 4.24)	**1.76 (0.52, 3.02)**	1.02 (−0.19, 2.23)	0.94 (−0.40, 2.28)	2.83 (1.57, 4.09)	**1.99 (0.65, 3.35)**	2.83 (1.57, 4.09)	**2.33 (0.80, 3.86)**
EQ-5D	−37.21 (−60.95, −13.48)	−2.25 (−29.98, 25.48)	−19.55 (−41.49, 2.39)	−8.82 (−32.87, 15.21)	−37.46 (−61.84, −13.08)	−5.92 (−36.12, 24.27)	−37.46 (−61.84, −13.08)	−4.62 (−39.27, 30.02)
CRP	0.34 (0.05, 0.62)	0.26 (−0.13, 0.66)	−0.002 (−0.27, 0.27)	NA	0.21 (−0.09, 0.51)	NA	0.21 (−0.09, 0.51)	NA
ESR	0.2 (−0.03, 0.44)	−0.07 (−0.31, 0.18)	0.12 (−0.09, 0.34)	NA	0.22 (−0.02, 0.46)	0.007 (−0.24, 0.26)	0.22 (−0.02, 0.46)	0.14 (−0.16, 0.43)

CI, Confidence Interval; NA, Not Available (only variables with P < 0.1 in the univariable linear regressions were included in the subsequent multivariable regression analyses); WPAI:SpA, Work productivity and activity impairment questionnaire in AS; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; ASDAS, Ankylosing Spondylitis Disease Activity Score; ASQoL, Ankylosing Spondylitis Quality of Life; EQ-5D, EuroQol-5 Dimensions; CRP, C-Reactive Protein; ESR, Erythrocyte Sedimentation Rate. Bold values are significant difference.

56.6 to 20.1%, absenteeism decreased from 15.6 to 6.4% and total work productivity impairment decreased from 59.9 to 22.1% after 1 year's adalimumab treatment (11). In this study, similar results were found that presenteeism decreased from 43.9 to 29.2%, absenteeism decreased from 10.2 to 4.1% and total work productivity impairment decreased from 47.9 to 32.2% after 6 months' therapy. In another review (20), no significant difference was found in absenteeism after biologic treatment. Absenteeism is a late stage in terms of work impairment that is not reversed by biological therapy alone but likely also to be influenced by contextual factors. Besides, many other reasons including economic setting and social security system may contribute to this difference.

Factors such as age (25), ethnicity (26), disease duration, disease activity (27, 28), physical function (28, 29), and quality of life (28) were reported to significantly affect work outcomes in other studies. Disease duration, BASFI and ASQoL were found to be related to work outcomes in this study, which concurs with studies done in Western (27, 29) and Asia populations (28). The current study showed no significant difference was found between disease activity (such as BASDAI or ASDAS) and work outcomes, which was inconsistent with other studies (27, 28) and the reason may be that only patients with BASDAI $\geq$4 were included in this study. However, controlling disease activity is still of importance to improve work outcomes in AS patients.

This study has limitations such as observational design which is unable to determine causality between factors and work outcomes. Secondly, the sample of this study was relatively small and only patients with high disease activity were included. In addition, the follow-up was restricted to 6 months and long-term effect of adalimumab on work outcome and cost was not reported in this study. Further study with larger samples and longer follow-up should be conducted in order to explore the long-term effect of biological therapy on cost and work outcomes in SpA and AS patients.

In conclusion, disease burden of AS patients with adalimumab therapy was huge in China. After 6 months' adalimumab therapy, improvement of disease activity, physical function, QoL and work outcomes was observed. Long disease duration, poor physical function and low quality of life were found to be related to poor work outcomes. Improvement of the social insurance system, early diagnosis and patient education would help to alleviate work disability in AS patients.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of third affiliated hospital of Sun Yet-sen University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JG: had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. JG, LT, and YX: study concept, design, and drafting the manuscript. All authors: acquisition, analysis, or interpretation of data, critical revision of the manuscript for important intellectual content, and final approval of the article.

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

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Can We Apply WHOQOL-AGE to Asian Population? Verifying Its Factor Structure and Psychometric Properties in a Convenience Sample From Taiwan

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Objectives: To translate and validate a recently developed quality of life instrument (WHOQOL-AGE) on geriatric population into Chinese.

Method: Using cross-sectional observational design, the WHOQOL-AGE was conducted among older people through interview. Confirmatory factor analysis (CFA) was used to examine the factor structure and multigroup CFA used to examine the measurement invariance.

Results: Through convenience sampling, 522 older adults (mean age = 73.42) participated in the study. Among them, 194 were males, 213 had an educational level at primary school or below, 398 were residing in the community, and 307 were aged 70 years or above. A bifactor structure (items Q1–Q8 are embedded in the factor 1; items Q9–Q13 embedded in the factor 2; and all the items embedded in an additional construct of QoL) was confirmed by the CFA in both the entire sample ($\chi^2 = 25.4$; df = 51; $p = 0.999$) and the subgroup sample with age 70 years or above ($\chi^2 = 25.28$; df = 51; $p = 1.000$). Multigroup CFAs results supported the measurement invariance for the WHOQOL-AGE across genders, having different educational levels, living in different settings and age groups. It also shows good known-groups validity.

Conclusions: The promising psychometric properties of the WHOQOL-AGE were found in our convenience sample of older Taiwanese. The supported measurement invariance indicates that the older people in different conditions of gender, educational level, and living setting interpret the WHOQOL-AGE similarly. However, our results should be interpreted with cautious because of the sample representativeness.

Keywords: Asia, confirmatory factor analysis - CFA, elders, measurement invariance (MI), quality of life

INTRODUCTION

Due to modern medicine and improved technology, life expectancy has been extended worldwide (1). How to maintain quality of life (QoL), especially those aged over 65 years, has become a global concern (2). The World Health Organization (WHO) proposed the concept of QoL and developed corresponding measures in the 1990s (3). Specifically, QoL instruments are based on patient-reported outcomes (PROs), a primary outcome proposed by the U.S. Food and Drug Administration (4) to help healthcare professionals make clinical decisions using clients' feelings (5). With such unique characteristics, the number of QoL instruments has been growing in the literature, including those used in the elderly. Indeed, several generic QoL instruments have been verified as useful for assessing QoL among the older population (2, 6, 7).

Although generic QoL instruments have the advantage of comparing people with different conditions (8), some criticisms have been made. Taking the elderly population as an example, generic QoL instruments may not capture the most important aspects of QoL for the elderly (e.g., older people usually have worse hearing and vision than other adults, and this aspect is not included in the generic QoL instruments). Therefore, some researchers have developed more appropriate QoL instruments for the older population. For example, the Elderly Quality of Life Index (EQOLI) was developed in Brazil for longitudinal assessments of QoL change and potential impacts from behavior, intervention, and treatment (9, 10). The Quality of Life Scale for Elderly (QOLS-E) was developed in Japan using a sample of institutionalized people (11). The WHOQOL-OLD was developed as a supplementary module of the WHOQOL-BREF (12, 13).

However, a time concern has been raised for both the EQOLI and WHOQOL-OLD. Specifically, the EQOLI has 43 items, and the WHOQOL-OLD should be used together with the 26-item WHOQOL-BREF. Therefore, completing the EQOLI or WHOQOL-OLD plus WHOQOL-BREF may be a substantial burden for older people (14). Moreover, the QOLS-E was found to have somewhat low internal consistency (11). As a result, there is a need to develop a QoL instrument for older people with satisfactory psychometric properties.

In order to overcome the aforementioned problems, Caballero et al. (15) developed a stand-alone QoL instrument that assesses older people's QoL: WHOQOL-AGE. The 13-item WHOQOL-AGE was designed according to the characteristics of aging populations and was developed by integrating previous WHOQOL instruments, including the EUROHIS-QOL and the WHOQOL-OLD short form (12). The WHOQOL-AGE shows promising psychometric properties in nationally representative samples from Finland, Poland, and Spain (15). Moreover, older people from these three European countries somewhat interpreted the WHOQOL-AGE similarly (16). With good psychometric properties and a short administration time, the WHOQOL-AGE seems to be a feasible and appropriate instrument for use in large-scale population studies and busy clinical settings. Unfortunately, current literature shows that only two European studies (15, 16) have investigated the psychometric properties of the WHOQOL-AGE. Apart from the languages spoken in Finland, Poland, and Spain, the WHOQOL-AGE is not available in any other languages. Given that comparing QoL between people living in different countries requires the use of the same instrument, translating the WHOQOL-AGE into other languages is needed. Moreover, psychometric properties highly rely on the tested population; therefore, a sound instrument should be tested using different psychometric methods across different populations (8). If the requirements can be fulfilled, the psychometric evidence of the WHOQOL-AGE can be accumulated.

In addition to the lack of versions in other languages, the factor structure of the WHOQOL-AGE has not yet been confirmed, and the measurement invariance of the WHOQOL-AGE has never been examined across genders, educational levels, settings, and age groups. Although Santos et al. (16) applied confirmatory factor analysis (CFA) to examine whether the WHOQOL-AGE fits a two-factor model or a bifactor model better (for detailed information of the bifactor model, see Statistical Analysis section below), a model with cross-loading on item Q1 (How would you rate your quality of life?) found by Caballero et al. (15) was not compared. Santos et al. (16) found that the bifactor model fits better than the two-factor model and further demonstrated the partial invariance of the WHOQOL-AGE across countries in the bifactor model. However, it is unclear whether the WHOQOL-AGE has invariant factor structures across other important grouping factors. Specifically, gender, education, living context, and age usually impact an individual's cognition and, thus, results in different interpretations for the same item. Interpreting the items in a different way between groups may result in measurement bias between groups. Use education with the Q1 item (How would you rate your quality of life?) as an example. Those graduated from elementary school may think about basic needs (e.g., eating and living) when rating this item; those graduated from university may think about self-actualization (e.g., being respected). However, without the measurement invariance testing, we do not have the evidence to indicate whether the WHOQOL-AGE has the problem of measurement invariance in certain factors. Therefore, it is important to examine the measurement invariance of the WHOQOL-AGE across genders (male vs. female), educational levels (primary school or below vs. junior high school or above), living contexts or settings (community vs. institution, such as a nursing home), and age groups (below 70 vs. 70 years or above) after confirming its factor structure.

In order to fill the gap in the literature regarding the assessment of QoL among the elderly, the present study had the following aims. First, we aimed to translate the WHOQOL-AGE for an East Asian sample (i.e., Taiwanese). Second, to verify the factor structure of the WHOQOL-AGE among the Taiwanese elderly. After ensuring the factor structure of the WHOQOL-AGE, measurement invariance was examined to understand whether elderly people with different genders, educational levels, living settings, and ages interpret the WHOQOL-AGE differently.

METHODS

Participants and Procedure

The main survey was conducted between October 2016 and March 2017. Participants were elderly persons aged 50 years and over who consented to be interviewed. Those who could not communicate (e.g., those with poor cognitive function or severe hearing impairment or who could not understand spoken Mandarin or Taiwanese) were excluded. Convenience sampling, mainly from the southern region of Taiwan (79%), was conducted to collect data from two groups: relatively healthy participants living in communities; patients or residents living in hospitals or long-term care (LTC) facilities with mild-to-severe dependency. All the participants were interviewed by experienced interviewers who fully understood the study aims. Interviews were conducted in the participants' homes, a quiet space nearby (for those living in the community), or the institution (for those living in an institution). The average time of each interview was about 10 min. Before collecting data, written informed consent was obtained from each participant. The study (A-ER-104-384) was approved by the Human Research Ethics Committee of National Cheng Kung University Hospital, and there were no conflicts of interest between the authors and the goals of this study. In total, 522 valid questionnaires were collected, including 398 (76.2%) from the communities and 124 (23.8%) from the institutions.

Instruments: WHOQOL-AGE and Barthel Index

The WHOQOL-AGE contains 13 items and was developed from several European countries with nationally representative samples (15, 16). All the items are rated using a five-point Likert scale, the same scale that is used in the WHOQOL-BREF (17). Moreover, for the WHOQOL-AGE, items Q9–Q13, responses are classified as unipolar (e.g., *not at all* to *completely*) and for items Q1–Q8, responses are classified as bipolar (e.g., *very bad* to *very good*). Different factor structures have been proposed for the WHOQOL-AGE (for detailed information, please see Statistical Analysis section below), and the scoring method was proposed by Caballero et al. (15). In brief, a higher score indicates a better level of QoL. The psychometric properties of the WHOQOL-AGE have been verified in European countries: Cronbach's $\alpha = 0.84$ to 0.91 (15); partial invariance across three European countries (Finland, Poland, and Spain) (16).

Translation Procedure of the WHOQOL-AGE

Given that some WHOQOL-AGE items are identical to items in the WHOQOL-BREF and the Taiwan version of the WHOQOL-BREF has strong psychometric properties (17), those identical items were directly retrieved from the WHOQOL-BREF Taiwan version without translation. For the other WHOQOL-AGE items, they were first translated from English into Chinese by a bilingual translator and then back-translated into English by another bilingual translator. A bilingual expert in gerontology fine-tuned the Chinese WHOQOL-AGE (an interim version) after reviewing the forward translation, back translation, and the original English version of the WHOQOL-AGE. The interim version was then discussed and reviewed. The face-validity of the Chinese WHOQOL-AGE was confirmed by the experts committee.

Statistical Analysis

Participants' characteristics were first analyzed using descriptive statistics. Independent *t*-tests and χ^2 tests were used to compare the characteristics between participants living in the community and those living in an institution.

Four structural models were further tested using CFA. The four models included a one-factor model (Model 1), two two-factor models (Models 2 and 3), and a bifactor model (Model 4). Specifically, Model 1 had all items loaded on the same construct of QoL. Model 2, proposed by Santos et al. (16), had items Q1–Q8 embedded in Factor 1 and items Q9–Q13 embedded in Factor 2. Model 3, suggested by Caballero et al. (15), was a two-factor model with cross-loading on item Q1: items Q1–Q8 were embedded in Factor 1; items Q1 and Q9–Q13 were embedded in Factor 2. Model 4 was a bifactor model proposed by Santos et al. (16), in which items Q1–Q8 were embedded in Factor 1; items Q9–Q13 embedded in Factor 2, and all items embedded in an additional construct of QoL (Model 4).

The four models were examined using several fit indices to indicate whether the data fit these models. The fit indices included a χ^2 test (in which a nonsignificant finding indicates fit), a comparative fit index (CFI; in which a value higher than 0.9 indicates fit), a Tucker-Lewis index (TLI; in which a value higher than 0.9 indicates fit), a standardized root mean square residual (SRMR; in which a value <0.08 indicates fit), and a root mean square error of approximation (RMSEA; in which a value <0.08 indicates fit) (18–20). Apart from the fit indices, the four models were compared using the χ^2 difference test. Specifically, if a model had a significantly lower χ^2 than another model, the former model had better fit (21). If some models had similar fits (i.e., no significant difference in the χ^2 difference test), the simplest structure was viewed as the best model given the parsimony principle.

The best model determined using the χ^2 difference test and the structure complexity was further used to examine measurement invariance across different conditions, including gender (male vs. female), educational level ($\leq$elementary vs. $\geq$junior high), setting (community vs. institution), and age group (<70 vs. ≥ 70 years). Four sets of multigroup CFAs with nested models were applied to determine whether measurement invariance was supported across gender, educational level, setting, and age group. For each set of multigroup CFAs, there were three nested models, including a configural model, a model that constrained all the loadings to be equal between subgroups, and a model that constrained all the loadings and item intercepts to be equal between subgroups (22, 23). The three nested models were then compared using the χ^2 difference test, the ΔCFI, and the ΔRMSEA. A nonsignificant χ^2 indicated invariance across subgroups; however, the χ^2 test is not recommended for use when sample size is large (i.e., $n > 200$) (18). Alternatively, $\Delta\text{CFI} > -0.01$ and $\Delta\text{RMSEA} < 0.01$ also indicated invariance across subgroups (24, 25).

TABLE 1 | Participants' characteristics.

Characteristic	Total sample, $N = 522$	Sample aged over 70, $N = 307$
Age (years)		
Mean (SD)	73.42 (10.76)	80.72 (6.78)
Range	50–105	70–105
Age		
Below 65 years	112 (21.5)	0 (0.0)
65 years and above	406 (77.8)	307 (100.0)
Missing	4 (0.7)	0 (0.0)
Gender, *n* (%)		
Male	194 (37.2)	131 (42.7)
Female	328 (62.8)	176 (57.3)
Marital status, *n* (%)		
Single	18 (3.4)	6 (2.0)
Married	299 (57.3)	140 (45.6)
Separated/Divorced	24 (4.6)	9 (2.9)
Widowed	177 (33.9)	151 (49.2)
Missing	4 (0.8)	1 (0.3)
Education, *n* (%)		
Primary school or below	213 (40.8)	169 (55.0)
Junior high school (9th grade) or above	305 (58.4)	138 (45.0)
Missing	4 (0.8)	0 (0.0)
Living alone, *n* (%)		
Yes	91 (17.4)	64 (20.8)
No	431 (82.6)	243 (79.2)
Setting, *n* (%)		
Community	398 (76.2)	209 (68.1)
Institution	124 (23.8)	98 (31.9)

TABLE 2 | Model comparisons.

Model	χ^2 (df)/*p*	CFI[e]	TLI[e]	SRMR[e]	RMSEA[e]	90% CI for RMSEA
			Entire sample			
M1[a]	91.77 (65)/0.016	0.994	0.993	0.055	0.029	0.013, 0.042
M2[b]	82.97 (64)/0.056	0.996	0.995	0.052	0.024	0.000, 0.038
M3[c]	82.49 (63)/0.050	0.995	0.994	0.052	0.025	0.000, 0.039
M4[d]	25.40 (51)/0.999	1.000	1.009	0.029	0.000	0.000, 0.000
			Sample aged over 70 years			
M1[a]	71.34 (65)/0.275	0.997	0.997	0.060	0.018	0.000, 0.041
M2[b]	67.26 (64)/0.366	0.999	0.998	0.059	0.013	0.000, 0.038
M3[c]	65.14 (63)/0.402	0.999	0.999	0.058	0.011	0.000, 0.037
M4[d]	25.28 (51)/0.999	1.000	1.016	0.035	0.000	0.000, 0.000

[a]*Model 1 is a one-factor model that all items loaded on the same construct (QoL).*
[b]*Model 2 is a two-factor model proposed by Santos et al. (16): items Q1–Q8 in the factor 1; items Q9–Q13 in the factor 2.*
[c]*Model 3 is a two-factor model suggested by Caballero et al. (15): items Q1–Q8 in the factor 1; items Q1, Q9–Q13 in the factor 2.*
[d]*Model 4 is a bifactor model proposed by Santos et al. (16): items Q1–Q8 in the factor 1; items Q9–Q13 in the factor 2; all the items embedded in an additional construct of QoL.*
[e]*CFI, comparative fit index; TLI, Tucker-Lewis index; SRMR, standardized root mean square residual; RMSEA, root mean square error of approximation.*

Because participants aged 70 years or above may have different perceptions on QoL from those aged below 70 years, we consider testing the WHOQOL-AGE only on those aged 70 years or above as a sensitivity analysis. The same sets of CFAs and multigroup CFAs were analyzed for the subgroup with age equal to or older than 70 years. However, multigroup CFAs on setting and age were not performed in the subgroup with age equal to or older than 70 years.

All the CFAs, including multigroup CFAs, were estimated using the diagonally weighted least square (DWLS) to tackle the Likert type responses in the WHOQOL-AGE (26). Cronbach's α and McDonald's ω were then applied to the confirmed structure of the WHOQOL-AGE to understand its internal consistency. A Cronbach's $\alpha > 0.7$ and a McDonald's $\omega > 0.7$ were considered as acceptable (26, 27). Moreover, known-group validity was tested to understand whether the WHOQOL-AGE could effectively distinguish the different levels of QoL between older people living in the community and those living in an institution. An independent *t*-test with effect size calculation (i.e., Cohen's *d*, where 0.2, 0.5, and 0.8 indicated small, moderate, and large effect size) was used for the known-group validity. According to our prior experience, interaction with the geriatric population, and the literature (28), we hypothesized that older people living in the community would have better QoL compared to those living in an institution.

All the analyses were done using the R software (R-3.5.1 for Windows). Additionally, CFAs and multigroup CFAs were performed using the lavaan package (http://lavaan.ugent.be/); Cronbach's α and McDonald's ω were calculated using the psych package (https://cran.r-project.org/web/packages/psych/index.html).

RESULTS

The mean age of the sample was 73.42 (SD = 10.46) years. Among the 522 participants, 194 (37.2%) were males, 213 (40.8%) had an educational level of primary school or below, and 398 (76.2%) were residing in a community. Additional demographic information is presented in **Table 1**. Moreover, **Table 1** presents the characteristics of our participants who were aged 70 years or above ($N = 307$).

All the proposed models (in both the entire and the subgroup samples) had satisfactory fit indices (CFI = 0.994–1.000, TLI = 0.993–1.009, SRMR = 0.029–0.060, and RMSEA = 0.000–0.029). Moreover, all the models had nonsignificant χ^2 (p = 0.050–1.00), except for Model 1 in the entire sample ($p = 0.016$). When we used the χ^2 difference test to compare the four models, Model 4 significantly outperformed Models 1 ($p < 0.001$), 2 ($p < 0.001$), and 3 ($p < 0.001$) in both the entire and the subgroup samples. Indeed, the fit indices of Model 4 were the best among all the proposed models (**Table 2**).

Measurement invariance was examined using the best-fitting model among the four proposed models (i.e., Model 4). As shown in **Table 3** (entire sample results) and **Table 4** (results from those aged 70 years or above), the χ^2 difference test

TABLE 3 | Measurement invariance of bifactor model across gender, educational level, and setting using entire sample.

	χ^2 or ($\Delta\chi^2$)	df or (Δdf)	*p*-value	CFI or (ΔCFI)[a]	RMSEA or (ΔRMSEA)[a]
Gender (male vs. female)					
1. Configural	41.25	102	1.00	1.000	0.000
2. Loadings constrained	65.02	125	1.00	1.000	0.000
3. Loadings and intercepts constrained	72.51	135	0.98	1.000	0.000
2. vs. 1.	(23.77)	(23)	0.42	(0.000)	(0.000)
3. vs. 2.	(7.49)	(10)	0.68	(0.000)	(0.000)
Educational level (≤elementary vs. ≥junior high)					
1. Configural	49.80	102	1.00	1.000	0.000
2. Loadings constrained	92.32	125	0.99	1.000	0.000
3. Loadings and intercepts constrained	104.67	135	0.98	1.000	0.000
2. vs. 1.	(42.52)	(23)	0.008	(0.000)	(0.000)
3. vs. 2.	(12.35)	(10)	0.26	(0.000)	(0.000)
Setting (community vs. institution)					
1. Configural	38.39	102	1.00	1.000	0.000
2. Loadings constrained	71.76	125	1.00	1.000	0.000
3. Loadings and intercepts constrained	77.91	135	1.00	1.000	0.000
2. vs. 1.	(33.37)	(23)	0.07	(0.000)	(0.000)
3. vs. 2.	(6.16)	(10)	0.80	(0.000)	(0.000)
Age (< 70 years vs. ≧ 70 years)					
1. Configural	52.54	102	1.00	1.000	0.000
2. Loadings constrained	80.23	125	0.999	1.000	0.000
3. Loadings and intercepts constrained	82.48	135	1.00	1.000	0.000
2. vs. 1.	(27.69)	(23)	0.23	(0.000)	(0.000)
3. vs. 2.	(2.25)	(10)	0.99	(0.000)	(0.000)

[a]*CFI, comparative fit index; RMSEA, root mean square error of approximation.*

TABLE 4 | Measurement invariance of bifactor model across gender, educational level, and setting using sample aged over 70 years.

	χ^2 or ($\Delta\chi^2$)	df or (Δdf)	*p*-value	CFI or (ΔCFI)[a]	RMSEA or (ΔRMSEA)[a]
Gender (male vs. female)					
1. Configural	41.96	102	1.00	1.000	0.000
2. Loadings constrained	63.22	125	1.00	1.000	0.000
3. Loadings and intercepts constrained	67.76	135	1.00	1.000	0.000
2. vs. 1.	(21.26)	(23)	0.57	(0.000)	(0.000)
3. vs. 2.	(4.54)	(10)	0.92	(0.000)	(0.000)
Educational level (≤elementary vs. ≥junior high)					
1. Configural	40.06	102	1.00	1.000	0.000
2. Loadings constrained	82.06	125	0.999	1.000	0.000
3. Loadings and intercepts constrained	91.69	135	0.998	1.000	0.000
2. vs. 1.	(42.00)	(23)	0.009	(0.000)	(0.000)
3. vs. 2.	(9.63)	(10)	0.47	(0.000)	(0.000)

[a]*CFI, comparative fit index; RMSEA, root mean square error of approximation.*

showed no significant differences across gender between the configural model and the constrained loadings model ($p = 0.42$ and 0.57) and between the constrained loadings model and the constrained loadings and intercepts model ($p = 0.68$ and 0.92). Although significant differences were found between the configural model and the constrained loadings model across educational levels ($p = 0.008$ and 0.009), both ΔCFI (0.000) and ΔRMSEA (0.000) supported invariant loadings across educational levels and settings. Given that the χ^2 test is sensitive to and easily significant in a large sample size (i.e., n>200), the ΔCFI and ΔRMSEA are the major indices to decide whether the measurement invariance is supported. The χ^2 difference test showed no significant differences across educational levels between the constrained loadings model and the constrained

loadings and intercepts model ($p = 0.26$ and 0.47). Furthermore, in the entire sample, no significant differences were found across settings and age groups between the configural model and the constrained loadings model ($p = 0.07$ and 0.23) and between the constrained loadings model and the constrained loadings and intercepts model ($p = 0.80$ and 0.99).

Because the measurement invariance of the WHQOL-AGE was supported, we used the confirmed structure (i.e., Model 4) to test the internal consistency of the WHOQOL-AGE. Specifically, the entire WHOQOL-AGE and the two factors in the WHOQOL-AGE were examined using both Cronbach's α and McDonald's ω. Cronbach's α was 0.90 for the entire WHOQOL-AGE, 0.84 for Factor 1, and 0.81 for Factor 2. McDonald's ω was 0.91 for the entire WHOQOL-AGE, 0.88 for Factor 1, and 0.86 for Factor 2. The known-group validity further showed that older people living in the community had a better WHOQOL-AGE total score (Mean ± SD = 3.52 ± 0.57) than those living in an institution (Mean ± SD = 3.16 ± 0.63; $t = 5.68$; $p < 0.001$) with a moderate effect size (Cohen's $d = 0.60$).

DISCUSSION

With the rapid growth of the aging population (29), using validated instruments to assess the elderly's QoL is deemed to be important. From the perspective of healthy aging, reducing the possibilities of disease for older people can ease the caregiving burden for both society and family (29). A validated QoL instrument for older people can efficiently screen the health condition and provide timely and early intervention to prevent serious illnesses. Our study, thus, provides psychometric evidence of a brief and efficient QoL instrument specifically for use in the older population (i.e., WHOQOL-AGE) to echo the aforementioned needs. Moreover, our results show that the WHOQOL-AGE has promising construct validity (a bifactor structure) as verified by the satisfactory fit indices in CFA, and the WHOQOL-AGE had invariant factor structures across genders, educational levels, living settings, and ages.

To the best of our knowledge, only two studies (15, 16) have evaluated the psychometric properties of the WHOQOL-AGE prior to this study. Our results are comparable to those of the other two studies (15, 16). Specifically, satisfactory internal consistency for the WHOQOL-AGE was found in the study by Caballero et al. (15) as well as our study. Moreover, the satisfactory internal consistency was supported by different psychometric methods, including Cronbach's α [0.84–0.91 in Caballero et al.'s study (15); 0.81–0.90 in our study] and McDonald's ω (0.85–0.92 in our study).

Both our study and Santos et al.'s study (16) demonstrate that the bifactor model was the best fitting model with excellent fit for the WHOQOL-AGE. Therefore, we can ensure that the WHOQOL-AGE has promising construct validity and can assess global QoL by using all 13 items. Two factors were found in the WHOQOL-AGE, and Factor 1 items (i.e., Q1–Q8) seemed to share the *satisfaction in personal asset* concept while Factor 2 items (i.e., Q9–Q13) seemed to share the *self-efficacy in activities of daily living* concept. Nevertheless, Santos et al. (16) proposed another explanation for why there are two factors in the WHOQOL-AGE: The two factors were constructed because of their response scale (Factor 1 items are rated using bipolar response; Factor 2 items are rated using unipolar response). The different response scales can be considered as a method effect in the factor structure, and a similar type of method effect (e.g., positively and negatively worded items) has been illustrated in other QoL instruments (22, 30, 31). Therefore, the bifactor model verified that, after tackling the method effects, the WHOQOL-AGE can provide valid estimations of global QoL for older people.

We can further extend the findings from Santos et al.'s study (16) regarding the measurement invariance. Santos et al. (16) show the partial invariance of the WHOQOL-AGE across three European countries (Finland, Poland, and Spain). However, current literature provides no further information on the measurement invariance of the WHOQOL-AGE. Our study, thus, extends the findings of invariance across European countries to across genders, educational levels, living settings, and ages. Gender and educational level are obvious factors that may influence an individual to think differently and may lead to different interpretations of the same item descriptions (2). Therefore, it is important to evaluate whether the WHOQOL-AGE items are interpreted similarly across genders and educational levels. The supported measurement invariance found from our results indicated that neither gender nor educational level influenced the psychometric properties of the WHOQOL-AGE. Hence, the WHOQOL-AGE can be used to compare QoL between males and females and between those with low and high levels of education.

Moreover, apart from living in the community, older people can also live in unique settings; that is, LTC institutions or nursing homes. Given that the living context is different (32), older people may have different perceptions and considerations when they answer the items of the WHOQOL-AGE. Therefore, ensuring the measurement invariance of the WHOQOL-AGE across different living settings is important. The supported measurement invariance found from our results indicates that living context did not influence the psychometric properties of the WHOQOL-AGE. Hence, the WHOQOL-AGE can be used to compare QoL between those living in the community and those living in an institution.

As the measurement invariance was supported for the WHOQOL-AGE across different settings, we tested the known-group validity of the WHOQOL-AGE. Our results reveal consistent findings with the literature (28), which shows that older people living in the community had better QoL than those living in an institution. Moreover, our results on known-group validity showed that the WHOQOL-AGE had a moderate effect size in distinguishing QoL between different settings. Therefore, we anticipate that the WHOQOL-AGE would be a sensitive tool for detecting differences in QoL among older people. However, future studies may further investigate whether the WHOQOL-AGE is also sensible for detecting intervention effects.

There are some limitations in this study. First, we did not assess the test–retest reliability of the WHOQOL-AGE. Therefore, the reproducibility and stability of the

WHOQOL-AGE remain unknown. Second, all the participants were recruited in Southern Taiwan through convenience sampling; thus, the representativeness is restricted, and the generalizability of our findings is limited. Third, although we tested the known-group validity of the WHOQOL-AGE using living settings, no other external criteria were assessed. Therefore, we are unsure whether the WHOQOL-AGE has satisfactory concurrent validity to support its underlying QoL concept. Future studies are, thus, warranted to investigate this topic using other validated QoL-related instruments (e.g., WHOQOL-BREF). Fourth, the present study did not examine the feasibility, reliability, and responsibility for the WHOQOL-AGE. Because a high-quality QoL instrument needs the information to potentiate its use, future studies are warranted to examine the feasibility, reliability, and responsibility of the WHOQOL-AGE in Asia. Last and importantly, although we have ensured the linguistic validity of the Taiwan version WHOQOL-AGE during the translation process, we did not design culturally specific items for the Taiwan version. Given that the WHOQOL-AGE was developed from European countries and that European and Taiwanese lifestyles are different, the translated WHOQOL-AGE may not be able to detect the QoL for Taiwanese people specifically. Future studies may consider developing and incorporating culturally specific items into the Taiwan version WHOQOL-AGE.

CONCLUSIONS

Our findings may supplement the use of QoL on older people in the current literature. Specifically, WHOQOL-OLD is a well-established instrument with strong psychometric properties to assess QoL for older people, and our psychometric findings on WHOQOL-AGE may provide healthcare providers another choice to assess QoL for older people. That is, we may consider using them in different situations. Specifically, the WHOQOL-OLD has more items than does the WHOQOL-AGE; therefore, WHOQOL-OLD can provide more detailed QoL information than does the WHOQOL-AGE. Thus, the WHOQOL-OLD is a good instrument when a user wants to obtain detailed QoL information for older people. In contrast, the WHOQOL-AGE has fewer items and, therefore, can be used when a user wants to quickly obtain the QoL information of older people.

In conclusion, the present study demonstrates the promising psychometric properties of the WHOQOL-AGE in an East Asian sample through convenience sampling. With the strong psychometric properties found in this study, other Asian countries may consider translating the WHOQOL-AGE and examine whether it can efficiently assess QoL for the elderly. Moreover, the supported measurement invariance of the WHOQOL-AGE indicates that it can precisely assess QoL for older people in different conditions, including different genders, educational levels, and living settings. Nevertheless, future studies should consider using a representative sample to examine the psychometric properties of the WHOQOL-AGE (including test–retest reliability and concurrent validity that were not tested in the present study) to gather additional information to corroborate the usefulness of the WHOQOL-AGE in Asia. Specifically, results from the present study can only be generalized to a small portion of Taiwanese older people and additional evidence is needed.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Human Research Ethics Committee of National Cheng Kung University Hospital (A-ER-104-384), and no conflicts of interest between the authors and the goals of this study. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

C-YL: data analyses, preparation of the manuscript. J-DW: study design, validation of the WHOQOL-AGE translation version, proof reading of manuscript. L-FL: design of the research, fund raising, data collection, and preparation of the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Age-Related Disease Burden in China, 1997–2017: Findings From the Global Burden of Disease Study

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Background: The population is aging much faster in China than other low- and middle-income countries. With the accelerated aging of the population, incidence and disease burden of age-related diseases have also continued to increase. Exploring the burden of age-related diseases is crucial for early disease prevention, assessing the extent of population aging, and achieving the goal of healthy aging.

Methods: We used the dataset from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD), and selected data on incidence, prevalence, and disease burden in China, in 1997, 2007, and 2017. We classified age-related diseases, which were defined as diseases in which the incidence rate increased quadratically with age in the adult population. Additionally, we described the changes in age-related diseases during the study period by different GBD categories. It also measured changes in the age-related disease burden in our study period, including disability-adjusted life years (DALY), years of life lost (YLL), and years lived with disability (YLD). Finally, we compared the differences in the age-related disease burdens for men and women.

Results: Among the 293 diseases listed in the GBD study, 69 in 2017, 78 in 1997 and 72 in 2007 were identified as age-related diseases. More than half of the age-related diseases belonged to non-communicable diseases (NCDs) in our study period. The rate of age-standardized age-related disease burden decreased between 1997 and 2017. DALYs decreased by 24.89% for non-age-related diseases and by 50.15% in age-related diseases from 1997 to 2017. The age-related disease burden of men was higher than that of women; we found a decreasing trend, with −46.23% in men and −54.90% in women. Conclusions: Comparing characteristics of the aging population in China and the world, we found that China does not have the typical disease characteristics of aging society. Currently, China faces the dual threat of NCDs and communicable diseases, and NCDs account for the vast majority of the age-related disease burden. Our health systems should focus on disease prevention and early detection among the entire population, instead of treatment. Further studies should focus on reducing the duration and severity of morbidity in later life.

Keywords: age-related disease, disease burden, Chinese population, non-communicable diseases, healthy aging

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INTRODUCTION

According to the report of World Health Organization (WHO), the global elderly population is expected to increase from 12 to 22% by 2050 (1). In China, the aging population is expected to grow faster than it has previously. China's elderly population (over 65 years old) is likely to rise to 330 million, or approximately one-quarter of its total population by 2050 (2, 3). It is highly probable that, as the expected human lifespan increases, these additional years are likely to be accompanied by decline in physical and mental abilities (4). With these age-related declines, the related burden will likely increase over the foreseeable future in China (5). However, not all people over 60 years of age experience such changes. Early prevention of age-related diseases can decrease the negative impact of aging and the burden of disease in the elderly population (6).

WHO has developed a new concept of healthy aging as being much more than the absence of disease (7). Based on this conceptualization, the Global Strategy and Action Plan on Aging and Health provides a political mandate for the actions required to ensure that everyone has the opportunity to enjoy a long, healthy life (8). The 2030 Agenda for Sustainable Development also makes it clear that neither a healthy life nor the right to health starts or ends at a specific age. Increasing recognition that many of the determinants of healthy aging are found in earlier life has prompted focus on how life course approaches might be used to identify critical periods during which action can be taken (9). Therefore, we should address what can be done both at younger ages and in the second half of life to improve the chances of healthy aging.

Health problems in older age go beyond what can be caused by disease alone, such as impairments in cognition, mood, and physical performance (10). Thus, many researchers (11–13) currently believe that we have reached "the end of the disease era"; however, it is possible to reduce the incidence of age-related diseases by taking early action. To prevent age-related diseases and extend the healthy and maximal lifespan, it is necessary to decrease the negative effects of aging over time (14). Many countries have begun to strengthen national capacities to formulate evidence-based policies for healthy aging. Age-related disease has recently gained increasing attention, given the growth in the older adult population (4, 14–16). More people have died in recent years from age-related diseases than ever before (17), such as cancer, hypertension, and stroke; however, these diseases are difficult to eliminate. Many studies (18–20) explored the burden of disease based on one or more age-related diseases, but there is no clear definition as to what extent the burden impacts one's overall well-being. Researchers (18, 20) have shown that glaucoma, atherosclerosis, obesity, diabetic complications, tumors, prostatic hyperplasia, Alzheimer's disease, Parkinson's disease, age-related macular degeneration, and osteoarthritis are closely related to aging, suggesting a common underlying process. Furthermore, several studies have focused on the burden of age-related disease. For example, Bani (4) analyzed the age-related disease burden in India, and found that the incidence of cardiac abnormalities was the most common cause in all age groups. Chang et al. (16) defined 92 age-related diseases, which accounted for 51.3% of the total disease burden globally based on the data from the 2017 GBD. It is crucial to identify what diseases are age-related and from there determine their disease burden. Unfortunately, there is little evidence to clarify which diseases are most associated with aging in China.

In our study, we attempted to screen out age-related diseases in the Chinese population by using GBD data, and compared the changes in the types of age-related diseases in 1997, 2007, and 2017 and analyzed the burden of age-related and non-age-related diseases during those 3 years. In this paper, to improve current understanding of the health problems faced by older adults, we analyzed the characteristics of age-related diseases in China. Furthermore, we analyzed the types and changing trends of age-related diseases to provide a basis for targeted interventions, such as early disease prevention and health management among older populations. Our findings could help clarify the sequencing and effectiveness of interventions, as well as develop design policies to support healthy aging in different contexts.

MATERIALS AND METHODS

Data Sources

In this study, data were extracted from the GBD, which collected data from 195 countries from 1990–2017. We used the GBD interactive data visualization tool "GBD Compare" to retrieve estimates for levels and trends of disease incidence and prevalence cases, disability-adjusted life years (DALYs) and their components, years of life lost (YLLs), and years lived with disability (YLDs) for 293 diseases found in adults in China (GBD 2017 Results. Seattle, United States: Institute for Health Metrics and Evaluation, 2017; http://vizhub.healthdata.org/gbd-compare/). To compare the trends over two decades, we analyzed the related data in 1997, 2007, and 2017. The GBD study design and methods have been described in previous literature (21–23).

GBD Causes List

In the GBD study, 293 causes of disease were organized into hierarchical levels. Level 1 contains three broad cause groups: communicable, maternal, neonatal, and nutritional diseases (CMNN), non-communicable diseases (NCDs), and injuries. Since many previous studies (16, 24) have shown age-related diseases to be mainly associated with NCDs, we divided NCDs into 12 groups, including neoplasms, cardiovascular diseases, chronic respiratory diseases, digestive diseases, neurological disorders, mental and substance use disorders, diabetes and kidney diseases, skin and subcutaneous diseases, sense organ diseases, musculoskeletal disorders and other NCDs. Thus, we have divided the age-related diseases and their related burden in the 14 GBD disease groups.

Selection of Age-Related Diseases

In our study, we used the same approach as the previous study performed by Chang et al., to screen for age-related diseases and their burden in the Chinese population; meanwhile, we defined age-related diseases as diseases with incidence rates that increased quadratically with age among adult population (10, 16, 25–27). Adults were defined as individuals aged 25 years

and older (28). To identify age-related diseases, we applied a two-step regression framework for the incidence rates using the GBD datasets for China from 1997, 2007, and 2017. A detailed description of the regression framework can be found in previous literature on age-related disease (16). For a small subset of GBD causes without incidence estimation, we used prevalence estimation under the same framework.

Figure 1 presents the flowchart of the selection process performed in the present study to select the data in 2017. First, we removed 17 diseases that had neither incidence nor prevalence data, and 59 diseases that did not have incidence data, from 293 GBD diseases list of China. Among the remaining 211, we excluded 106 diseases that did not show a positive relationship between incidence rates and age, and 48 that did not have a positive term for the quadratic term (i.e., the relationship between incidence rate and age was not convex). Out of the 59 causes with no incidence data, we applied the same methodology using prevalence rates, and included 11 causes that met the criteria. Overall, we identified 69 diseases associated with age.

Defining Age-Related Disease Burden

Age-related disease burden was considered the sum of all DALYs for age-related diseases in adults. We analyzed the age-related disease burden, which is the proportion of age-related disease burden out of the total health burden. For cross-period comparisons, we also analyzed the age-standardized rates per 1,000 adults, which were adjusted for population size and age structure.

DALYs

DALYs are a measure of overall disease burden, expressed as the cumulative number of years lost due to ill health, disability, or early death. One DALY can be thought of as one lost year of healthy life. The sum of these DALYs across the population, or the burden of disease, can be thought of as a measurement of the gap between current health status and an optimal health, in which the entire population lives to an advanced age, free of disease or disability.

DALYs for a disease or health condition are calculated by adding the YLLs due to premature mortality in the population and the YLDs for people living with the health condition or its consequences. YLLs are calculated by multiplying the number of deaths associated with the condition by the remaining life expectancy. YLDs are calculated by multiplying the number of cases with a certain health outcome by the weight of the specified disability.

Statistical Analysis

All analyses were conducted by Stata version 12.0. To understand the relationship between age and disease prevalence at the population level, disease-specific data for both genders were summarized. Unless otherwise stated, all rates were expressed as age-standardized for the GBD reference population. This study

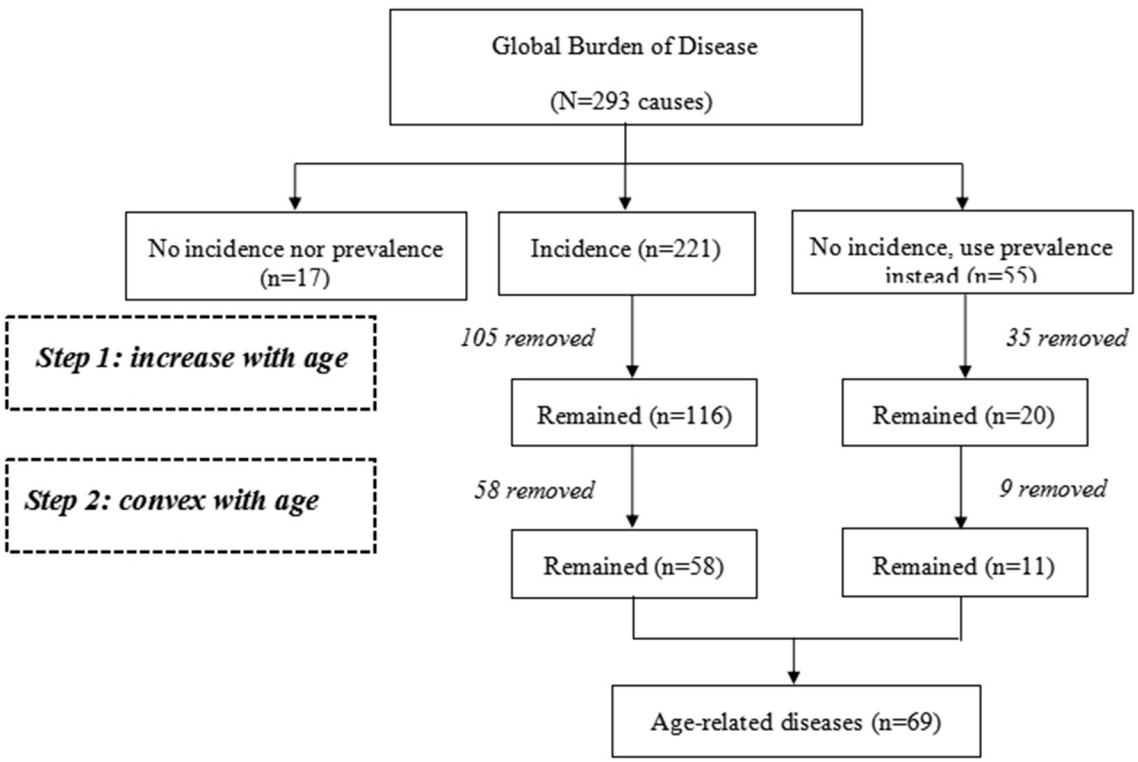

FIGURE 1 | Flow chart of age-related diseases selection in 2017.

followed the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) 20 recommendations.

Uncertainty Analysis

We used the same techniques found elsewhere in GBD research design to propagate uncertainty. The final estimate was calculated using an average estimate of 1,000 samples, while 95% of the uncertainty interval (UI) was determined based on the 25th and 975th bit-sorted values of all 1,000 samples.

Sensitivity Analysis

To verify the stability of the results, we excluded incidence data for ages 80 and above for sensitivity analysis. The analysis showed that age-related disease outcomes between 25 and 80 years were consistent with those identified in the adults ages 25 and above.

RESULTS

Age-Related Diseases

In 2017, 69 (23.5%) age-related diseases were identified among the 293 GBD causes; 78 (26.6%) and 72 (24.6%) were identified in 1997 and 2007, respectively. In 2017, among the 69 conditions, 14 (20.29%) were CMNNs, 7 (10.14 %) were injuries, and 48 (69.57%) were NCDs. No significant change or injury was observed in the age-related CMNNs during the study period, but the number of age-related NCDs decreased. Additionally, we also found that several emerging age-related diseases, such as other pneumoconiosis, acute glomerulonephritis, age-related macular degeneration, and near vision loss increased in 2017 (**Table 1**).

Age-Related Disease Burden

A total of 248.34 DALYs were due to the age-standardized, age-related disease burden; however, 400.41 DALYs were caused by non-age-related disease. In terms of proportion, age-related disease burden accounted for 38.28% (248.34/648.75) of the total disease burden. Causes of non-age-related disease burden included neoplasms (19.91%), injuries (13.12%), neurological disorders (11.91%), CMNNs (11.59%), and musculoskeletal disorders (10.39%). For age-related diseases, the burden was primarily due to cardiovascular disease (44.16%), other NCDs (12.71%), chronic respiratory disease (12.01%), injuries (7.44%), and neoplasms (6.72%). The burden of age-related disease was greater in the cardiovascular, chronic respiratory, and other chronic disease groups than in the non-age-related group (**Table 2**).

In 2017, the burden of disease in China was 648.81 DALYs, of which 59.40% were caused by death and 40.60% by disability (**Table 3**). YLLs, YLDs, and DALYs showed a gradual decline from 1997 to 2017. The non-age-related disease DALYs decreased by 24.89% from 1997 to 2017. Furthermore, 50.15% reduction occurred in age-related diseases burden.

The data of different years were segregated separately for gender. The disease burden of men was higher than women. From 1997 to 2017, the proportion of age-related disease burden in all populations showed decreasing trend (−46.23%), which was more apparent among women (−54.90%) (**Table 4**).

DISCUSSION

Our study showed that the number of age-related diseases decreased from 1997 to 2017, with more than half classified as NCDs, such as cardiovascular disease, chronic respiratory disease, and other NCDs. Over the past two decades, the disease burden has declined in China, especially for age-related diseases (50.15%). The burden of age-related NCDs was higher than CMNNs and injuries in 2017. Additionally, men had a higher disease burden than women.

The number of age-related diseases was less in China (69 diseases) than globally based on the results of a study performed by Angela Chang and colleagues (92 diseases) (16) in 2017, as was the proportion of age-related NCDs. This may be due to different disease conditions in China and the rest of the world. China entered became an aging society in only 18 years (1981–1999), and the aging population is growing faster than ever. From 1990 to 2020, the world's elderly population grew at an average annual rate of 2.5%, compared with 3.3% in China over the same period (30–32). The rapid aging process in China is also the main reason for the discrepancy between China and the world adult disease spectrum. Besides, China was recently faced with the double challenge of infectious and chronic diseases; current trends indicating a transition from a higher prevalence of CMNNs to higher numbers of NCDs (5, 33). The patients, especially with chronic diseases, are currently getting younger in China, which is also the main reason for the decrease in the number of age-related diseases. For example, the prevalence of hypertension and diabetes increased significantly, but the onset age was younger.

Our main finding was that age-standardized age-related disease burden decreased from 2007 to 2017. On one hand, it may be related to the decrease of age-related diseases during the study period. On the other hand, with the development of economy and society, people's health improved, the decrease of overall disease burden is not surprising. Whereas, one of the serious problems associated with population aging is the increasing burden of NCDs, and the prevalence of NCDs will increase along with the increasing disease burden. According to current projections, China's rapidly aging population is expected to increase the burden of NCDs by at least 40% by 2030 (3, 34). Thus, more resources should be devoted to primary health care in China, which would likely make for a more efficient health care system (34).

The burden of age-related disease was greater in the cardiovascular, chronic respiratory, and other chronic disease groups; those diseases need better predictors of their occurrence. It is crucial to study an intervention on how to block the causal mechanisms at an early stage. Published studies have shown that only about 25% of our lifespan is determined by our genes; the other 75% is determined by our lifestyles and the choices we make every day (2, 35, 36). We should therefore pay more attention to practicing a healthy lifestyle, including increased exercise and reduction in food intake and obesity. Furthermore, physiological aging is inevitable; however, pathological aging can be prevented or delayed. However, until now, the mechanisms underlying the causes of aging have not been thoroughly understood.

TABLE 1 | Age-related diseases, by different GBD disease category in China, in 1997, 2007, and 2017.

GBD category	1997 (China)	2007 (China)	2017 (China)	2017 (Global)*
Communicable, maternal, neonatal, and nutritional diseases (80 diseases)	Diarrheal diseases; Lower respiratory infections; Pneumococcal meningitis; H influenzae type B meningitis; Meningococcal meningitis; Other meningitis; Encephalitis; Tetanus; Cystic echinococcosis; Trachoma; Dengue; Acute hepatitis C; Drug-susceptible tuberculosis; Multidrug-resistant tuberculosis without extensive drug resistance; Extensively drug-resistant tuberculosis (15)	Diarrheal diseases; Lower respiratory infections; Pneumococcal meningitis; H influenzae type B meningitis; Meningococcal meningitis; Other meningitis; Encephalitis; Tetanus; Trachoma; Dengue; Protein-energy malnutrition; Acute hepatitis C; Drug-susceptible tuberculosis; Multidrug-resistant tuberculosis without extensive drug resistance; Extensively drug-resistant tuberculosis (15)	Diarrheal diseases; Lower respiratory infections; Pneumococcal meningitis; H influenzae type B meningitis; Meningococcal meningitis; Other meningitis; Encephalitis; Tetanus; Trachoma; Dengue; Acute hepatitis C; Drug-susceptible tuberculosis; Multidrug-resistant tuberculosis without extensive drug resistance; Extensively drug-resistant tuberculosis (14)	Diarrhoeal diseases; encephalitis; lower respiratory infections; pneumococcal meningitis;trachoma (5)
Neoplasms (42 diseases)	Liver cancer due to hepatitis C; Prostate cancer; Colon and rectum cancer; Lip and oral cavity cancer; Gallbladder and biliary tract cancer; Pancreatic cancer; Malignant skin melanoma; Bladder cancer; Thyroid cancer; Mesothelioma; Non-Hodgkin lymphoma; Other malignant neoplasms; Non-melanoma skin cancer (squamous-cell carcinoma); Non-melanoma skin cancer (basal-cell carcinoma); Other leukemia; Myelodysplastic, myeloproliferative, and other hematopoietic neoplasms; Liver cancer due to NASH (17)	Liver cancer due to hepatitis C; Prostate cancer; Colon and rectum cancer; Lip and oral cavity cancer; Gallbladder and biliary tract cancer; Malignant skin melanoma; Testicular cancer; Bladder cancer; Mesothelioma; Other malignant neoplasms; Non-melanoma skin cancer (squamous-cell carcinoma); Non-melanoma skin cancer (basal-cell carcinoma); Myelodysplastic, myeloproliferative, and other hematopoietic neoplasms; Liver cancer due to NASH (14)	Liver cancer due to hepatitis C; Prostate cancer; Colon and rectum cancer; Gallbladder and biliary tract cancer; Malignant skin melanoma; Testicular cancer; Bladder cancer; Mesothelioma; Other malignant neoplasms; Non-melanoma skin cancer (squamous-cell carcinoma); Non-melanoma skin cancer (basal-cell carcinoma); Myelodysplastic, myeloproliferative, and other hematopoietic neoplasms; Liver cancer due to NASH (13)	Acute lymphoid leukemia; acute myeloid leukemia; benign and *in-situ* intestinal neoplasms; bladder cancer; brain and nervous system cancer; breast cancer; chronic lymphoid leukemia; chronic myeloid leukemia; colon and rectum cancer; gallbladder and biliary tract cancer; Hodgkin lymphoma; kidney cancer; larynx cancer; lip and oral cavity cancer; liver cancer due to NASH; liver cancer due to alcohol use; liver cancer due to hepatitis C; malignant skin melanoma; mesothelioma; multiple myeloma; myelodysplastic, myeloproliferative, and other hematopoietic neoplasms; non-Hodgkin lymphoma; non-melanoma skin cancer (basal-cell carcinoma); non-melanoma skin cancer (squamous-cell carcinoma); esophageal cancer; other benign and *in-situ* neoplasms; other leukemia; other malignant neoplasms; ovarian cancer; pancreatic cancer; prostate cancer; stomach cancer; thyroid cancer; tracheal, bronchus, and lung cancer; uterine cancer (29)
Cardiovascular diseases (17 diseases)	Rheumatic heart disease; Ischemic heart disease; Ischemic stroke; Intracerebral hemorrhage; Subarachnoid hemorrhage; Hypertensive heart disease; Endocarditis; Myocarditis; Other cardiomyopathy; Non-rheumatic calcific aortic valve disease; Non-rheumatic degenerative mitral valve disease; Other non-rheumatic valve diseases (12)	Ischemic heart disease; Ischemic stroke; Intracerebral hemorrhage; Hypertensive heart disease; Endocarditis; Myocarditis; Other cardiomyopathy; Non-rheumatic calcific aortic valve disease; Non-rheumatic degenerative mitral valve disease; Other non-rheumatic valve diseases (10)	Ischemic heart disease; Ischemic stroke; Intracerebral hemorrhage; Hypertensive heart disease; Endocarditis; Myocarditis; Other cardiomyopathy; Non-rheumatic calcific aortic valve disease; Non-rheumatic degenerative mitral valve disease; Other non-rheumatic valve diseases (10)	Atrial fibrillation and flutter; endocarditis; hypertensive heart disease; intracerebral hemorrhage; ischaemic heart disease; ischaemic stroke; myocarditis; non-rheumatic calcific aortic valve disease; non-rheumatic degenerative mitral valve disease; other cardiomyopathy; other cardiovascular and circulatory diseases; other non-rheumatic valve diseases; peripheral artery disease (13)
Chronic respiratory diseases (8 diseases)	Chronic obstructive pulmonary disease; Asbestosis; Interstitial lung disease and pulmonary sarcoidosis (3)	Chronic obstructive pulmonary disease; Asbestosis (2)	Chronic obstructive pulmonary disease; Other pneumoconiosis (2)	Asbestosis; chronic obstructive pulmonary disease; coal worker pneumoconiosis; interstitial lung disease and pulmonary sarcoidosis; other pneumoconiosis; silicosis (6)

(Continued)

TABLE 1 | Continued

GBD category	1997 (China)	2007 (China)	2017 (China)	2017 (Global)*
Digestive diseases (16 diseases)	Cirrhosis and other chronic liver diseases due to other causes; Peptic ulcer disease; Appendicitis; Paralytic ileus and intestinal obstruction; Vascular intestinal disorders; Gallbladder and biliary diseases; Pancreatitis; Cirrhosis due to NASH (8)	Cirrhosis and other chronic liver diseases due to other cause; Peptic ulcer disease; Appendicitis; Paralytic ileus and intestinal obstruction; Vascular intestinal disorders; Gallbladder and biliary diseases; Pancreatitis; Cirrhosis due to (8)	Peptic ulcer disease; Appendicitis; Paralytic ileus and intestinal obstruction; Vascular intestinal disorders; Gallbladder and biliary diseases; Pancreatitis (6)	Cirrhosis due to NASH; pancreatitis; paralytic ileus and intestinal obstruction; peptic ulcer disease; vascular intestinal disorderss (5)
Neurological disorders (8 diseases)	Alzheimer's disease and other dementias; Multiple sclerosis; Other neurological disorders (3)	Alzheimer's disease and other dementias; Multiple sclerosis; Other neurological disorders (3)	Alzheimer's disease and other dementias; Multiple sclerosis;Other neurological disorders (3)	Alzheimer's disease and other dementias; motor neuron disease; Parkinson's disease (3)
Mental and substance use disorders (18)	N/A	N/A	N/A	N/A
Diabetes and kidney diseases (8 diseases)	Chronic kidney disease due to glomerulonephritis; Chronic kidney disease due to other and unspecified causes (2)	Chronic kidney disease due to glomerulonephritis; Chronic kidney disease due to other and unspecified causes (2)	Acute glomerulonephritis; Chronic kidney disease due to glomerulonephritis; Chronic kidney disease due to other and unspecified causes (3)	Chronic kidney disease due to glomerulonephritis; Chronic kidney disease due to other and unspecified causes (2)
Skin and subcutaneous diseases (15 diseases)	Cellulitis; Pyoderma; Fungal skin diseases; Decubitus ulcer (4)	Cellulitis; Pyoderma; Fungal skin diseases; Decubitus ulcer (4)	Cellulitis; Pyoderma; Fungal skin diseases; Decubitus ulcer (4)	Cellulitis; decubitus ulcer; fungal skin diseases; other skin and subcutaneous diseases; pyoderma (5)
Sense organ diseases (8 diseases)	Glaucoma; Cataract; Age-related macular degeneration; Other vision loss (4)	Glaucoma; Cataract; Other vision loss (3)	Glaucoma; Cataract; Age-related macular degeneration; Other vision loss; Near vision loss (5)	Age-related and other hearing loss; age-related macular degeneration; cataract; glaucoma; other sense organ diseases; other vision loss; refraction disorders (7)
Musculoskeletal disorders (6 diseases)	N/A	N/A	N/A	N/A
Other NCD (37 diseases)	Urinary tract infections; Neural tube defects;G6PD trait; Endocrine, metabolic, blood, and immune disorders (4)	Urinary tract infections; Endocrine, metabolic, blood, and immune disorders; G6PD trait (3)	Urinary tract infections; G6PD trait (2)	Congenital musculoskeletal and limb anomalies; digestive congenital anomalies;endocrine, metabolic, blood, and immune disorders; other haemoglobinopathies and haemolytic anaemias (4)
Injuries(29 diseases)	Other transport injuries; Falls; Drowning; Self-harm by firearm; Self-harm by other specified means; Environmental heat and cold exposure (6)	Other transport injuries; Falls; Drowning; Non-venomous animal contact; Other unintentional injuries; Self-harm by firearm; Self-harm by other specified means; Environmental heat and cold exposure (8)	Other transport injuries; Drowning; Non-venomous animal contact; Other unintentional injuries; Self-harm by firearm; Self-harm by other specified means; Environmental heat and cold exposure (7)	Drowning; environmental heat and cold exposure; falls; foreign body in other body part; other transport injuries; other unintentional injuries (6)
Total age-related diseases	78 diseases	72 diseases	69 diseases	92 diseases

**The resource come from the study performed by Chang et al. (16).*

The disease burden and proportion of age-related burden among all burdens was lower for women than for men, and the disease burden decreased more for women than men during our study period. The contribution to the disease burden between men and women was unequal, due to the higher prevalence of chronic disease risk factors in men (29). In addition, the China Women's Development Foundation introduced screenings for gynecological diseases, and the screening rate for common diseases among women reached 75.5% in 2018. This can help strengthen public awareness of the prevention and treatment of common diseases and enhance women's capacity for self-efficacy in healthcare.

In the absence of population level aging metrics that inform longevity, health status and disease severity in China, based on the GBD database, this is the first study to explore the age-related disease burden among Chinese adults. Furthermore, we

TABLE 2 | Distribution of non-age-related burden and age-related burden by different GBD category in China, in 2017, measured in DALYs.

GBD category	Non-age-related disease		Age-related disease		All disesaes
	Age-standardized DALY rate (per 1,000)	Proportion among all (%)	Age-standardized DALY rate (per 1,000)	Proportion among all (%)	Age-standardized DALY rate (per 1,000)
Communicable, maternal, neonatal, and nutritional diseases	46.41(33.74, 64.43)	11.59	18.71 (16.09,22.55)	6.59	65.12 (49.83,86.99)
Neoplasms	79.68 (71.88,86.34)	19.91	19.09 (16.86,21.56)	6.72	98.77 (88.74,107.90)
Cardiovascular diseases	11.62 (9.76,13.48)	2.90	125.45 (115.55, 133.81)	44.16	137.07 (125.30,147.29)
Chronic respiratory diseases	4.43 (3.19,6.01)	1.11	34.13 (31.93,36.97)	12.01	38.55 (35.11,42.98)
Digestive diseases	14.66(11.34,19.83)	3.66	3.98(3.49, 4.87)	1.40	18.63(14.82,24.69)
Neurological disorders	17.68(11.87,25.37)	4.42	13.74 (12.52,15.09)	4.84	31.42(24.39,40.46)
Mental and substance use disorders	47.68(32.72,65.49)	11.91	0.00(0.00,0.00)	0.00	47.68(32.72,65.49)
Diabetes and kidney diseases	20.27(15.75,25.43)	5.06	3.67 (3.16,4.20)	1.29	23.94(18.90,29.63)
Skin and subcutaneous diseases	14.59(8.67,22.92)	3.64	1.53(3.15,0.69)	0.54	16.12(9.36,26.08)
Sense organ diseases	17.49(11.78,24.59)	4.37	6.55(3.79,10.52)	2.31	24.05(15.57,35.48)
Musculoskeletal disorders	41.60(28.55,58.89)	10.39	0.00(0.00,0.00)	0.00	41.60(28.55,58.89)
Other NCD	31.66(23.32,43.47)	7.91	36.11(32.20,41.95)	12.71	67.77(55.52,85.42)
Injuries	52.53(43.50,61.43)	13.12	21.13(19.29,23.50)	7.44	73.66(62.80,84.94)
All causes	400.41(306.13,518.21)	100	248.34(223.72,276.66)	100	648.75(529.85,794.87)

TABLE 3 | The non-age-related burden and age-related burden by different burden indicator in China, in 1997, 2007 and 2017.

Category	YLLs			YLDs			DALYs		
	1997	2007	2017	1997	2007	2017	1997	2007	2017
Non-age-related group	314.17	233.70	181.76	219.03	224.03	218.72	533.2	457.73	400.48
Age-related group	448.59	261.21	203.62	49.64	43.38	44.73	498.23	304.59	248.35
Total	762.76	494.91	385.38	268.67	267.41	263.45	1,031.43	762.32	648.83
Proportion of age-related burden among all burden(%)	58.81	52.78	52.84	18.48	16.22	16.98	48.30	39.96	38.28

TABLE 4 | The change of non-age-related burden and age-related burden by different sex in China, in 1997–2017.

Sex	Year	Age-related burden rate (per 1,000 adults)	Non-age-related burden rate (per 1,000 adults)	All disease burden rate (per 1,000 adults)	Proportion of age-related burden among all burden (%)	Percentage change in Age-related burden 1997–2017(%)
Male	1997	182.92 (162.30,200.48)	190.67 (149.43,242.61)	373.60 (311.74,443.09)	48.96	−46.23
	2007	119.03(110.59,127.73)	163.94(131.04,204.87)	282.98(241.64,332.61)	42.06	
	2017	98.35(89.09,108.88)	145.11(113.17,183.91)	243.46(202.26,292.80)	40.40	
Female	1997	149.29(129.40,165.29)	164.65(124.53,218.30)	313.95(253.94,383.60)	47.55	−54.90
	2007	84.49(77.82,91.63)	141.15(107.58,184.32)	225.64(185.41,275.96)	37.44	
	2017	67.33(59.54,76.47)	121.86(89.98,162.52)	189.19(149.52,239.00)	35.59	

have found changes in the overall burden of age-related disease over 20 years in China. Our study has several limitations. First, while the GBD list of diseases is comprehensive, we may have missed including some diseases that are important to China's aging population. Second, we used the same methods as Chang and colleagues (16) to identify which diseases are associated with age. The difference between China and the rest of the world could lead to different results. However, as shown in our analysis, we characterized the aging of the Chinese population, which is meaningful for providing a public health framework for actions that can be taken to promote healthy aging. Third, we did not consider the influence of multimorbidity on disease burden. Many people have multiple chronic diseases at the same time (37); however, our study was meant to draw attention to the age-related disease burden, rather than disease interactions.

CONCLUSION

Identifying age-related diseases is a prerequisite for providing promising therapeutic strategies to promote healthy aging in the future. Comparing the characteristics of the aging population in China and the world, we found that China does not have the typical disease characteristics of an aging society. Currently, China faces the dual threat of NCDS and communicable diseases, and NCDs account for the vast majority of the age-related disease burden. Our health systems should focus on disease prevention and early detection among the entire population, instead of treatment. Further studies should focus on reducing the duration and severity of morbidity in later life.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: http://ghdx.healthdata.org/gbd-results-tool.

AUTHOR CONTRIBUTIONS

DH and JC contributed to the conception and design of the study. WY, JZ, and DH conducted the data reduction and analyses. YZ helped validate the disease screening. DH wrote the manuscript, guided the whole process, and reviewed the manuscript. All authors read and approved the manuscript before submission.

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Health-Related Quality of Life and Its Influencing Factors for Elderly Patients With Hypertension: Evidence From Heilongjiang Province, China

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Objective: Hypertension is one of the most common public health issues worldwide. However, few existing studies examining health-related quality of life (HRQoL) were conducted on elderly patients with hypertension in China. Hence, this study aimed to assess the HRQoL of elderly patients with hypertension and its influencing factors using EuroQol five-dimensional-three-level (EQ-5D-3L) in China.

Methods: Data were obtained from the 6th National Health Service Survey in Heilongjiang province from June to July 2018, with a stratified multistage random cluster sampling method. All eligible participants were interviewed using a standardized questionnaire, which included the EQ-5D-3L, socio-demographics characteristics, clinical and lifestyle characteristics. The mean EQ-5D index scores for the different subgroups were evaluated using ANOVA. A Tobit regression model was also employed to analyze the potential factors influencing HRQoL.

Results: A total of 705 elderly patients with hypertension were included in this study. The mean EQ-5D utility score was 0.79 [standard deviation (SD) = 0.23]. The proportion of participants reporting pain/discomfort problems was the highest (57.0%), while problems in self-care was the lowest (17.2%). Influencing factors of HRQoL for elderly patients with hypertension included gender, age, income, education level, physical activity, health examination and coexisting diseases. Specifically, the female gender, being above 80 years old, having a lower education and/or higher income, and the presence of coexisting diseases were associated with lower utility index. In contrast, regular physical activity and medical examination had a positive impact on the HRQoL of elderly hypertension patients.

Conclusion: Overall, elderly patients with hypertension in China have a lower HRQoL than the general population. To improve the HRQoL of elderly patients with hypertension,

it is imperative that better public health education is provided to enhance the knowledge of hypertension, encourage the adoption of healthy habits such as regular physical activity and medical examination, and improve the management of coexisting diseases. More care should also be directed to males with hypertension who are above 80 years old.

Keywords: hypertension, elderly patients, health-related quality of life, EQ-5D-3L, utility score

INTRODUCTION

Hypertension is amongst the most common non-infectious chronic diseases. It has been identified as the leading risk factor for mortality, and is ranked third as a cause of disability-adjusted life years (DALYs) worldwide (1–3). It is estimated that up to 9.4 million pre-mature deaths and 92 million DALYs were attributable to hypertension each year (1), and is predicted that by the year 2025, there will be 1.56 billion people with hypertension (4). Likewise, hypertension as a public health challenge is similarly observed in China. A recent large population survey in China revealed that in 2019, ∼245 million Chinese adults have hypertension (5). Moreover, hypertension tends to occur more frequently among older adults, where after the age of 69, the prevalence of hypertension rises to one in two individuals (6).

Health-related quality of life (HRQoL) is a concept commonly used in the subjective evaluation of a patient's health status, reflecting the patient's physical, psychological, social and emotional well-being (7, 8). As the HRQoL comprehensively examines the impact of the disease on the patient's life, as well as factors corresponding to their physical and mental health, a growing number of clinicians and policymakers are applying HRQoL in clinical treatment, drug research, preventive health care, health decision-making and health economic evaluation (9, 10). HRQoL can be measured using multi-attribute utility instruments (MAUI), which are divided into two categories: generic instruments and specific disease instruments (8, 11, 12). EuroQol five-dimension (EQ-5D) is one of the most commonly used generic instruments in the world. It has been translated into more than 170 languages and is used to measure the HRQoL of the general population and several patient populations (13). As a preference-based tool, EQ-5D can measure the health state utility (HSU) of the population to estimate the quality-adjusted life years (QALYs) (14). The three-level version of the EQ-5D (EQ-5D-3L) was introduced in 1990 (15). It has demonstrated validity and reliability (16–18), and has been widely used to measure the HRQoL of several medical conditions including hypertensive patients in China (16–25).

Previous studies have examined the relationship between HRQoL and hypertension in elder populations (26, 27). For example, a study in China reported that elderly patients with hypertension have low HRQoL (28). Another study in Vietnam found that advanced age and comorbidity were negatively associated with HRQoL (29). However, most of the studies conducted with Chinese elder population have measured HRQoL using generic instruments comprising of many items, such as the Medical Outcomes 36-Item Short Form Health Survey (SF-36) (30, 31). To date, few studies have evaluated the HRQoL of elderly patients with hypertension in China using well-validated MAUI, such as the EQ-5D.

Therefore, the current study aimed to: (1) estimate the HRQoL of elderly patients with self-reported diagnosis of hypertension, and (2) identify factors of the HRQoL that are associated with hypertension.

METHODS

Study Design and Data Collection

Data was extracted from the 6th National Health Services Survey (NHSS) conducted in Heilongjiang, a province located in northeastern China with a population of 38.7 million and a middle-income economy in terms of its gross domestic product per capita (32).

NHSS is a cross-sectional household questionnaire survey conducted in China once every 5 years, and is overseen by the Center for Health Statistics Information. The 6th NHSS was conducted from June to July 2018.

In the 6th NHSS, a multi-stage stratified cluster random sampling method was adopted, involving 6,627 individuals from 3,000 households in five counties/districts, comprising of 25 towns/sub-districts and 50 villages/residential committees. Well-trained interviewers used standardized questionnaires installed on tablets to collect information. Each field site had a survey supervisor who revisited 5% of the participating households to validate the information that was collected (33).

The questionnaire included items on demographic (e.g., age, sex, and ethnicity) and socioeconomic (e.g., residency, marital status, educational attainment, employment, income, housing, and health insurance) data, clinical status (e.g., chronic conditions), and lifestyle (e.g., smoking, alcohol consumption, health examination, and physical activity) of the participants (34). Inclusion criteria for the participants were: (1) having answered "Yes" to the question "Have you been diagnosed with hypertension by a doctor?," and (2) being 60 years old and above. This resulted in a final sample of 705 participants for the purpose of this study.

Measurements

The EQ-5D-3L was used as a tool to measure the HRQoL of elderly patients with hypertension in the present study (15). The EQ-5D-3L contains a short health description system questionnaire (EQ-5D descriptive system) and a visual analog scale (EQ-VAS). EQ-VAS is used for respondent's own global rating of their overall health, on a scale from 0 (worst

TABLE 1 | Characteristics of elderly patients with hypertension ($N = 705$).

Characteristics	$N = 705$
Gender (*n*, %)	
Male	324 (46.0%)
Female	381 (54.0%)
Age group (years, mean ± SD)	67.9 ± 6.11
60-	477 (67.7%)
70-	189 (26.8%)
80-	39 (5.5%)
Area (*n*, %)	
Urban	328 (46.5%)
Rural	377 (53.5%)
Education (*n*, %)	
Illiterate	152 (21.6%)
Primary school	298 (42.3%)
Junior high school	153 (21.6%)
Senior high/technical school	81 (11.5%)
College and above	21 (3.0%)
Medical insurance (*n*, %)	
No	30 (4.3%)
Yes	675 (95.7%)
Marital status (*n*, %)	
Married	540 (76.6%)
Single	2 (0.3%)
Divorced	12 (1.7%)
Widowed	151 (21.4%)
Employment status (*n*, %)	
Employed	127 (18%)
Retired	240 (34.1%)
Unemployed	338 (47.9%)
Smoking status (*n*, %)	
No	527 (74.8%)
Yes	178 (25.2%)
Drinking status (*n*, %)	
No	562 (79.7%)
Yes	143 (20.3%)
Physical activity (*n*, %)	
No	302 (42.8%)
Yes	403 (57.2%)
Health examination (*n*, %)	
No	366 (51.9%)
Yes	339 (48.1%)
Comorbidity (*n*, %)	
No	295 (41.8%)
Yes	410 (58.2%)
Income	
Low	241 (34.2%)
Middle	216 (30.6%)
High	248 (35.2%)

possible health) to 100 (best health possible). The description system of the EQ-5D-3L consists of five health dimensions: "Mobility," "Self-care," "Usual Activities," "Pain/Discomfort," and "Anxiety/Depression." Each dimension has three response categories: "no problems," "some problems," and "extreme problems." Thus, the EQ-5D-3L defines a total of 243 (3^5) health states, with the best heath state indicated by the response "11111" and the worst health state indicated by the response "33333." In the current study, EQ-5D-3L health states were (33) converted into a single healthy utility index score using a scoring algorithm that is based on the public preferences of the Chinese population (35).

TABLE 2 | Frequency of response in each dimension of the EQ-5D-3L ($N = 705$).

	No problems	Moderate problems	Extreme problems
Mobility (%)	60.2	36.5	3.3
Self-care (%)	82.8	13.2	4.0
Usual activities (%)	71.1	18.4	10.5
Pain/discomfort (%)	43.0	52.5	4.5
Anxiety/depression (%)	76.9	21.3	1.8

Statistical Analysis

We compared the utility scores of the FCs with those of the local general population norm which were available from a representative sample of the local population in Heilongjiang as part of the fourth National Health Services Survey, involving 15,875 individuals (from 5,530 households) in 13 cities and counties (33). To explore the factors associated with the HRQoL, health utility score of the patient were compared between the different socio-demographic groups (gender, age, area, level of education, marital status, medical insurance, annual household income, and employment status), which have been commonly used in studies on HRQoL of patients with hypertension (21, 26, 36). Consistent with other studies on HRQoL of patients with hypertension (20, 22, 37), comorbidity and lifestyle characteristics, such as smoking status, alcohol consumption, health examination, and physical activity, were also included as these are potential factors associated with HRQoL.

All data analyses were performed using STATA 15.0 software. Statistical significance was defined as $p < 0.05$. Descriptive statistics were calculated for the basic demographic variables of HRQoL. Mean and standard deviations (SD) were calculated for continuous variables, while frequencies and percentages were calculated for categorical variables. Student *t*-tests (for two groups) and one-way ANOVA tests (for multiple groups) were used to examine how EQ-5D utility scores may differ on different levels of each variable. All variables tested by the ANOVA-test were entered into the Tobit regression model. Previous studies recommend Tobit regression to deal with data of such a censored nature (38, 39), because they have theoretical advantages over the ordinary least squares estimator (40). In the present study, 34.1% of the respondents had the highest possible score of 1.0. As the EQ-5D utility data was censored, a Tobit regression model was hence employed to identify associated factors of HRQoL among elderly patients with hypertension.

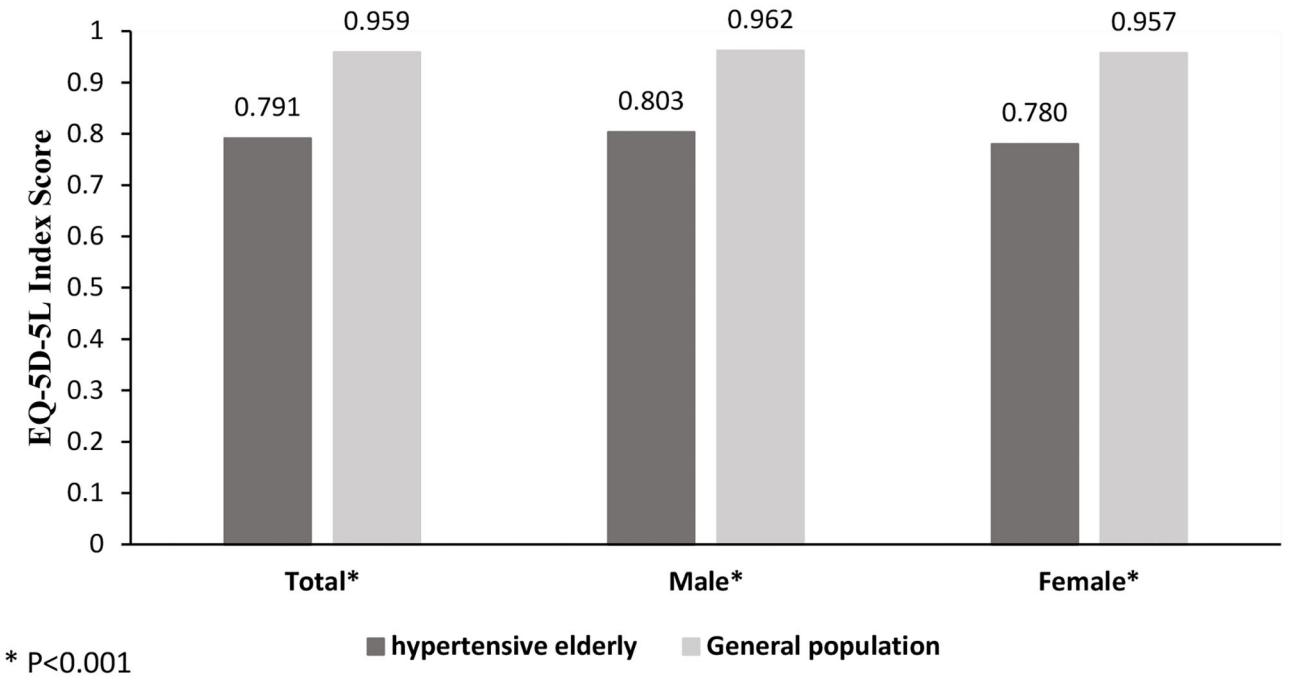

FIGURE 1 | Health utility of elderly patients with hypertension compared to the general population.

Results

The majority of the elderly patients with hypertension in the sample had the following characteristics: female (54%), rural residents (53.5%), primary school education level (42.35%), covered by medical insurance (95.7%), married (76.6%), and unemployed (47.9%). Respondents were less likely to smoke (74.8%), drink (79.7%), and take a health examination (51.9%). Furthermore, 57.2% of the respondents regularly participate in physical activities (**Table 1**).

The dimension of the EQ-5D-3L with the highest proportion of elderly patients reporting "no problem" was "self-care" at 82.8%, followed by "anxiety/depression" at 76.9%. As for the dimensions of "usual activities" and "mobility," the proportion of respondents rating "no problem" were 71.1 and 60.2%, respectively. In contrast, the "Pain/Discomfort" dimension exhibited the lowest proportion of "no problem" responses (43.0%). Overall, a total of 241 participants (34.1%) reported "no problems" in any of the five dimensions (**Table 2**).

Figure 1 depicts the comparison of the EQ-5D-3L utility scores between elderly patients with hypertension and the general population in Heilongjiang, China. Patients had a significantly lower utility score than the general population (0.79 vs. 0.96, $p < 0.001$). When classified by gender, the utility score of the patients were also significantly lower than those of their respective counterparts in the general population ($p < 0.001$).

Lower healthy utility index scores were found among respondents who were older ($p < 0.001$), lived in urban areas ($p = 0.016$), had a lower education level ($p < 0.001$), or were unemployed ($p < 0.001$). In contrast, higher utility scores were found in hypertensive respondents who drunk ($p < 0.001$), exercised regularly ($p < 0.001$), had no comorbidity ($p < 0.001$), and had a lower income level ($p = 0.002$). The index scores are described in **Table 3**.

Findings from the Tobit regression model further confirmed that gender, age, education level, physical activity, health examination, comorbidity, and income level were associated with the HRQoL of elderly patients with hypertension (**Table 4**).

DISCUSSION

The present study quantified the utility scores of elderly patients with self-reported diagnosis of hypertension, and identified factors that influenced HRQoL using the EQ-5D-3L. To the best of our knowledge, this makes the present study the first of its kind in Heilongjiang province, China.

Findings showed that older adults with hypertension reported significantly more problems in each of the EQ-5D domains and have a lower health utility index than the local general population (33). This indicates that hypertension has an adverse effect on older mainland Chinese. Similar to previous studies, the present study found that the utility score was lower for respondents with hypertension than those without (19–21). Nonetheless, it is important to note that in previous studies, the mean utility score of the respondents with a diagnosis of hypertension were lower [i.e., 0.96 in Yao et al.'s (20), 0.92 in Zhang et al.'s (21), and 0.85 in Liang et al.'s (19) studies] than in the present study. Moreover, current respondents reported more problemsin all five dimensions of the EQ-5D-3L than reported in other studies (20, 21). This may be mainly due to differences in age. Participants in the current study were elderly patients aged 60 years and

TABLE 3 | EQ-5D-3L health utility index scores on each characteristic of elderly patients with hypertension.

Characteristics	Mean ± SD	Median (range)	*P*-values
Gender			0.183
Male	0.803 ± 0.220	0.869 (−0.149–1)	
Female	0.780 ± 0.234	0.862 (−0.149–1)	
Age group			<0.001***
60-	0.816 ± 0.209	0.869 (−0.149–1)	
70-	0.754 ± 0.243	0.783 (−0.149–1)	
80-	0.646 ± 0.293	0.610 (−0.149–1)	
Area			0.016**
Urban	0.771 ± 0.214	0.783 (−0.005–1)	
Rural	0.812 ± 0.241	0.869 (−0.149–1)	
Education			<0.001***
Illiterate	0.714 ± 0.262	0.770 (−0.149–1)	
Primary school	0.779 ± 0.221	0.862 (−0.149–1)	
Junior high school	0.845 ± 0.193	0.869 (−0.03–1)	
Senior high/ technical school	0.846 ± 0.216	0.869 (−0.149–1)	
College and above	0.897 ± 0.141	1.000 (0.45–1)	
Medical insurance			0.127
No	0.852 ± 0.197	0.869 (0.114–1)	
Yes	0.787 ± 0.229	0.869 (−0.149–1)	
Marital status			0.025**
Married	0.803 ± 0.222	0.869 (−0.149-1)	
Single	0.885 ± 0.163	0.885 (0.77–1)	
Divorced	0.741 ± 0.243	0.770 (−0.149–1)	
Widowed	0.818 ± 0.237	0.869 (0.22–1)	
Employment status			<0.001***
Employed	0.842 ± 0.181	0.869 (0.056–1)	
Retired	0.828 ± 0.226	0.869 (−0.149–1)	
Unemployed	0.744 ± 0.236	0.770 (−0.149–1)	
Smoking status			0.115
No	0.782 ± 0.239	0.869 (−0.149–1)	
Yes	0.814 ± 0.190	0.869 (0.22–1)	
Drinking status			<0.001***
No	0.773 ± 0.237	0.862 (−0.149–1)	
Yes	0.859 ± 0.168	0.869 (0.22–1)	
Physical activity			<0.001***
No	0.706 ± 0.271	0.770 (−0.149–1)	
Yes	0.854 ± 0.162	0.869 (0.22–1)	
Health examination			0.141
No	0.778 ± 0.245	0.869 (−0.149–1)	
Yes	0.803 ± 0.207	0.869 (−0.149–1)	
Comorbidity			<0.001***
No	0.874 ± 0.176	1.000 (−0.149–1)	
Yes	0.730 ± 0.241	0.770 (−0.149–1)	
Income			0.002***
Low	0.831 ± 0.196	0.870 (−0.005–1)	
Middle	0.767 ± 0.250	0.862 (−0.149–1)	
High	0.771 ± 0.231	0.857 (−0.149–1)	

*$P < 0.1$, **$P < 0.05$, ***$P < 0.01$.

TABLE 4 | Factors influencing the EQ-5D-3L utility scores from the Tobit regression model.

Variables	Coefficient	SE	*P*-values
Gender			
Male	Ref.		
Female	−0.059	0.024	0.017**
Age group			
60-	Ref.		
70-	−0.035	0.029	0.224
80-	−0.118	0.041	0.004***
Area			
Urban	Ref.		
Rural	−0.025	0.057	0.655
Education			
Illiterate	Ref.		
Primary school	0.062	0.025	0.015**
Junior high school	0.119	0.041	0.004***
Senior high/technical school	0.105	0.039	0.007***
College and above	0.146	0.073	0.046**
Medical insurance			
No	Ref.		
Yes	−0.035	0.049	0.476
Marital status			
Married	Ref.		
Single	0.293	0.189	0.122
Divorced	0.014	0.086	0.867
Widowed	−0.039	0.022	0.086
Employment status			
Employed	Ref.		
Retired	−0.072	0.053	0.176
Unemployed	−0.055	0.047	0.244
Smoking status			
No	Ref.		
Yes	0.027	0.032	0.397
Drinking status			
No	Ref.		
Yes	0.060	0.037	0.106
Physical activity			
No	Ref.		
Yes	0.149	0.044	0.001***
Health examination			
No	Ref.		
Yes	0.066	0.029	0.023**
Comorbidity			
No	Ref.		
Yes	−0.195	0.077	0.011**
Income			
Low	Ref.		
Middle	−0.088	0.042	0.037**
High	−0.060	0.029	0.037**

*$P < 0.1$, **$P < 0.05$, ***$P < 0.01$.

older, while previous studies included all adults over 18 years old. Moreover, the present study found that the HRQoL of those aged 60 years and above with hypertension gradually decreased with age. It is possible that hypertension is a chronic disease which progresses with age and increasingly affects health (41). The functions and immunity of the body gradually decline with

age, and especially in the northeast of China where the winters are cold and long, the elderly people spend less time outside and have lesser physical activity (42). In addition, it is difficult for the elderly with high blood pressure to acquire knowledge on the management of hypertension, especially when information is largely obtained through the Internet in recent times (43).

Likewise, the HRQoL of elderly females with hypertension was also lower compared to their male counterparts in the present study. Similar gender differences in HRQOL of patients with hypertension have been found in Japan and South Korea populations (44, 45). This may be due to variances in social position and opportunities between males and females in different societies. In China, there are the gender inequities in areas such as socioeconomic status (20), education (21), and health (19). Hence, a low HRQoL among elderly females with hypertension would be expected.

The present study also found that patients with higher education levels demonstrated better HRQoL. This is consistent with the findings reported by Andrade et al. (46), Zhang et al. (21) and Saleem et al. (47). A possible explanation for this is that people with higher educational levels tend to have higher levels of health literacy, such as reducing salt intake, quitting smoking, restricting alcohol, and complying with medical advice, which are considered helpful for improving HRQoL (48).

Regular physical exercise is one of the important influencers of HRQoL in elderly people with hypertension, which is consistent with the conclusion of a previous study that utilized the SF-36 (49). Moreover, the HRQoL of patients with hypertension who underwent health examinations in the past year was significantly higher than that of patients who did not. These findings are consistent with the results in a previous study (20). Health management, such as regular physical exercise and medical examination, is beneficial in preventing and treating hypertension. For example, regular physical exercise could promote blood circulation and metabolism, reduce blood pressure, increase fat burning, and body shape maintenance (50). As for regular health examinations, it can help to detect chronic diseases including hypertension at an early stage, and help patients be mindful of their own health, improve their living habits, and pay attention to the prevention and treatment of hypertension and other comorbidities (20).

The present research also confirmed that elderly patients with hypertension and other comorbidities tended to have lower HRQoL, which is consistent with findings of previous studies (19, 20, 28, 51). Patients with hypertension are susceptible to a range of comorbidities, such as myocardial infarction, angina pectoris, stroke, and kidney failure, which is considered as one of main risk factors that reduce HRQoL (52). A previous study found that nearly 20% of the HRQoL scores could be caused by comorbidity, while only 2% of that are due to hypertension (53). It could be postulated that this variance of HRQoL is more serious in elderly patients with hypertension. Therefore, it is essential to consider commodity when evaluating HRQoL among elderly patients with hypertension, and prevent and treat comorbidity that may further decrease HRQoL.

We acknowledge that the current research has the following limitations. First, although the study sample is a regionally representation, findings from the present study may not be generalizable to other geographic areas in China. Second, as the present study utilized a cross-sectional design, it is difficult to ascertain the causal relationship between HRQoL and associated factors. Third, the cases of hypertension included in this study are restricted to those 60 years and above with a self-reported diagnosis of hypertension by a doctor, hence accuracy may be affected.

CONCLUSIONS

Overall, elderly patients with hypertension in China have a lower HRQoL than the general population. To improve the HRQoL of elderly patients with hypertension, it is imperative that better public health education is provided to enhance the knowledge of hypertension, encourage the adoption of healthy habits such as regular physical activity and health examination, and improve the management of coexisting diseases. More care should also be directed to females with hypertension who are above 80 years old.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The data and code are available from the corresponding author upon reasonable request. Requests to access these datasets should be directed to weidong218@126.com.

AUTHOR CONTRIBUTIONS

YW, QW, and WH contributed to the conception and design of the study. EZ, JiX, JuX, JL, MZ, BL, RL, MS, ZZ, YL, HYa, and HYu conducted the data reduction and analyses. XZ and WH wrote the manuscript. YW, QW, WH, and WT reviewed the manuscript. All authors read and approved the manuscript before submission.

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Measuring Hypertension Progression With Transition Probabilities: Estimates From the WHO SAGE Longitudinal Study

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This paper assessed the transition probabilities between the stages of hypertension severity and the length of time an individual might spend at a particular disease state using the new American College of Cardiology/American Heart Association hypertension blood pressure guidelines. Data for this study were drawn from the Ghana WHO SAGE longitudinal study, with an analytical sample of 1884 across two waves. Using a multistate Markov model, we estimated a seven-year transition probability between normal/elevated blood pressure (systolic $\leq$129 mm Hg & diastolic $<$80 mm Hg), stage 1 (systolic 130-139 mm Hg & diastolic 80-89 mm Hg), and stage 2 (systolic $\geq$140mm Hg & diastolic$\geq$90 mm Hg) hypertension and adjusted for the individual effects of anthropometric, lifestyle, and socio-demographic factors. At baseline, 22.5% had stage 1 hypertension and 52.2% had stage 2 hypertension. The estimated seven-year transition probability for the general population was 19.0% (95% CI: 16.4, 21.8) from normal/elevated blood pressure to stage 1 hypertension, 31.6% (95% CI: 27.6, 35.4%) from stage 1 hypertension to stage 2 hypertension, and 48.5% (45.6, 52.1%) for remaining at stage 2. Other factors such as being overweight, obese, female, aged 60+ years, urban residence, low education and high income were associated with an increased probability of remaining at stage 2 hypertension. However, consumption of recommended servings of fruits and vegetables per day was associated with a delay in the onset of stage 1 hypertension and a recovery to normal/elevated blood pressure. This is the first study to show estimated transition probabilities between the

stages of hypertension severity across the lifespan in sub-Saharan Africa. The results are important for understanding progression through hypertension severity and can be used in simulating cost-effective models to evaluate policies and the burden of future healthcare.

Keywords: elevated blood pressure, hypertension, multi-state model, transition probabilites, ACC/AHA 2017 hypertension guidelines, sub-Saharan Africa

INTRODUCTION

Uncontrolled hypertension—or elevated blood pressure (BP) is a leading risk factor of cardiovascular diseases and global mortality (1–3). The increase in demographic aging, urbanization, consumption of energy dense and nutrient poor foods, and the globalization of unhealthy lifestyles has increased the risk of hypertension especially, for populations where universal health coverage remains low and inaccessible to many (2). This is most predominant in sub-Saharan Africa (SSA), where the prevalence of hypertension is the highest, affecting 46% of adults older than 25 years compared to 35% in the America's and 40% for the rest of the world (2). This health risk has the potential to decrease the life expectancy of populations in these regions, where majority have no awareness of their hypertensive status (4, 5), and those who are even aware have a lower likelihood of treating and controlling the disease (6). An assessment of the state of hypertension care in 44 Low- and Middle-Income Countries (LMICs) showed that for those with hypertension, 29.9% had received treatment and only 10.3% had achieved control, with worse performances for countries in SSA (7).

To diagnose and control hypertension, the measurement of BP—categorized based on either internationally recognized or arbitrary thresholds—is used in determining the level of severity and the required treatment in cases of values with increased risk of cardiovascular diseases (CVD) (8). The American College of Cardiology/American Heart Association (ACC/AHA) recently developed a new guideline for the prevention, detection, evaluation, and management of high BP among adults in the United States (9). This guideline is an updated version of the Seventh report of the Joint National Committee (JNC-7) on Prevention, Detection, Evaluation, and Treatment of high BP published in 2003 and aimed at improving hypertension treatment and control (10). The new guideline defines normal BP as Systolic BP <1 20/Diastolic BP < 80 mm Hg; elevated BP as 120–129/<80 mm Hg; stage 1 hypertension as 130–139 or 80–89 mm Hg, and stage 2 hypertension as ≥ 140 or ≥90 mm Hg (9, 11). These new cut-offs relative to the 2003 version (10) are touted to increase the number of people diagnosed as having hypertension in each age group (12). Although critiqued for the psychosocial effects it could have on previously healthy people who will now be labeled as hypertensive and the potential to increase financial burden on households and governments (12), the new guidelines have the potential of detecting early, elevated BP or Stage 1 hypertension which have been found to increase the likelihood of CVD (13). While its applicability to developing countries has been questioned (12), the urgent need for early detection, treatment, and control of hypertension with the potential to decrease cardiometabolic diseases and mortality makes its application warranted. Untreated hypertension could open the gateway to all kinds of CVDs, which are now on the increase in LMICs (3, 14, 15).

The need to control and manage the risk of hypertension has become even more critical due to the detrimental consequences it has on the individual, families, communities, and governments at large. At the individual level, it leads to a deterioration of health, exposure to several diseases and health risks such as ischemic heart disease, stroke, blindness, rupture of blood vessels, cognitive impairment, arrhythmias, vascular dementia, and kidney failure (2, 16). Households carry much of the physical, emotional, and financial burden when family members experience complications with hypertension. For some, this financial drain has the potential to lead to a decline in household income and increase impoverishment (17). Within the community, it could lead to both, human capital and financial losses (18). At the national level, this has the potential to escalate healthcare expenditure putting the management of other critical diseases at a deficit and could also stifle economic development. Additionally, underdeveloped health systems in regions such as SSA compound the problem as several people with hypertension may go undiagnosed, untreated, and uncontrolled thereby increasing the burden of diseases and risk of mortality (2, 19).

To better manage and target policies and resources toward the prevention of hypertension, it is useful to understand the probabilities associated with transitioning from one stage of this medical condition to the other. Knowledge of the burden associated with this health risk and its management has the potential to improve medical and financial decisions aimed at reducing mortality associated with hypertension. Thus, knowing how long it takes a population to transition from normal BP to elevated BP, or stage 1 or stage 2 hypertension is vital for public health and government fiscal policies and planning. Therefore, this study aimed at estimating the transition probabilities between the different stages of hypertension severity (normal/elevated BP, stage 1 hypertension, and stage 2 hypertension) over a seven-year period.

Previous studies on LMICs have tried to estimate the relationships between the stages of hypertension and associated factors using random effects multinomial logistic regression (18). However, such studies do not estimate sojourn times at a disease state or transition probabilities to a worse state or recovery to a healthy state. The use of multistate models presents a novel statistical approach in analyzing the progression between the different stages/states of hypertension severity as used in previous studies to describe the complexities of diseases involving multiple states (20–22).

Although several multistate models have been used to estimate transition probabilities (23), we use the Markov model, which describes the processes by which individuals progress through a finite number of health states in a unit of time (24), to estimate the transition probabilities between three distinct states of hypertension. We hypothesize that:

(1) The transition probability in the general population from normal/elevated BP to stage 1 hypertension will be higher than the transition probability to stage 2 hypertension over a 7-year period.
(2) The probability of reverting back to normal/elevated BP from stage 1 will be higher than transitioning to stage 2 hypertension.
(3) The probability of staying at stage 2 will be higher than the probability of staying at stage 1 over the 7-year period.
(4) The transition probability to a more severe hypertensive state will be higher for obese participants than those with normal weight over a 7-year period.

MATERIALS AND METHODS

Study Population

We used data from the World Health Organization Study on global AGEing and adult health (WHO SAGE) for this study. The WHO SAGE is a longitudinal study on the health and well-being of adult populations aged ≥50 years in six countries: China, Ghana, India, Mexico, Russian Federation, and South Africa. It also collects sample data of younger adults, aged 18–49 years for comparison (25). For this study, a combination of data from both the younger and older cohorts were used. In Ghana, SAGE collected individual-level data from nationally representative households of adults using stratified, multistage cluster design. Primary sampling units were stratified by region and locality (rural/urban) at baseline and the same was used at waves 1 (2007/2008) and 2 (2014/2015). At wave 1 and wave 2, 5,110 and 4,704 respondents, respectively, aged 18 years and older participated in the study. However, an analytical sample of 1,884 was used for those who participated in wave 1 and 2, after the exemption of pregnant women. The SAGE data is unique because of the objective measurements made on hypertension, anthropometric measurement on Body-Mass Index (BMI), and socio-demographic characteristics which are covered in the individual survey. Systematic replacement was used in Wave 2 to account for losses to the sample from Wave 1.

Classification of Hypertension Stages

The measure of hypertension was taken from objective measurements of respondents' BP (systolic/diastolic), which were taken 3 times. Measurements were conducted using a Boso Medistar Wrist Blood Pressure Monitor Model S. To take the readings, respondents were asked to sit quietly with their legs uncrossed and relaxed (26). The wrist cuff of the device was then wrapped around the respondent's left wrist and secured with the Velcro strap for a snug fit. The respondent was then made to place the wrist against their chest approximately at the level of their heart (27). Additionally, the hand was made to rest approximately at the level of the shoulder, the elbow at the waist, and the arm against the body. The free hand was then placed under the elbow to support the arm with the device on the wrist. The respondent was asked to take 3 deep, slow breaths before the measurement started. With each measurement, the staff recorded the systolic BP, diastolic BP, and pulse rate. After each recording, the respondent rested for a minute until the next reading for all three recordings (27).

The mean of all three recordings was used as a diagnosis for scores on BP, which was normally distributed and then categorized based on the new guidelines by the ACC/AHA (9). The ACC/AHA recognize four BP groups in adults: Normal BP (SBP < 120 and DBP <80 mmHg); elevated BP (120–129 & <80 mm Hg); stage 1 hypertension (130–139/80–89 mm Hg), and stage 2 hypertension (≥140/≥90 mm Hg)(9, 11). At stage 1, lifestyle and behavioral changes including tobacco cessation, weight loss, moderation in alcohol intake, increased physical activity, reduced sodium intake, and consumption of a healthy diet are recommended. Adults are encouraged to adhere to these changes over a long period to maximize the benefit of a healthy lifestyle (9). At stage 2, doctors will prescribe a combination of BP medication and lifestyle changes. In order to assess the transition probability between extreme forms of hypertension, we merged normal and elevated BP to create three categories instead of four. Hypertension stages were differentiated into normal/elevated BP (SBP ≤ 129 and DBP <80 mmHg); stage 1 hypertension (SBP:130–139/DBP: 80–89 mm Hg), and stage 2 hypertension (SBP≥140/DBP ≥ 90 mm Hg).

Classification of Body Mass Index

Respondents were measured for their body weight and height by trained assessors using standard protocol (27). Pregnant women were exempted from weight measurements in both surveys (27). BMI was calculated as the person's weight in kilograms divided by the square of their height in meters (kg/m^2). WHO classifications were used to categorize BMI as follows: normal/healthy weight, BMI ≥18.5 and <25.0 kg/m^2; underweight, BMI < 18.5; overweight, BMI = 25.0 and <30.0 kg/m^2; and obesity as BMI ≥30.0 kg/m^2 (28).

Other Covariates

Other covariates used in this study included sex, coded as "1= female" vs. "2= male;" age, coded as "1= ≤40 years," "2 = 41–60 years," and "3 = above 60 years;" and level of education which was coded as "1 = less than high school" vs. "2 = high school and above." Place of residence was coded as "1 = rural" vs. "2 = urban;" household wealth index constructed from a total of 22 assets/ characteristics/ items were converted into wealth quintiles (lowest, low, moderate, high, higher) (29, 30); and fruits and vegetables intake per day if they consumed ≥5 servings of fruits and/or vegetables per day (equivalent to 400 g), coded as "1 = met requirement" and "2 = below requirement" according to international standards (31). Even though self-reported medication or therapy over the past 12 months is reported in the summary statistics, this was not used in the model because of 90% (Wave 1) and 99% (Wave 2) missing reported data.

Statistical Analysis: Calculation of Transition Probabilities

We conducted descriptive analysis of the sample. Next, we estimated a multistate Markov model (24) as described elsewhere (32). Seven-year transition probabilities from the cohort were estimated using a validated multistate continuous-time Markov model in the "msm" package in R (24). A transition probability meets the requirement of the Markov assumption that the conditional distribution of future states of the process given current and past states depends only on the current state and not on the past states (24). The Markov model has been applied and validated in several previous clinical studies (21, 22). In this study, we applied a three-hypertension-states model with states labeled as normal and elevated, stage 1 and stage 2 (**Figure 1**). In this model, the underlying progression into a specific state rather than the observed progression is emphasized since transition may have mostly occurred outside the follow-up dates and a two-step movement (i.e., movement into the next two states) is not necessarily instantaneous. Thus, a person with normal or elevated BP at time $t = 0$, may pass through the stage 1 hypertension state before ending in the stage 2 hypertension at time $t = 7$.

Since the exact time of transition is not observed but evolved continuously in time, and is presumed to have occurred before the next assessment, the state-to-state transitions are interval-censored (21, 22, 24). Thus, due to unknown exact transition time and irregular follow-up times for assessment among individual observations, the standard multistate model could not be used. Rather, we employed the time-homogenous continuous-time Markov model that can accommodate such irregularities to calculate transition intensities and the transition probabilities (24). At time t in the model, the individual is in state $S(t)$. Movement into the next state is guided by a set of transition intensities, (i.e., the rate at which an individual has the likelihood of moving from one state i to another state j at a given time (t). The intensities form a "3 × 3" matrix Q whose rows sum to zero. The diagonals of the matrix are the rates at which individuals do not transition and remain in their state whereas the off-diagonals represent the rates at which individuals transition into other states (21, 22, 24). The model specified that an individual transitioning to a nonadjacent state (e.g., from normal/elevated BP to stage 2 hypertension) must have passed through the immediate adjacent state (i.e., stage 1 hypertension state) rather than a direct movement to a nonadjacent state. Therefore, the maximum likelihood estimate was zero for the nonadjacent states (i.e., a two-step movement).

Under the assumption that Q is constant over time, the transition probability $P(t)$, which is the chance of transitioning from one stage to the other is calculated by taking the matrix exponential of the scaled transition intensity matrix as follows:

$$\boldsymbol{P(t) = Exp(tQ)}\ t\ \geq\ 0.$$

In this study, a 7-year transition probability was calculated. Additionally, using the unadjusted model, we calculated the mean sojourn times (i.e., the average time spent in a specific state before transitioning into another state) for each state. Due to the model flexibility, covariates including sex, age, educational level, place of residence and household wealth status were fitted in separate models to examine if these factors changed the probabilities.

To validate the estimated transition probabilities, a Markov model was developed in TreeAge Pro 2018 (TreeAge Software Inc. Williamstown, Massachusetts, USA). Four Markov states were included in the model, that is, normal or elevated BP, stage 1 and stage 2 hypertension and death. Simulated subjects' transit between states using the calculated transition probabilities. Age-specific mortality risk was taken from the Ghanaian life table (33). A 5-year interval cohort analysis and prevalence of the three hypertension states were compared to the observed prevalence in Wave 2. The probabilities were valid if the observed prevalence in Wave 2 fell within the 95% CI of the estimated expected prevalence or if the observed prevalence in Wave 2 falls 1% lower or higher above the expected prevalence.

Statistical analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria) and validation was assessed using TreeAge Pro 2018.

RESULTS

The sample characteristics are shown in **Table 1**. An analytical sample of 1,884 respondents was examined at both time points. Of this sample, 25.3% had normal/elevated BP, 22.5% could be classified as having stage 1 hypertension, 52.2% as stage 2 hypertension at wave 1. By wave 2, 42.5% could be classified as

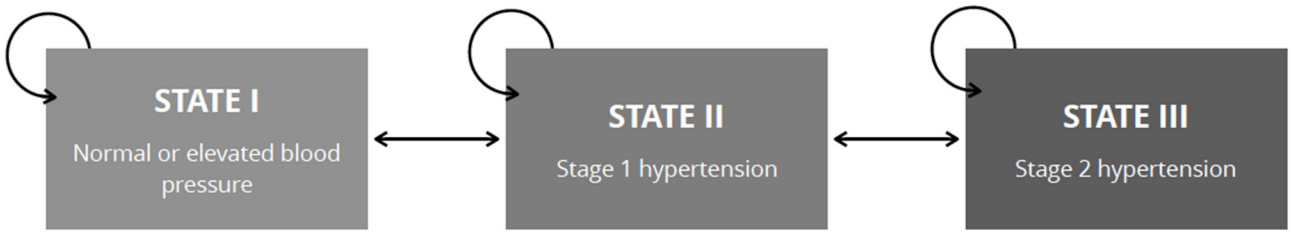

FIGURE 1 | Allowable transitions between hypertension severity states used to estimate 7-year transition probabilities. The arrows illustrate the possible transitions between states. State transition can be a transition into the immediate next state, previous or into itself. A bidirectional transition is allowed. A two-step movement is allowed; however, the subject may pass through the immediate adjacent state first. Respondent can be in only one state at a time.

having normal/elevated BP, 21.1% at stage 1 hypertension, 36.4% at stage 2 hypertension. The sex distribution was the same across both time points, with males constituting 56% and females 44%. By wave 2, 2.7% were <40 years, 29.1% were between 41–60 years, and 68.2% were more than 60 years old. Of the 1,884 respondents, 13.4% were underweight, 55.1% had normal weight, 20.4% were overweight, and 11.1% were obese.

We show the prevalence (95% CI) of the three hypertension stages in 2007/2008 and 2014/2015 in **Table 2**. While the prevalence of normal BP increased, stage 1 and 2 hypertension decreased in wave 2.

TABLE 1 | Descriptive statistics of variables used in assessing progression in hypertension severity between 2007/2008 to 2014/2015.

Variables	Wave 1 (2007/8) *n* (%)	Wave 2 (2014/15) *n* (%)
Sample size	1884	1884
Hypertension stages		
Normal/elevated BP	477 (25.3)	801 (42.5)
Stage 1	424 (22.5)	397 (21.1)
Stage 2	983 (52.2)	686 (36.4)
Sex		
Males	1055 (56.0)	1055 (56.0)
Females	829 (44.0)	829 (44.0)
Age group, years		
≤40	97 (5.2)	51 (2.7)
41-60	942 (50.0)	548 (29.1)
>60	845 (44.9)	1285 (68.2)
BMI categories		
Underweight	237 (12.6)	252 (13.4)
Normal weight	1112 (59.0)	1038 (55.1)
Overweight	364 (19.3)	385 (20.4)
Obesity	171 (9.1)	209 (11.1)
Educational status		
High	505 (26.8)	514 (27.3)
Low	1379 (73.2)	1370 (72.7)
Place of residence		
Rural	1160 (61.9)	1167 (61.9)
Urban	724 (38.1)	717 (38.1)
Wealth index		
Lowest	339 (18.0)	237 (12.6)
Low	397 (21.1)	463 (24.6)
Moderate	422 (22.4)	401 (21.3)
High	391 (20.8)	419 (22.2)
Higher	335 (17.8)	364 (19.3)
Medications or other treatment in the past 12 months		
No response	1695 (90)	1,866 (99)
No	40 (2.1)	8 (0.4)
Yes	149 (7.9)	10 (5)
Fruit and vegetable intake		
Below requirement	1,316 (69.9)	832 (44.2)
Met requirement	568 (30.2)	1,052 (55.8)

BP, Blood Pressure; (%), percentages.

Table 3 shows the frequency of transition between the three hypertension stages from 2007/2008 at the beginning to 2014/2015 at the end. Transitions occurred between all three stages observed in this study. Ninety-three transitioned from normal BP to stage 1 hypertension, with 80 transitioning from normal BP to stage 2 hypertension over the 7-year period. One hundred and ninety-nine transitioned from stage 1 hypertension to normal /elevated BP, 89 remained at stage 1, while 136 progressed to stage 2 hypertension. Two hundred and fifteen transitioned from stage 2 hypertension to stage 1,298 from stage 2 to normal/elevated BP, while 470 remained at stage 2 hypertension.

Table 4 shows the transition intensity matrix of the maximum likelihood estimates (95% CI) over a 7-year period. The results do show a likely transition from normal/elevated BP to stage 1 hypertension (0.129) and a recovery from stage 2 hypertension to stage 1 hypertension (0.185); however, this likelihood increased for a transition from stage 1 hypertension to normal BP/elevated BP (0.321) and stage 1 hypertension to stage 2 hypertension (0.264). The mean sojourn time from normal/elevated BP to stage 1 hypertension was $-1/(-0.129) = 7.75$ years, $-1/(-0.584) = 1.7$ years for stage 1 hypertension to stage 2 hypertension or recover back to normal/elevated BP, and $-1(-0.185) = 5.4$ years from stage 2 hypertension to stage 1 hypertension.

Using the information from the two waves, the 7-year transition probabilities were estimated and are shown in **Table 5**. The 7-year transition probability from normal/elevated BP to stage 1 hypertension was 19% (95% CI: 16.4, 21.8%) and from normal/elevated BP to stage 2 hypertension was 16.9% (95%

TABLE 2 | Prevalence (95% CI) of hypertension severity between 2007/2008 to 2014/2015.

		Wave 1 Prevalence (95% CI)	Wave 2 Prevalences (95% CI)
n		1884	1,884
Hypertension Stages	Normal/elevated BP	25.3 (23.4, 27.3)	42.5 (40.3, 44.8)
	Stage 1 Hypertension	22.5 (20.7, 24.4)	21.1 (19.3, 23.0)
	Stage 2 Hypertension	52.1 (49.9, 54.4)	36.4 (34.3, 38.6)

Wave 1 = 2007/2008; Wave 2 =2014/2015.

TABLE 3 | Total number of transitions between three hypertension states from 2007/2008 to 2014/2015.

	To:		
From: wave 1 Hypertension severity	**Wave 2 Normal/elevated blood pressure**	**Stage 1 hypertension**	**Stage 2 hypertension**
Normal/elevated BP	304	93	80
Stage 1 hypertension	199	89	136
Stage 2 hypertension	298	215	470

Wave 1 = 2007/2008; Wave 2 =2014/2015.

TABLE 4 | Transition intensity matrix for a Multistate Markov Model of the transition between normal/elevated blood pressure, Stage 1 and Stage 2 hypertension across adults (18+ years) in Ghana between 2007/2008-2014/2015.

	To					
From	**Normal/elevated BP**		**Stage 1 Hypertension**		**Stage 2 Hypertension**	
Hypertension state	MLE[a]	95% CI	MLE	95% CI	MLE	95% CI
Normal/elevated BP	−0.129	−0.167, −0.100	0.129	0.100, 0.167	0[b]	–
Stage 1 hypertension	0.321	0.260, 0.395	−0.584	−0.678, −0.504	0.264	0.203, 0.343
Stage 2 hypertension	0[b]	–	0.185	0.152, 0.225	−0.185	0.225, −0.152

BP, Blood Pressure; CI, Confidence intervals; MLE, Maximum Likelihood Estimates; the mean time spent in the Normal/elevated BP state before a transition was made into another state was −1/ (−0.129) =7.8 years, a mean of −1/ (−0.584) =1.7 years for State 1 Hypertension, and a mean of −1/ (−0.185) =5.4 years for State 2 Hypertension; [a]MLE, maximum likelihood estimate; [b]MLE was zero for the nonadjacent states.

CI: 14.1, 19.6%). After 7 years, the probability of transitioning from stage 1 hypertension to normal/elevated BP was 47.3% (95% CI: 43.6%, 51.2%) and stage 1 hypertension to stage 2 hypertension was 31.6% (95% CI: 27.6, 35.4%). For respondents who were at stage 2 hypertension 7 years ago, the probability of transitioning to stage 1 hypertension was 22.1% (95% CI: 19.9, 24.5%), reverting to normal BP/elevated BP was 29.4% (95% CI: 26.7, 31.8%), and remaining at stage 2 hypertension was 48.5% (95% CI: 45.6, 52.1%).

The validity of our calculated transition probabilities was assessed to be good. The observed prevalence for normal/elevated BP, stage 1 hypertension, and stage 2 hypertension at wave 2 was 42.5, 21.1, and 36.1% respectively. The calculated prevalence from the Markov models for normal/elevated BP was 42.2% (95% CI: 41.3, 42.9%), stage 1 hypertension was 21.1% (95%CI: 21.0, 21.3%), and stage 2 hypertension was 36.7% (95% CI: 35.7, 37.7%). All calculated prevalence estimates for hypertension severity fell within the 95% CI or were 1% lower than the observed prevalence of the three states of hypertension severity.

The results for the explanatory variables show an increased transition probability from normal/elevated BP to stage 1 hypertension and stage 1 hypertension. Over a 7-year period, being a male increased the transition probability from normal/elevated BP to stage 1 hypertension (20%; 95% CI: 16.5, 23.4%), stage 1 to stage 2 hypertension (28.2%; 95% CI: 23.7, 32.7%), and remaining at stage 2 hypertension (46.5%, 95% CI: 42.2, 50.6%). Comparatively, females had a higher transition probability from stage 1 to stage 2 hypertension (females: 36.6%; males: 28.2%) and for remaining at stage 2 hypertension (females: 50.6%; males: 46.5%). Between the three age cohorts examined in this study, the transition probability from normal/elevated BP to stage 1 hypertension (19.6%; 95% CI:15.7, 23.6%) and from stage 1 to stage 2 hypertension (36.3%, 95% CI: 30.6, 21.8%) was higher for those aged 41–60 years and those above 60 years, respectively. However, the probability of remaining at stage 2 hypertension was consistently higher for all age groups (≤40: 40.4%; 41–60: 43.7%; >60: 53.9%) but highest among those above 60 years. For BMI categories, the transition probability from normal/elevated BP to stage 1 hypertension increased most for those underweight (21.8%, 95% CI: 12.9, 29.1%) compared to normal weight, overweight, and obesity. However, the probability of transitioning from stage 1 to stage 2 hypertension was much higher among those overweight (35.8%) and obese (41.5%). The transition probability of remaining at stage 2 hypertension was consistently higher across all four BMI cohorts (underweight: 43.7%; normal weight: 48.1%; overweight: 48.6%; obesity: 54.6%), but highest among the obese. Having less than high school education relative to high school or more education (19.7 vs.16.8%), rural relative to urban residence (19.2 vs. 18.3%), lowest wealth quintile relative to higher wealth (20.7 vs.16.1%) increased the transition probability from normal/elevated BP to stage 1 hypertension. Differently, high relative to low education (32.5 vs. 31.2%), urban relative to rural residence (35.2 vs. 29.6%), higher relative to low wealth quintile (40.4 vs. 26.7%) were associated with a higher transition probability from stage 1 to stage 2 hypertension. The transition probability of those who met the WHO recommendation for the intake of fruit and vegetables was 90.8% for remaining at normal/elevated BP, 8.1% for transitioning to stage 1, and 1.2% for transitioning to stage 2. The transition probability back from stage 1 to normal/elevated BP was 90.8% but 18.8% to stage 2 hypertension. Comparatively, those who did not meet the recommended servings of fruits and vegetables had a transition probability of 89% for remaining at normal/elevated BP, 9.6% to transition to stage 1, and 1.3% to stage 2. However, the transition probability back to normal/elevated BP from stage 1 hypertension was 22.3% and 18.2% to stage 2 hypertension.

The transition probability of remaining at stage 2 hypertension was consistently higher for those with both low and high education (49.1 and 46.8%), rural and urban residence (47.1 and 50.3%), lowest, low, moderate, high, and higher wealth quintile (48.6, 50.6, 45.5, 51.5, and 47.4%), and those who met the WHO recommendation for the intake of fruits and vegetables and those who did not meet the requirement (84.1 and 85.3%).

The hazard ratios **Appendix A** in Supplementary Material were estimated to determine the vector of covariates that were significant predictors of either forward and backward transitions.

DISCUSSION

This study estimated the transition probabilities between the stages of hypertension severity—normal and elevated BP, stage 1 hypertension, and stage 2 hypertension—and the length of time an individual might spend at a particular disease state. With hypertension being a leading risk factor of CVD and

TABLE 5 | Seven-year transition probabilities between hypertension severity states calculated from Ghana WHO-SAGE Waves 1 and 2 for the general population and subgroups.

			To		
		From	**Normal Blood Pressure Prob. (95% CI)**	**Stage 1 Hypertension Prob. (95% CI)**	**Stage 2 Hypertension Prob. (95% CI)**
General population	Hypertension states	Normal/elevated Blood Pressure	0.641 (0.600, 0.683)	0.190 (0.164, 0.218)	0.169 (0.141, 0.196)
		Stage 1 Hypertension	0.473 (0.436, 0.512)	0.211 (0.192, 0.233)	0.316 (0.276, 0.354)
		Stage 2 Hypertension	0.294 (0.267, 0.318)	0.221 (0.199, 0.245)	0.485 (0.456, 0.521)
Sex	Male	Normal/elevated Blood Pressure	0.653 (0.601, 0.706)	0.200 (0.165, 0.234)	0.147 (0.116, 0.185)
		Stage 1 Hypertension	0.496 (0.445, 0.538)	0.222 (0.197, 0.253)	0.282 (0.237, 0.327)
		Stage 2 Hypertension	0.302 (0.267, 0.337)	0.233 (0.204, 0.267)	0.465 (0.422, 0.506)
	Female	Normal/elevated Blood Pressure	0.622 (0.551, 0.694)	0.176 (0.137, 0.221)	0.203 (0.158, 0.250)
		Stage 1 Hypertension	0.438 (0.378, 0.495)	0.196 (0.172, 0.228)	0.366 (0.302, 0.429)
		Stage 2 Hypertension	0.287 (0.246, 0.319)	0.208 (0.177, 0.240)	0.506 (0.465, 0.558)
Age group, years	≤40	Normal/elevated Blood Pressure	0.739 (0.626, 0.899)	0.161 (0.063, 0.253)	0.100 (0.028, 0.185)
		Stage 1 Hypertension	0.705 (0.342, 0.788)	0.159 (0.100, 0.356)	0.136 (0.065, 0.355)
		Stage 2 Hypertension	0.455 (0.168, 0.596)	0.141 (0.076, 0.377)	0.404 (0.255, 0.607)
	41-60	Normal/elevated Blood Pressure	0.648 (0.592, 0.708)	0.196 (0.157, 0.236)	0.156 (0.119, 0.194)
		Stage 1 Hypertension	0.417 (0.415, 0.518)	0.230 (0.204, 0.260)	0.299 (0.250, 0.351)
		Stage 2 Hypertension	0.313 (0.275, 0.353)	0.250 (0.217, 0.280)	0.437 (0.398, 0.486)
	>60	Normal/elevated Blood Pressure	0.616 (0.551, 0.684)	0.184 (0.144, 0.227)	0.200 (0.157, 0.245)
		Stage 1 Hypertension	0.442 (0.385, 0.493)	0.195 (0.169, 0.229)	0.363 (0.306, 0.418)
		Stage 2 Hypertension	0.262 (0.223, 0.297)	0.198 (0.169, 0.230)	0.539 (0.496, 0.587)
BMI categories	Underweight	Normal/elevated Blood Pressure	0.615 (0.524, 0.763)	0.218 (0.129, 0.291)	0.167 (0.091, 0.230)
		Stage 1 Hypertension	0.522 (0.352,0.610)	0.222 (0.174, 0.305)	0.257 (0.163, 0.382)
		Stage 2 Hypertension	0.342 (0.224, 0.421)	0.221 (0.147, 0.319)	0.437 (0.354, 0.563)
	Normal weight	Normal/elevated Blood Pressure	0.638 (0.587, 0.689)	0.201 (0.167, 0.235)	0.161 (0.129, 0.1932)
		Stage 1 Hypertension	0.471 (0.419, 0.519)	0.225 (0.199, 0.253)	0.305 (0.258, 0.356)
		Stage 2 Hypertension	0.286 (0.253, 0.319)	0.232 (0.205, 0.262)	0.481 (0.443, 0.526)
	Overweight	Normal/elevated Blood Pressure	0.646 (0.529, 0.759)	0.154 (0.097, 0.220)	0.200 (0.123, 0.282)
		Stage 1 Hypertension	0.467 (0.382, 0.547)	0.175 (0.142, 0.226)	0.358 (0.270, 0.443)
		Stage 2 Hypertension	0.323 (0.254, 0.379)	0.191 (0.149, 0.239)	0.486 (0.432, 0.569)
	Obesity	Normal/elevated Blood Pressure	0.722 (0.493, 0.870)	0.125 (0.048, 0.250)	0.153 (0.060, 0.308)
		Stage 1 Hypertension	0.399 (0.260, 0.544)	0.186 (0.135, 0.272)	0.415 (0.254, 0.553)
		Stage 2 Hypertension	0.246 (0.159, 0.304)	0.209 (0.144, 0.282)	0.546 (0.472, 0.668)
Educational status	High	Normal/elevated Blood Pressure	0.692 (0.613, 0.763)	0.168 (0.124, 0.223)	0.140 (0.097, 0.189)
		Stage 1 Hypertension	0.454 (0.379, 0.525)	0.221 (0.184, 0.267)	0.325 (0.2595, 0.393)
		Stage 2 Hypertension	0.286 (0.236, 0.332)	0.246 (0.203, 0.289)	0.468 (0.415, 0.534)
	Low	Normal/elevated Blood Pressure	0.623 (0.573, 0.672)	0.197 (0.168, 0.229)	0.180 (0.147, 0.214)
		Stage 1 Hypertension	0.480 (0.437, 0.518)	0.208 (0.188, 0.233)	0.312 (0.268, 0.357)
		Stage 2 Hypertension	0.297 (0.264, 0.326)	0.212 (0.190, 0.239)	0.491 (0.458, 0.531)
Place of residence	Rural	Normal/elevated Blood Pressure	0.644 (0.593, 0.695)	0.194 (0.161, 0.228)	0.163 (0.133, 0.196)
		Stage 1 Hypertension	0.493 (0.443, 0.535)	0.211 (0.189, 0.240)	0.296 (0.252, 0.343)
		Stage 2 Hypertension	0.309 (0.270, 0.343)	0.221 (0.193, 0.252)	0.471 (0.431, 0.516)
	Urban	Normal/elevated Blood Pressure	0.635 (0.556, 0.708)	0.183 (0.142, 0.236)	0.182 (0.132, 0.231)
		Stage 1 Hypertension	0.439 (0.378, 0.497)	0.209 (0.181, 0.247)	0.352 (0.285, 0.414)
		Stage 2 Hypertension	0.275 (0.232, 0.311)	0.222 (0.189, 0.257)	0.503 (0.460, 0.560)
Wealth index	Lowest	Normal/elevated Blood Pressure	0.601 (0.526, 0.686)	0.207 (0.153, 0.263)	0.192 (0.133, 0.251)
		Stage 1 Hypertension	0.490 (0.386, 0.564)	0.209 (0.171, 0.263)	0.301 (0.221, 0.387)
		Stage 2 Hypertension	0.309 (0.234, 0.374)	0.205 (0.153, 0.271)	0.486 (0.408, 0.580)
	Low	Normal/elevated Blood Pressure	0.658 (0.565, 0.745)	0.205 (0.145, 0.268)	0.137 (0.090, 0.199)
		Stage 1 Hypertension	0.513 (0.421, 0.588)	0.220 (0.179, 0.279)	0.267 (0.193, 0.359)

(Continued)

TABLE 5 | Continued

		From	To		
			Normal Blood Pressure Prob. (95% CI)	Stage 1 Hypertension Prob. (95% CI)	Stage 2 Hypertension Prob. (95% CI)
		Stage 2 Hypertension	0.278 (0.215, 0.331)	0.216 (0.171, 0.271)	0.506 (0.437, 0.581)
	Moderate	Normal/elevated Blood Pressure	0.668 (0.574, 0.754)	0.195 (0.137, 0.262)	0.137 (0.088, 0.194)
		Stage 1 Hypertension	0.501 (0.421, 0.568)	0.225 (0.188, 0.280)	0.274 (0.198, 0.360)
		Stage 2 Hypertension	0.306 (0.247, 0.356)	0.239 (0.195, 0.292)	0.455 (0.399, 0.525)
	High	Normal/elevated Blood Pressure	0.645 (0.553, 0.736)	0.173 (0.119, 0.235)	0.182 (0.123, 0.250)
		Stage 1 Hypertension	0.489 (0.399, 0.562)	0.183 (0.148, 0.239)	0.328 (0.244, 0.416)
		Stage 2 Hypertension	0.296 (0.233, 0.347)	0.189 (0.150, 0.239)	0.515 (0.460, 0.592)
	Higher	Normal/elevated Blood Pressure	0.639 (0.520, 0.746)	0.161 (0.105, 0.232)	0.200 (0.128, 0.287)
		Stage 1 Hypertension	0.371 (0.288, 0.468)	0.225 (0.186, 0.281)	0.404 (0.312, 0.480)
		Stage 2 Hypertension	0.280 (0.209, 0.329)	0.245 (0.196, 0.297)	0.474 (0.415, 0.575)
Fruit and vegetable intake	Met requirement	Normal/elevated Blood Pressure	0.908 (0.864, 0.940)	0.081 (0.051, 0.122)	0.012 (0.007, 0.020)
		Stage 1 Hypertension	0.241 (0.177, 0.317)	0.571 (0.484, 0.641)	0.188 (0.124, 0.281)
		Stage 2 Hypertension	0.025 (0.018, 0.035)	0.134 (0.099, 0.177)	0.841 (0.794, 0.881)
	Below requirement	Normal/elevated Blood Pressure	0.890 (0.856, 0.916)	0.096 (0.072, 0.128)	0.013 (0.010, 0.018)
		Stage 1 Hypertension	0.223 (0.181, 0.273)	0.595 (0.540, 0.640)	0.182 (0.141, 0.232)
		Stage 2 Hypertension	0.021 (0.017, 0.026)	0.126 (0.105, 0.154)	0.853 (0.823, 0.876)

Wave 1: 2007/2008; wave 2: 2014/2015.

worldwide mortality (1–3), the ability to estimate how long a population stays at a particular health state and when the affected population would either transition to a better or worse state is critical for government and healthcare fiscal policies and planning. Our results show that after a 7-year period, one in five of the general population had a probability of transitioning from normal/elevated BP to stage 1 hypertension; three in ten progressed from stage 1 to stage 2 hypertension; and almost one in two remained at stage 2 hypertension. The novel approach used in this study makes it the first in SSA to examine progression in hypertension states, which has implications for prevalence control, government health expenditure, and cost-effective interventions in managing this medical condition. By the application of the ACC/AHA new guidelines for the prevention, detection, evaluation, and management of high BP in adults, this study shows the importance of having a guideline that will at least facilitate the early detection of hypertensive cases, with the potential for control and treatment. In testing our hypotheses, several important findings were made in this study which are worth discussing and do contribute to the literature on hypertension.

First, over a 7-year period, the probability of progressing from normal/elevated BP to an adjacent state, that is, stage 1 hypertension was 19%, greater than progressing to a non-adjacent state, stage 2 hypertension which was 16.9%. Since an individual can be at a single state at a particular time point (24), the probabilities for stage 1 and stage 2 hypertension are indicative of the high risk of potential disease outcomes and the consistency of our findings with more recent studies showing an increase in the prevalence of hypertension (34).

Second, the probability of recovering from stage 1 hypertension to normal/elevated BP (47.3%) was greater than progressing to stage 2 hypertension (31.6%). Thus, more people recovered to a better health state than those who progressed to a worse health state. This could be due to lifestyle changes, the effectiveness of community based interventions (35), or improved access to hypertension services (36). However, once at stage 2, the probability of remaining at that state even after 7 years was much higher for every one out of two persons, than recovering back to either stage 1 hypertension or even normal/elevated BP. At this stage, the risk of stroke, myocardial infarction, kidney failure, diabetes, and the sequelae of CVD is very high (37) requiring treatment with medication and lifestyle changes including eating a heart-healthy diet with less salt, engaging in regular physical activity, maintaining a healthy weight or losing weight if overweight or obese, and limiting the intake of alcohol to avoid the compounding effect of mortality. However, these changes come at a price to patients, who may not have the finances to consistently buy these medications or the ability to engage in regular physical activity due to functional disabilities and old age. Additionally, the onset of comorbidities may further delay the recovery process.

Again, with a higher likelihood of remaining at stage 2, the financial burden associated with treatment and control is much higher suggesting an increase in healthcare expenditure for governments and out-of-pocket payments for individuals. These facts call for urgent policies and interventions aimed at the prevention of transitions to a worse state and health expenditure projects targeted at treating stage 2 hypertensive populations.

A significant finding of this study is the importance of the new thresholds developed by the ACC/AHA in early detection, control, and treatment of this medical condition (9). Using the current thresholds, we now know that it takes an average of 7 years 10 months to transition from normal/elevated BP to

stage 1 hypertension, 1 year 8 months to transition from stage 1 hypertension to either stage 2 hypertension or recover to normal/elevated BP, and 5 years 5 months to transition from stage 2 hypertension to stage 1 hypertension. This provides evidence of the time-window at which awareness and systematic screening can occur to forestall any disease progression, with knowledge that early detection of elevated BP makes it amenable to control and treatment (38), which is effective in reducing the incidence of mortality. Additionally, based on the new ACC/AHA hypertension thresholds, our study provides new transition probabilities for researchers who aim at predicting the risk, evaluating the financial burden, or patient directed care associated with hypertension.

Fourth, to succeed at the implementation of hypertension prevention interventions, knowledge of who to screen plays a key role. In this study, we made important discoveries on various subgroups within the general population. Males had a higher transition probability from normal/elevated BP to stage 1 hypertension; while females compared to males, had a higher transition probability from stage 1 to stage 2 and remaining there. This finding is consistent with previous studies which show that females are more at risk of more severe stages of hypertension than males (18, 39). Similar evidence among older adults; that is, those 60 years and above can also be confirmed in this study.

Previous studies have found a significant association between higher scores of BMI and hypertension. For instance, Boateng et al. (18) found that both overweight and obesity were associated with an increased risk of stage 1 and stage 2 hypertension relative to normal/prehypertension in Ghana. Additional evidence from a systematic review and meta-analysis on hypertension among older adults in Africa (39) did show that overweight and obesity were independently associated with hypertension. The results of our study do not only confirm these relationships but go a step further to show that overweight and obese populations have a higher probability of progressing from stage 1 to stage 2 hypertension, with a lower likelihood of recovery to normal/elevated BP. This could be attributed to a number of factors as obesity stimulates the activation of the renin-angiotensin-aldosterone system, an increase in sympathetic activity, which further promotes insulin and leptin resistance, and an increase in procoagulatory activity and endothelial dysfunction (40). Among these, insulin resistance is most critical as it impairs vascular function, leading to impaired nitric oxide mediated vasorelaxation that contributes to hypertension and to an increased risk of atherosclerosis (41). Consequently, it is not surprising that overweight and obese populations have a lower probability of recovering to normal/elevated BP but a higher probability of progressing from stage 1 to stage 2 hypertension, as insulin resistance may be reversed with regular physical exercise, medication, and weight loss.

Another significant finding in this study relates to the relationship between socio-economic status and the probability of hypertension severity. The results of our study do show that while lower education, rural residence, and lower wealth were associated with a higher probability of progressing to stage 1 hypertension; higher education, urban residence, and higher wealth acquisitions were associated with a higher probability of progressing to a more severe form of hypertension. This is consistent with the findings of Tenkorang and Kuuire (42) on the negative social gradient in health in which Ghanaians with a higher socio-economic status were more likely to live with non-communicable diseases than those with low socio-economic status. At the core of this quandary is the association of overweight and obesity with success, wealth, and good health (43). This false sense of health and well-being creates a condition where an increase in wealth leads to changes in food preference, increase in food consumption, and poor choices with dietary intake (32), culminating in severe hypertension and other cardiometabolic diseases.

Conversely, we provided the needed evidence that shows that an intake of healthy foods such as fruits and vegetables of any quantity per day had the potential of delaying a population's transition from normal/elevated BP to Stage 1 hypertension. However, those who consumed the recommended serving of fruits and vegetables a day had a higher recovery from stage 1 hypertension to normal/elevated BP than those who did not consume the recommended servings, which is an equivalent of 400 grams of fruits and/or vegetables per day. This finding is consistent with existing literature, which prescribes the consumption of more servings of fruits and vegetables per week as a mechanism for delaying or managing severe hypertension (44, 45). Taken singly or together, these sub-groups provide novel start-points for the development and implementation of interventions geared toward hypertension prevention.

The primary strength of this paper is in the use of a longitudinal data which enables a better estimation of progression in disease state than cross-sectional data, which only estimate the prevalence of a disease at a single time point. With the lack of longitudinal data in most SSA countries, the WHO SAGE longitudinal study presents a suitable dataset to estimate such transitions. Second, the use of transition probabilities in estimating progression across hypertension severity states presents a more robust approach to past models which have attempted to predict the likelihood of being in either state at a single time point. Third, this paper provides estimates useful for the calculation of the impact hypertension may have on quality or disability adjusted life years as well as the simulation of cost-effective models to evaluate policies and the burden of future healthcare.

There are some limitations in this study that provide opportunities for future research. First, the WHO SAGE data while ideal, has fewer respondents below the age of 41, which is disproportional to those above 50. Consequently, transitions estimated among the younger cohort should be interpreted with caution as the data may not be representative of the younger cohort in Ghana. Second, our inability to account for the past medical condition of these respondents and the medical treatments received may provide an incomplete picture of disease progression, especially, for those who started at hypertension stage 1 and 2 in 2007/2008. This was due to over 90% of missing data on the intake of anti-hypertensive medication over the period of data collection. However, the Markov assumption that the future of a disease state depends on the current state, and not on the history of the disease state makes our analysis adequate

(38). Again, without data on those who received medication after the assessment of their hypertension status in wave 1, it is difficult to estimate the exact time it takes individuals on medications to recover from a worse hypertensive state. Future studies should consider past medical conditions, use of medication, and treatment in estimating transition probabilities. Third, by grouping normal and elevated BP together, we assume that respondents in both categories are in a healthy state, which may not be so for those in the elevated cohort. However, the diastolic threshold for both normal and elevated BP are the same, making it easier to be able to create a common cut-off point in creating the normal/elevated BP state. Lastly, the AHA/ACC recommends that to establish or diagnose hypertension, at least two measurements from two separate visits be conducted before BP status is assigned (10). However, in both waves of this study, BP status was assigned based on a single visit, which may account for misclassification of BP status in wave 1 leading to a possible decline of stage 2 hypertension at wave 2. Future studies may need to diagnose elevated BP based on at least two separate visits to ensure the validity of BP groups.

CONCLUSIONS

This paper contributes new knowledge to the epidemiology of chronic diseases across the life course in four ways. First, this study is the first to measure progression in hypertensive severity in SSA; highlighting the transition probability from normal/elevated BP to stage 1 hypertension or to stage 2 hypertension and the recovery from the latter. Additionally, it shows the importance of having new thresholds for early diagnosis of hypertension. Second, the findings suggest that the consumption of recommended servings of fruits and vegetables per day has the potential to delay the onset of severe hypertension and the recovery from same. Third, the findings in this study can be used in simulating cost-effective measures in the management, control, and treatment of hypertension. Next, the findings provide approximate sojourn and transition times that are adequate in evaluating the performance of an intervention or targeting interventions to specific subgroups with better health outcomes. Finally, the estimates generated from these data are important in calculating the impact hypertension may have on quality/disability-adjusted life years, life expectancy, and the total costs of treating and controlling hypertension within Ghana's population.

DATA AVAILABILITY STATEMENT

Data for this study were drawn from the World Health Organization Study on global AGEing and adult health (WHO-SAGE). Details of the data can be found at: http://www.who.int/healthinfo/sage/cohorts/en/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by WHO Ethics Review Committee (reference number RPC149) with local approval from the University of Ghana Medical School Ethics and Protocol Review Committee (Ghana). The necessary permission was obtained from the World Health Organization to use these data. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GB, SL, PB, ZT: conceptualization. GB, SL, RB, PK: data curation. GB, SL, LS, CM: formal analysis. GB, SL, PB, LS, CM: methodology. IL: supervision. GB, SL, PB, LS, RB, PK, CM, ZT, AP, IL: writing—original draft and writing—review and editing. All authors: contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.571110/full#supplementary-material

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Does Economic Support Have an Impact on the Health Status of Elderly Patients With Chronic Diseases in China? - Based on CHARLS (2018) Data Research

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Objective: The economic support of elderly patients with chronic diseases may affect their health status. This study assessed the impact of economic support on the health status of elderly patients with chronic diseases in China and explored the relationship between regional economic differences and the impact of economic support on health status.

Methods: This study used the data of 3,416 elderly patients with chronic diseases from the China Health and Retirement Longitudinal Study (CHARLS) in 2018. Logit model and stepwise regression method were used to analyze and compare the influence of economic support on self-rated health, mental health, and activities of daily living (ADL) of elderly patients with chronic diseases. Sub-regional comparison was used for the research of regional differences in the impact of economic support on health.

Results: we find that economic support has a positive effect on the health status of elderly patients with chronic diseases in China. Socioeconomic support has a positive effect on self-rated health and mental health of elderly patients with chronic diseases, and the effect on activities of daily living (ADL) is no longer significant after the gradual inclusion of control variables. Family economic support has no significant impact on the health dimensions of elderly patients with chronic diseases. With respect to regional differences, socioeconomic support can improve mental health in central China and improve self-rated health in western China, while it can improve overall health status in eastern China. The influence of family economic support on different health dimensions in different regions is still insignificant.

Conclusions: The health status of elderly patients with chronic diseases is affected by socioeconomic support in China. In order to improve the health of elderly patients with chronic diseases, it is necessary to increase socioeconomic support. Meanwhile, it is also essential to pay attention to the differences in economic support between different regions and increase the socioeconomic support for elderly patients with chronic diseases in undeveloped regions so as to improve their health status.

Keywords: elderly patients, chronic disease, health status, regional differences, economic support

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INTRODUCTION

China's rapid economic development has brought both improvements in living standards and medical technology since the 21st century. Life expectancy has risen significantly, but so has the proportion of the elderly in the population. Compared with other countries, China's aging is characterized by high degree and rapid progress (1–3). Meanwhile, China's spectrum of disease is changing against the backdrop of aging and a dramatic rise in life expectancy (4). Infectious diseases have been effectively controlled, the maternal mortality rate and the population mortality rate have been significantly reduced (5). However, the number of patients with chronic diseases is increasing, showing an upward trend year by year. It is expected to increase by 50% by 2030 without effective control measures (6–8). According to data from the China Health Statistics Yearbook, the prevalence of chronic diseases among residents over 65 years old in the regions surveyed in 2018 was as high as 62.3%. It shows a trend that the prevalence of chronic diseases in the elderly is high and chronic diseases are more common in the elderly (9).

Chronic diseases have the characteristics of high morbidity, low cure rate, and high mortality. Many chronic diseases require long-term care and are lifelong diseases, which directly lead to the continuous medical expenditure of patients (10, 11). Chronic diseases of the elderly also present the characteristics of high disability rate and multiple diseases. Diseases affect each other, and the group of elderly suffering from two or more chronic diseases is gradually expanding (12–14). Numerous studies have also shown that the chronic diseases not only bring damage to the physical health of the elderly, but also affect the mental health of elderly patients with chronic diseases (15, 16). Some scholars have pointed out that elderly patients with chronic diseases will suffer psychological burden due to the continuous economic expenditure brought by chronic diseases (17, 18). Therefore, chronic diseases have become an important factor affecting the health-related quality of life of most elderly people (19–21).

The World Health Organization (WHO) estimates that more than two thirds of all deaths worldwide are caused by chronic diseases, and these diseases are usually related to the elderly. It reveals that economic conditions are closely linked to chronic diseases. Because of the refractory characteristics of chronic diseases, the medical treatment of elderly patients with chronic diseases needs long-term economic support. Christy Pu states that economic conditions have a significant impact on the health of the elderly (22). However, among the elderly in China, the number of people with earned income is relatively small. Family pension is the most common source, and the elderly needs to rely on family economic support when there is no or insufficient pension (23). Under the circumstance of low-income, the cost of health care for chronic diseases quickly drains household savings and pushes millions into poverty each year (24).

Most existing studies have focused on the impact of economic support on the health of the elderly or patients with chronic diseases, only a few studies combine the elderly and patients with chronic diseases. Elderly patients with chronic diseases are different from others in that most of them have no income from work and need to rely on pension or long-term family economic support to treat chronic diseases. With respect to economic support, most of the studies only consider a single type of economic support as factor which affects health effect. The economic support stipulated in this paper combines earned income, pension, and family economic support, could better represent the economic conditions in elderly patients with chronic diseases.

Three dimensions of health including self-rated health, mental health, and activity of daily life (ADL) are used to measure health status. Self-rated health is one of the most common indicators used by various databases and scholars to measure the status of individual health, which could effectively represent the status of individual health (25). Studies also have shown that self-rated health can accurately assess the physical and mental health (19, 26). Chronic diseases will make elderly patients suffer from psychological burden as well (27). Therefore, mental health is applied in this paper. Self-rated health and mental health are both based on patients' subjective judgment and are vulnerable to interference. An objective indicator activity of daily life (ADL) is also included in this paper to measure the health status by inquiring the respondents whether they have the basic ability to care for their own needs independently.

Considering the large regional economic disparity, this paper divides China into eastern, central, and western regions based on the geographic location. We study the economic support of elderly patients with chronic diseases in three regions respectively, to measure whether there are regional differences in the influence of economic support on different health dimensions of elderly patients with chronic diseases.

On this basis, this paper uses data of China Health and Retirement Longitudinal Study (CHARLS) conducted by Peking University in 2018, taking elderly patients with chronic diseases aged 60 and above as the research object, examining the impact of economic support on the health status of elderly patients with chronic diseases in China.

METHODS

Study Design and Sample Selection

Based on the China Health and Retirement Longitudinal Study (CHARLS) database, this paper studied the impact of economic support on the health status of elderly patients with chronic diseases in China. The China Health and Retirement Longitudinal Study (CHARLS) national baseline was launched in 2011 and the data is tracked every 2–3 years. CHARLS has more than 17,000 respondents who are from various regions in China, covering 150 county-level units and 450 village-level units. When sampling, CHARLS uses PPS (Probability Proportional to Size) to select county level units first and then selects village or community level units. In each village or community, CHARLS randomly selects 25–36 residences from the map, and determines the number of samples of family households in each residence. Besides, there is a section of filter at the beginning of the CHARLS questionnaire which can

eliminate invalid questionnaires. Therefore, the data can well-represented the overall situation of China and the quality of data is guaranteed.

CHARLS includes basic information, family, health status and function, cognition and depression, health care and insurance, work and retirement, pensions, income expenditure and assets, real estate, and housing, with a wide range of information. It is a reliable database for studying health levels and influencing factors in middle-aged and elderly people.

Patients aged 60 and above with chronic diseases were selected as the research objects in this paper. After eliminating the samples lacking key variables, 3,416 samples were finally utilized. The database used in this paper is made available to the academic community with the approval of the Ethics Committee of Peking University, so ethical approval is not required.

Variable Description

The economic support of the elderly patients with chronic diseases studied in this paper consists of two parts, namely family economic support within 1 year and socioeconomic support within 1 year. Among them, family economic support includes those provided by children, parents and siblings. Socioeconomic support includes pensions and earned income of reemployment. Pensions refer to income of government organization and institution, enterprise worker primary endowment insurance, endowment insurance of urban and rural dweller, commercial endowment insurance, and other endowment insurance. Earned income refers to the salary received from work, including bonuses and various subsidies.

Self-rated health is based on the respondent's self-rating of current status of health, reflecting the respondents' assessment of their own health. Self-rated health in the CHARLS questionnaire is achieved by asking patients "How would you describe your health condition?" to measure. The question is divided into five levels, which are "very good," "good," "common," "poor," and "very poor." According to the results of the questionnaire, the OLS regression and ordered logit regression have been carried out, respectively. Although, same conclusions are obtained by the OLS regression and ordered logit regression, logit regression can judge the health status more directly. Meanwhile, ordered logit regression can eliminate the influence of threshold of dichotomous dependent variable on the significance of the estimated coefficient. All the statistical procedures in this article are implemented by STATA15.

A large number of studies have shown that depression is the most common mental health problem of the elder, which is representative of the individual's mental health status. Therefore, in this paper, the levels of mental health are measured through the depression status of the respondents (28). CHARLS used a 10-item central depression scale modified by Andresen in 1994. Due to its good reliability and validity, short response time, and high recovery rate, this scale has great potential to be applied in large-scale investigation and study (29), it is considered that this scale can effectively measure the depression level of the elderly in CHARLS data. The scale is composed of 10 symptoms description and respondents are asked to answer the frequency of described symptoms in last week. The symptom descriptions including "I was bothered by things that don't usually bother me," "I had trouble keeping my mind on what I was doing," "I felt depressed" "I felt everything was difficult," "I felt hopeful about the future," "I felt fearful," "I could not sleep well," "I was happy," "I felt lonely," "I found hard to keep going." The respond options include: "Rarely or none," "unusual," "sometimes or half of the time," and "most of the time." The result split into/falls into four categories. The four level are counted as 0, 1, 2, and 3 points. There are two questions with positive emotion options for reverse scoring, namely 3, 2, 1, and 0 points. The total score of the 10 items in this scale is between 0 and 30 points. It is considered that $\geq$10 points can be considered as mild depression, and $\geq$15 is considered as high depression. In this paper, according to the general standard, a score of $<$10 is assigned to a value of 0 to represent non-depression, while a score of 10–15 is assigned to 1 to represent mild depression and a score of $\geq$15 is assigned to 2 to represent severe depression.

Good functional status is the basis for maintaining the independence of the elderly. The elderly often suffer from a variety of chronic diseases, which cause health damage. The more types of chronic diseases, the greater risk of disability, which can lead to decreased ability of daily living (ADL) (30). ADL is an important indicator to measure the health status of the elderly, and its evaluation can provide a basis for the diagnosis of diseases, the prediction of social service needs of the elderly, the formulation of treatment plans, and the reasonable placement of the elderly (31). The ADL scale in the CHARLS questionnaire includes two parts: physical life scale (ADL) and instrumental daily life self-care scale (IADL). Since ADL stands for basic ability to act and can better reflect the health status of the respondents. This paper chooses the physical life scale (ADL) as the evaluation criteria that whether the respondents have difficulties in dressing, bathing, eating, getting up, using the toilet, controlling urination, and defecation. The respondents will be marked as'1' if they meet any criterion above and marked as '0' if none of symptom happened.

The control variables are divided into four categories: demographic characteristics, unhealthy lifestyles (drinking and smoking), physical activities, and medical insurance. Demographic characteristics include gender, age, marital status, education level, type of residence. Where in Marital status is reclassified according to the six options in the questionnaire. The six options are "married and living with a spouse," "married but temporarily not living with the spouse for work and other reasons," "separated, no longer living together as a spouse," "divorced," "widowed," and "never married," the first three options are reclassified into "married" and the last are reclassified into "single." Previous studies (Erpeng Liu) have pointed out that smoking and drinking will have an impact on health as unhealthy lifestyles (32). Meanwhile, physical exercise is also one of the factors affecting health. Narimasa Kumagai's research further shows that poor health behaviors have negative effect on daily physical activities, while increasing the intensity of daily physical activities has a positive impact on individual health status (33). Therefore, we regard "Whether Smoke" and "Drinking Frequency" as one type of control variable (unhealthy lifestyles), and "Physical Activity Intensity" as another type

of control variable. Zeng Yanbing's research shows that the type of medical insurance will affect whether the elderly seek medical treatment or not, and the medical insurance for urban workers will improve the utilization rate of outpatient services for the elderly (34). Therefore, this paper regards the type of medical insurance as control variable. The insurance type question corresponds to the questionnaire's EA001, in which CHARLS divides the medical insurance into 10 categories. This paper categorized the insurance with insignificant number of participants as "Other Insurance," (amongst are Government Medical Insurance, Medical Aid, Private Medical Insurance: Purchased by Work Unit, Private Medical Insurance: Purchased by Individual, Urban Non-Employed Person's Health Insurance, long-term Care Insurance). As result, this paper identified five medical insurance categories: Urban employee medical insurance, Urban, and rural resident medical insurance, Urban resident medical insurance, New rural cooperative medical insurance, and other insurance. At the same time, the medical insurance reimbursement expense of the sample population is also recognized as a control variable due to its significance as an economic indicator related to health. The description and assignment of variables are shown in **Table 1**.

Statistical Analysis

Since ADL has only two dimensions, namely healthy and unhealthy, this paper chooses Logit model to study the impact of economic indicators on ADL, and sets the model as follows:

$$\mathbf{H_i} = \alpha + \beta \mathbf{S_i} + \gamma \mathbf{X_i} + \varepsilon \quad (1)$$

Here, H_i represents the status of ADL. S_i is the key independent variable, representing the economic support the respondents received. X_i represents control variables, including demographic indicators (gender, age, marital status, education level, type of residence), health behavior (physical activity intensity, whether smoking, and drinking frequency), the type of medical insurance, and medical insurance reimbursement expense.

In this paper, the measurement of self-rated health and mental health is ordered multiple classification. We choose ordered Logit model to carry out regression analysis.

$$H_i^* = \alpha X_i + \varepsilon_i,\ i = 1, 2, 3(4, 5) \quad (2)$$

$$H_i = \begin{cases} 1, & H_i^* \le \beta_1 \\ 2, & \beta_1 \le H_i^* \le \beta_2 \\ 3, & \beta_2 \le H_i^* \le \beta_3 \end{cases} \quad (3)$$

Here, $\mathbf{H_i^*}$ is the latent variable, cannot observe the specific value. $\mathbf{H_i}$ represents the status of health (SRH, Depression). $\mathbf{X_i}$ represents control variables, including economic support, demographic indicators (gender, age, marital status, education level, type of residence), the type of medical insurance, and medical insurance reimbursement expense. **i** represents the observed value, α represents the value of the parameter variable to be estimated. ε is the random disturbance term, following the Logistic distribution. β is the boundary point of the interval.

TABLE 1 | Variable description.

Variable	Description of variable setting
SRH	Very poor = 0
	Poor = 1
	Normal = 2
	Good = 3
	Very good = 4
Depression	Non-depression = 0
	Mild depression = 1
	Severe depression = 2
ADL	No difficulty = 0
	Difficulty = 1
Gender	Male = 1
	Female = 2
Marital status	Single = 1
	Married = 2
Education	Primary school or below = 1
	Junior high school = 2
	Senior high school = 3
	College or above = 4
Residence	Village = 1
	Combination zone between urban and rural areas = 2
	The center of city/town = 3
Activity	Mild activity = 0
	Moderate activity = 1
	Vigorous-intensity activity = 2
Smoke	No = 0
	Yes = 1
Drink	Drink more than once a month = 1
	Drink but less than once a month = 2
	None of these = 0
Types of medical insurance	Urban employee medical insurance = 1
	Urban and rural resident insurance = 2
	Urban resident medical insurance = 3
	New rural cooperative medical insurance = 4
	Other = 5
Region	East = 1
	Central = 2
	West = 3

RESULTS

Basic Characteristics of Elderly Patients With Chronic Diseases

Table 2 shows the basic characteristics of the investigated patients with chronic diseases. Overall, women make up the majority of the respondents, accounting for 70% of the population. More than half of the population is between 60 and 70 years old, and people over 80 years old account for more than 10% of the total population, indicating that China's overall health is in a good status. The married rate is 70%, because the widowhood rate and divorce rate of the elderly group are higher than that of the

TABLE 2 | Descriptive Statistics.

	ALL (*N* = 3,416)	East (*N* = 1,107)	Central (*N* = 1307)	West (*N* = 1,002)
Ecosupport (tk, year)				
Socioeconomic support	0.99	0.74	0.95	0.65
Family economic support	0.34	0.30	0.33	0.39
Proportion (%)				
Gender				
Male	21.49	21.77	21.96	20.56
Female	78.51	78.23	78.04	79.44
Age				
60–70	52.08	54.47	54.17	46.71
70–80	34.22	31.17	33.21	38.92
Above	13.7	14.36	12.62	14.37
Marital status				
Single	24.62	22.58	23.26	28.64
Married	75.38	77.42	76.74	71.36
Education				
Primary school or below	76.84	74.25	73.91	85.13
Junior high school	13.47	14.45	15.68	9.48
Senior high school	7.99	8.85	8.49	6.39
College or above	1.7	2.44	1.91	0.6
Residence				
The center of city/town	23.45	22.94	25.4	21.46
Combination zone between urban and rural areas	8.05	6.68	10.02	6.99
Village	68.5	70.37	64.58	21.46
Types of medical insurance				
Urban employee medical insurance	16.19	12.48	17.52	12.48
Urban and rural resident medical insurance	12.41	11.38	8.57	11.38
Urban insurance medical insurance	5.04	4.29	7.12	4.29
New rural cooperative medical insurance	60.6	65.77	62.28	65.77
Other	5.77	6.96	4.51	61

general population, so they are more likely to be single. Similar to this is the level of education. Due to the low education level in China before the 1970's, more than 90% of the elderly have an education level below junior high school. It is worth noting that the proportion of the elderly with an education level below primary school level in western China is significantly higher than that in eastern and central China, which indicates the exists of certain level of educational inequality in China. From the point of residence, most of the respondents are in rural areas, accounting for nearly 70% of the total population. Although, the vast majority of respondents have medical insurance, most of them are the new rural cooperative medical insurance. The level of economic support for the elderly is also relatively low, with an overall average of only 13,300 RMB, of which the eastern region is the highest, with economic support of 16,700 RMB per capita. There is a consequential difference between the eastern regions and the other two regions. The economic support per capita in central and western china is 12,800 and 10,400 RMB, respectively. The differences in economic support among the elderly patients with chronic diseases in the three regions also reflect the regional differences in China's economic development.

Besides, we also find that the number of elderly patients with chronic diseases who have earned income of reemployment is few, the amount of earned income of reemployment per capita is less than the pension per capita. According to previous research, many elderly people in China share the responsibility of taking care of their grandchildren, which left limited time for them to work (35, 36). Meanwhile, elderly patients with chronic diseases are limited by their age and health status and these unfavoured characteristic restricted their choices (37). Therefore, pension is the main source of socio-economic support for elderly patients with chronic diseases.

We visualize the distribution of economic support for elderly patients with chronic diseases. The economic support distribution of elderly patients with chronic disease with different health status under three health dimensions is compared, and a density curve (**Figure 1**) is drawn on that basis. In order to show the differences of health level intuitively, we unify health level into dichotomous variables. "0" is unhealthy, "1" is healthy.

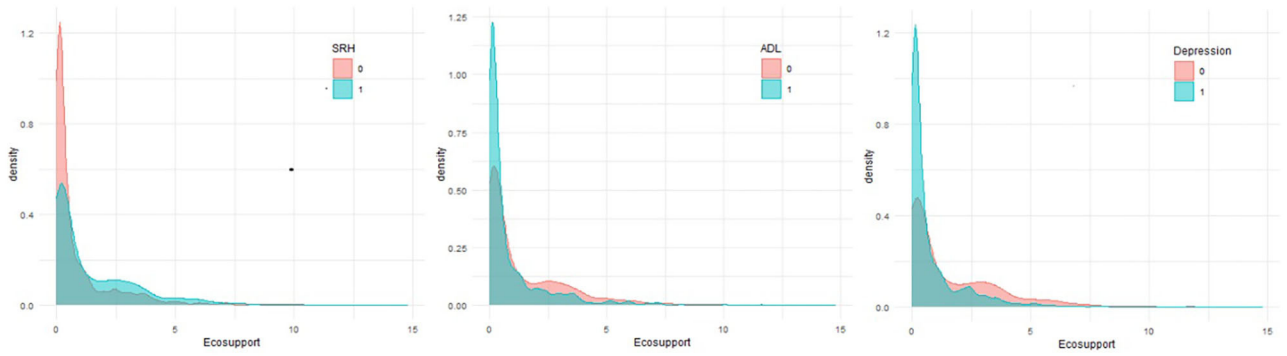

FIGURE 1 | Economic support for different health status.

The ordinate represents the distribution density of economic support, whereas, the abscissa depict the amount of economic support. Generally, people with different health condition are categorized into blue and red. In the self-rated health dimension, red describes people with poor health, and blue refered to people with relatively good health. Since mental health and ADL adopt inverse indicators, the color represents the opposite of self-rated health. According to the figure, it could be found that most of elderly patients with chornic disease received <20,000 economic support, the overall economic support level is low. Regardless the health dimension, elderly patients with chronic disease with poor health condition receive less economic support than those with better health. As shown in the figure, although the peak density is in a states of low economic support, the kurtosis of people with poor health is significantly higher than that of people with better health. Therefore, the above analysis suggests that most of the elderly people with chronic diseases with poor health have fairly low levels of economic support. Likewise, the result from the picture also appears to reinforce our conjecture that economic support will affect the condition of elderly patients with chronic diseases.

The Impact of Economic Support on the Health of Elderly Patients With Chronic Diseases

Table 3 shows the results of the stepwise regression of the influence of economic support on self-rated health. Key independent variables, demographic factors, unhealthy lifestyles (drinking and smoking), physical activities, and medical insurance-related data were included in the model. The results of the four models all show that socio-economic support was beneficial to improve the self-rated health of elderly patients with chronic diseases, and family economic support had no significant impact on self-rated health, indicating that the model was robust. Model 1 shows that without any control variables, socio-economic support has a significant positive impact on self-rated health in elderly patients with chronic diseases. As a component of economic support, both socioeconomic support, and family economic support can improve the self-rated health of elderly patients with chronic diseases, but family economic support fails to pass the significance test. In model 2, model 3 and model 4, demographic indicators, unhealthy lifestyles (drinking and smoking), physical activities, and data related to medical insurance were successively added as control factors. Socioeconomic support still had a significant positive impact on self-rated health of elderly patients with chronic diseases, but the impact was gradually reduced.

Since mental health and activity of daily life are different from self-rated health indicators, the self-rated health value 0 means unhealthy. Mental health and activity of daily life value 0 means healthy. Therefore, the regression results of mental health status and activity of daily life are presented in **Table 4**. Without any control variables, socioeconomic support had a significant positive effect on both. Similar to self-rated health, family economic support had no significant impact on mental health and activity of daily life. As the control variables included in sequence, the influence of socioeconomic support gradually decreased. When all the control variables were included, the influence of socioeconomic support on activity of daily life was no longer significant, and mental health status was still significant.

Regional Differences in the Impact of Economic Support on Health

Due to the uneven development among different regions in China, this paper divides the eastern, central, and western regions of China and makes regression analysis on their health status, respectively to study the difference of the impact of economic support on health among different regions. The regression results are shown in **Table 5**.

The results show that the influence of socioeconomic support on the health of elderly patients with chronic diseases is significantly different in regions with different levels of economic development, and the influence of family economic support on the health of elderly patients with chronic diseases is still not significant. In all regions, socioeconomic support had a significant impact on self-rated health. On the contrary, the activity of daily life, socioeconomic support only has an impact in developed regions, but not in undeveloped and less developed regions. In mental health, socioeconomic support has no effect on mental health in undeveloped areas but has a significant positive

TABLE 3 | SRH stepwise regression analysis.

SRH	Model 1	Model 2	Model 3	Model 4
Socioeconomic support	0.1848***	0.1092***	0.0994***	0.0783***
	−0.0188	−0.0237	−0.0243	−0.0238
Family economic support	0.0400	0.0383	0. 0393	0.0261
	−0.0437	−0.0438	−0.0438	−0.0435
Gender		−0.1323	−0.1305	−0.1748
		−0.0868	−0.0867	−0.1011
Age		−0.0066	−0.0069	−0.0014
		−0.0052	−0.0052	−0.0053
Marital status		0.1304	0.1255	0.1036
		−0.0849	−0.0850	−0.0853
Education		0.1554***	0.1499***	0.1282**
		−0.0577	−0.0577	−0.0577
Residence		0.1559***	0.1292***	0.1425**
		−0.0470	−0.0492	−0.0493
Types of medical insurance			−0.0636**	−0.0676**
			−0.0320	−0.0320
Reimbursement			−0.0108**	−0.0088***
			−0.0047	−0.0042
Smoke				−0.3248**
				−0.1417
Activity				0.3272***
				−0.0501
Drink				−0.2165***
				−0.0536

*Standard errors in parentheses *p < 0.1, **p < 0.05, ***p < 0.01.*

effect on central and western china. Thus, it might be suggested that the impact of economic support on health is affected by the economic development degree of the region. Economic supports in different regions have different impact on all aspects of health.

DISCUSSION

Based on CHARLS database, this paper studies the impact of economic support on the health of elderly patients with chronic diseases. Both stepwise regression and regional regression show that socioeconomic support have a significant impact on the health status of elderly patients with chronic diseases, which is basically the same as the previous research results of scholars (38–40).

Socioeconomic support can effectively improve the health status of elderly patients with chronic diseases, especially in terms of self-rated health and mental health. Since the daily life ability is greatly affected by individual unhealthy lifestyles and physical activities, the influence of socioeconomic support on daily life ability decreases after the inclusion of health behavior.

The condition of individual economy is an important factor affecting health, especially for the elderly. Andrews argues that higher levels of retirement income or wealth leads to increased general well-being, which improves the health of the elderly (41). According to Maslow's hierarchy of needs, the individuals will pursue further needs only when the basic survival need is fulfilled (42). The research of Zacharias Dermatis finds that the elderly with higher annual incomes have better quality of life in all aspects than the elderly with lower annual incomes (43). With a stable economic source, the elderly are more willing to pay attention to the improvement of their health condition. Patients with chronic diseases have a high degree of medicial treatment dependence, and the economic burden of drugs is significantly higher than that of other groups (44). Due to the lack of income sources and the high economic burden of the elderly, the level of economic support determines the quality of life of the elderly with chronic diseases. Elderly patients with chronic diseases with low economic support lack sufficient funds to maintain their own health status, and the deterioration of their own health will further aggravate the economic burden of drugs, forming a vicious circle. The deterioration of health status will also bring about a series of chain reactions. Elderly patients with chronic diseases suffer from chronic diseases for years, bringing psychological trauma. The degree of economic support can effectively alleviate the economic concerns of patients, so that they can face the diseases with a more relaxed emotion and attitude and then improve their psychological conditions.

Compared with socioeconomic support, the intervention effect of family economic support on health is not significant. Family economic support has no significant impact on health, whether it was self-rated health, mental health, or ability to live a daily life. This is because family economic support is significantly

TABLE 4 | Mental health/ADL stepwise regression analysis.

	Model 1		Model 2		Model 3		Model 4	
	Depression	**ADL**	**Depression**	**ADL**	**Depression**	**ADL**	**Depression**	**ADL**
Socioeconomic support	−0.3432***	−0.1976***	−0.1780***	−0.1068***	−0.1613***	−0.0803**	−0.1537***	−0.0517
	−0.0268	−0.0269	−0.0324	−0.0342	−0.0341	−0.0349	−0.0342	−0.0341
Family economic support	−0.0463	−0.0094	−0.0433	−0.0196	−0.0439	−0.0333	−0.0419	−0.0217
	−0.0437	−0.0047	−0.0448	−0.0051	−0.0448	−0.0051	−0.0448	−0.0052
Gender			0.2259**	0.2534**	0.2279**	0.2517**	0.2209**	0.3203***
			−0.0895	−0.1008	−0.0895	−0.1013	−0.1049	−0.1203
Age			−0.0050	0.0451***	−0.0047	0.0460***	−0.0075	0.0351***
			−0.0052	−0.0056	−0.0052	−0.0056	−0.0053	−0.0058
Marital Status			−0.1649*	−0.3593***	−0.1602*	−0.3424***	−0.1512*	−0.3106***
			−0.0851	−0.0906	−0.0852	−0.0911	−0.0853	−0.0932
Education			−0.3289***	−0.2181***	−0.3263***	−0.2021***	−0.3201***	−0.1783**
			−0.0663	−0.0728	−0.0663	−0.0731	−0.0663	−0.0737
Residence			−0.2600***	−0.1450***	−0.2434***	−0.1029*	−0.2457***	−0.1096*
			−0.0490	−0.054	−0.0504	−0.0564	−0.0505	−0.0572
Types of medical insurance					0.0510	0.1253***	0.0521	0.1307***
					−0.0350	−0.0379	−0.0350	−0.0385
Reimbursement					−0.0018	0.0236***	−0.0013	0.0201***
					−0.0036	−0.0061	−0.0036	−0.0061
Smoke							0.0190	0.1652
							−0.1425	−0.1616
Activity							−0.1313***	−0.5932***
							−0.0493	−0.056
Drink							0.0566	0.1386**
							−0.0555	−0.0663

*Standard errors in parentheses *p < 0.1, **p < 0.05, ***p < 0.01.*

lower than that of socioeconomic support. Although, the research of Xue Long and some other scholars believed that the economic support has an impact on health status, the *P*-value in their research is too large to be convinced as strongly significant (45). Children's economic support for their elders usually only ensures normal life needs but fails to meet their elders' deeper health needs (46). For the elderly chronic disease group with pension, family economic support is obviously insufficient in terms of quantity and stability compared with socioeconomic support, which has less impact on health. Elderly people with chronic diseases without adequate socioeconomic support are more likely to live in poor family economic conditions, and their children might unable to provide adequate economic security to maintain the health of patients. In addition, the rural population of CHARLS database is significantly higher than that of the urban population, accounting for about 70%. The higher rural sample proportion might lead to low family economic support, resulting in the overall low family economic support (47). In China, elder has a strong tradition mindset of the necessity of sufficient bank saving. They are less willing to invest in health consumption. When the economic support is low, the elderly with chronic diseases are more willing to keep their current assets like cash for the rainy day rather than investing in health (48). Therefore, there may be a counteractive effect of family economic support on health status. It can be explained that family economic support, compared with socioeconomic support, cannot play an effective role in improving the health status of elderly patients with chronic diseases.

As the economic support is limited by the degree of local economic development, this paper divides China into three parts according to the level of economic development and geographical factors, corresponding to undeveloped regions, less developed regions and developed regions in turn. The economic condition of the eastern region is significantly higher than that of the central and western regions (49). The level of economic support and health status of elderly patients with chronic diseases is also significantly higher than that of the other two regions. Family economic support in the three regions has no significant impact on health, and there are clear regional differences in the impact of socioeconomic support on health status.

Socioeconomic support cannot play a role in the self-rated health of the elderly patients with chronic diseases in the central regions, but significantly improve the health status of the elderly patients with chronic diseases in the western regions. Evans, MC study finds that economic difficulties have an impact on the health of low-income elderly persons and suggested that solving economic difficulties may help to promote the health of the elderly (50). The interpretation of this paper is

TABLE 5 | Regional differences in economic support.

	West			Central			East		
	SRH	**Depression**	**ADL**	**SRH**	**Depression**	**ADL**	**SRH**	**Depression**	**ADL**
Socioeconomic support	0.1754***	−0.0745	0.0726	0.0411	−0.1965***	0.0136	0.0670*	−0.1600***	−0.1789***
	−0.0657	−0.0709	−0.0791	−0.0441	−0.0652	−0.0388	−0.0308	−0.0509	−0.061
Family economic support	0.0088	0.0497	−0.0143	0.0583	0.0314	0.0521	0.076	−0.0979	0.0177
	−0.0094	−0.0939	−0.0119	−0.0793	−0.0859	−0.0091	−0.0631	−0.0676	−0.0076
Gender	−0.0507	0.5145***	0.1705	−0.1978	0.2798*	0.3302*	−0.2819	−0.0938	0.4099*
	−0.1865	−0.1943	−0.2238	−0.1614	−0.1667	−0.1844	−0.1819	−0.1918	−0.2325
Age	0.0153	−0.0073	0.0380***	−0.0094	−0.0055	0.0279***	−0.0047	−0.0138	0.0437***
	−0.0099	−0.0099	−0.0109	−0.0087	−0.0087	−0.0093	−0.0093	−0.0097	−0.0105
Marital status	0.1832	0.0539	−0.3203*	0.1227	−0.2110	−0.3445**	0.0251	−0.1997	−0.2187
	−0.1530	−0.1503	−0.1686	−0.1411	−0.1421	−0.1531	−0.1559	−0.1575	−0.1765
Education	0.1864	−0.4133***	−0.3561**	0.1430	−0.3292***	−0.2426**	0.0690	−0.2333***	0.0064
	−0.1274	−0.1381	−0.1699	−0.0902	−0.1051	−0.1106	−0.0949	−0.1125	−0.129
Residence	0.1244	−0.3652***	−0.2039*	0.1911**	−0.2328***	−0.118	0.1196	−0.2191***	−0.0476
	−0.0985	−0.0954	−0.1141	−0.0783	−0.0799	−0.0873	−0.0859	−0.0959	−0.1094
Types of medical insurance	0.0523	0.0684	0.2504***	−0.1281**	−0.0171	0.1396**	−0.055	0.0671	0.0111
	−0.0674	−0.0681	−0.0809	−0.0554	−0.0629	−0.064	−0.0509	−0.0566	−0.0659
Reimbursement	−0.0075	−0.0040	0.0321**	−0.0648***	0.0106	0.0288**	−0.0055***	0.0017	0.0136*
	−0.0118	−0.0106	−0.0131	−0.0159	−0.0120	−0.0131	−0.0036	−0.0041	−0.0082
Smoke	−0.6170**	0.3891	0.0634	−0.1074	0.0329	0.2014	−0.3239	−0.3178	0.174
	−0.2751	−0.2684	−0.3146	−0.2207	−0.2241	−0.2414	−0.2551	−0.2679	−0.3131
Activity	0.0884	0.0299	−0.4772***	0.4175***	−0.3081***	−0.6338***	0.4700***	−0.3178*	−0.6586***
	−0.0971	−0.0934	−0.1068	−0.0821	−0.0819	−0.0911	−0.0868	−0.0858	−0.1008
Drink	−0.3901***	0.0791	0.2723**	−0.1027	0.0057	0.0215	−0.1838*	0.0979	0.1817
	−0.988	−0.0970	−0.1225	−0.0869	−0.0914	−0.1025	−0.0964	−0.1036	−0.1298

*Standard errors in parentheses *p < 0.1, **p < 0.05, ***p < 0.01.*

that in undeveloped regions, the family economic condition cannot meet the normal health needs of elderly patients with chronic diseases, thus, worsening the health status of the elderly. Therefore, the socioeconomic support in the western region can effectively improve the self-rated health of the elderly. The socioeconomic support can guarantee the primary expenditure of elderly patients with chronic diseases and maintain the health status of elderly patients with chronic diseases. In the eastern region, the social and economic support has an impact on self-rated health, but the *P*-value is close to 0.1. The influence of economic support on self-rated health is far less than that in western China. When primary health needs are met, elderly patients with chronic diseases will have higher level of health needs, and psychological needs begin to appear gradually (51). Meanwhile, Gao et al. (52) find in their study that, under the influence of traditional Chinese family values, the elderly would also provide certain economic support to their children. Elderly patients with chronic diseases in the central region have a greater burden of economic support for their children, and the impact of socioeconomic support on mental health is more obvious than that in the eastern region. Unlike the results of stepwise regression, the socioeconomic support of the elderly patients with chronic diseases in the eastern region can effectively improve their activity of daily life. Due to the relatively developed economy in the eastern region, the elderly patients with chronic disease receive more socioeconomic support, and they are more willing to choose treatment or recuperation when there are physical abnormalities. The elderly patients with chronic diseases in the central and western regions are limited by economic pressure, and seldom pay attention to them.

Compared with previous studies, this study has some innovation. Firstly, this paper discusses the influence of economic support on health status from two dimensions: social and family. Previous studies mostly used single economic indicators, such as, pensions and family economic support, to study their impact on health, without taking into account the multidimensionality of economic support for the elderly (22, 23). Secondly, the measurement of health status in this paper reflects the health status of elderly patients with chronic diseases more comprehensively from the self-rated of health and mental health based on the subjective judgment of respondents and the daily life ability of objective judgment, and explores the impact of economic support on health under different health dimensions. The third, this paper divides China into different regions according to the level of regional economic development and geographical location, and further discusses the heterogeneity of the influence of economic support between different regions on the health status of elderly patients with chronic diseases,

which is conducive to the formulation and improvement of regional policies.

Our study also had some limitations. First of all, we used cross-sectional data. The research results can only reflect the impact of economic support on the health status of elderly patients with chronic diseases but cannot explain the causal relationship between the two. Secondly, we did not distinguish specific chronic diseases and studied the difference in the impact of economic support among different chronic diseases. Third, due to the limitation of CHARLS database, there are a large number of rural samples, which may lead to a lower level of economic support.

CONCLUSION

By analyzing the results of the study, we conclude that economic support has a significant positive impact on the health of elderly patients with chronic diseases. The government should pay special attention to the socioeconomic support for elderly patients with chronic diseases and formulate some policy that can improve the economic support for elderly patients with chronic diseases, such as, appropriately increasing the pension amount, expanding the scope of assistance for serious diseases and the scope of medical insurance reimbursement. In this paper socioeconomic support is composed of pension and earned income of reemployment, while the number of respondents who has earned income of reemployment is few. Therefore, increasing socio-economic support is mainly through increasing pension amount. These are key methods to improve the health status of elderly patients with chronic diseases. At the same time, we also find that there are huge regional differences in the impact of economic support on health. It is the long-term goal of the Chinese government to continuously reduce the economic differences among regions to improve the health imbalance of the elderly patients with chronic diseases among regions.

Tragically, large numbers of elderly patients with chronic diseases at the bottom are unable to get enough economic support to keep healthy. Many countries are still trying to take measures to deal with the health problems of elderly patients with chronic diseases (53, 54). The results of this paper suggest that economic support could improve the health status of elderly patients with chronic diseases. The communities and regions facing the triggers of the health state of elderly patients with chronic diseases could consider increasing economic support as a part of the policy. However, according to Daroudi et al. (55), the economic cost of improving health varies from country to country at different economic levels. Therefore, before deciding whether to increase social support to improve health, different countries need to conduct an accurate assessment of their level of development to make sure that improved social support has the same effect. It is worth noting that due to differences in the national conditions and cultural backgrounds, when formulating policies to increase economic support, other countries can consider which aspect to increase economic support for elderly patients with chronic diseases.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://charls.pku.edu.cn.

AUTHOR CONTRIBUTIONS

Study conception and design were performed by ST. Data analysis was performed by TY and DQ. The first draft of the manuscript was written by YX. ZL checked the data and edited the language. All authors commented on previous versions of the manuscript, contributed to the material preparation and data collection, read, and approved the final manuscript.

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The Prevalence of Metabolic Disease Multimorbidity and Its Associations With Spending and Health Outcomes in Middle-Aged and Elderly Chinese Adults

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Objective: Metabolic diseases have been a clinical challenge worldwide and a major public health issue. Very few studies from China investigated the impact of metabolic multimorbidity on healthcare and health outcomes at the national level. This study aims to examine the association of metabolic multimorbidity with health service utilization, spending, functional and mental health.

Materials and Methods: This is a nationally representative cross-sectional study, utilizing the data from the China Health and Retirement Longitudinal Study in 2015, including 11,377 participants aged 45 years and older. Multivariable regression models were used to assess the association of metabolic multimorbidity with healthcare, out-of-pocket expenditure (OOPE), the activities of daily living (ADL) limitation, the instrumental activities of daily living (IADL) limitation, and depression.

Results: Overall, 30.50% of total participants had metabolic multimorbidity in 2015 in China. Compared with single disease, metabolic multimorbidity were associated with the number of outpatient visits [incident rate ratio (IRR) = 1.30, 95% CI = 1.05, 1.62] and days of inpatient care (IRR = 1.52, 95% CI = 1.28, 1.81). Metabolic multimorbidity was positively associated with the OOPE on outpatient care (coefficient = 82.99, 95% CI = 17.70, 148.27) and physical functional difficulties, including ADL limitation (odds ratio = 1.36, 95% CI = 1.18, 1.57).

Conclusions: Metabolic multimorbidity is associated with higher levels of health-care service use, greater expenditure for outpatient care, and more difficulties in ADL among Chinese adults. China's health-care systems need to shift from single-disease models to new financing and service delivery models to effectively manage metabolic multimorbidity.

Keywords: metabolic disease, multimorbidity, healthcare spending, health outcome, Chinese adults

INTRODUCTION

Metabolic diseases have been a major public health issue and a clinical challenge worldwide, which is linked with the increased risk of cardiovascular diseases (1, 2) and all-cause mortality (3, 4). The prevalence of metabolic multimorbidity (defined as presence of two or more chronic conditions including hypertension, dyslipidaemia, diabetes, hyperuricemia and central obesity) is increasing rapidly. Recently, the Emerging Risk Factor Collaboration of 91 cohort studies showed that a particular form of cardiometabolic multimorbidity, was associated with a risk of death substantially greater than that for each of these diseases on their own. For example, at age 60 years, people with one cardiometabolic disease had a life expectancy 6–10 years shorter than those with no such disease, whereas people with cardiometabolic multimorbidity had a life expectancy shorter by up to 15 years (5). Over the past decade, a rapid increase was found in the number of individuals suffering from metabolic syndrome multimorbidity in China and low-and middle income countries (LMICs) (6–8).

Multimorbidity is associated with higher healthcare utilization, worse health status and depression in European countries, challenging the single-disease framework by which most of healthcare is configured (9). While there have been many studies conducted in high-income countries (HICs) on the impacts of chronic disease multimorbidity (10–12), this topic is still an emerging area of research inquiry in LMICs. Currently, only a couple of small studies in certain parts of China have examined this issue (13, 14), such as a study focused on Guangdong which looked at the health service utilization arising from multimorbidity of 162,464 subjects (15). Emerging evidence exists about the impact of single chronic condition alone. However, evidence is sparse about the economic and financial impact among people who have two or more metabolic conditions concurrently. No current study from China has estimated the impact of metabolic multimorbidity on functional limitation and mental health at the national level (16, 17). This study aims to systemically examine the association of metabolic multimorbidity with healthcare utilization, out-of-pocket expenditure (OOPE), functional health and depression, using nationally representative population-based data.

MATERIALS AND METHODS

Designated Population and Sample

This is a nationally representative cross-sectional study, using the newest round of data from the China Health and Retirement Longitudinal Study (CHARLS) conducted in 2015. CHARLS is a biennial survey conducted by the National School of Development at Peking University, which aimed to be representative of Chinese residents aged 45 years and older. The data was collected in a survey in which four-stage, stratified, cluster sampling was used to select eligible individuals (18). Brie?y, 150 counties were selected, proportional to population size. Then three villages/communities were selected from each county as primary sampling units (PSUs). In each of the 450 PSUs, 80 households were randomly selected. In each household, persons aged 45 years and over, as well as their spouses, were interviewed using structured questionnaires. The main questionnaire includes information on basic demographics, health status and functioning, healthcare and insurance, work, retirement and pensions, income and consumption, household assets, and several biomarkers. Written informed consent was obtained from all participants. CHARLS received ethics approval from the Peking University Biomedical Ethics Review Committee (Ref. no. IRB00001052-11015) in 2011 (18).

The total sample size of the CHARLS baseline survey was 17,708 individual respondents. Ongoing follow-up surveys were conducted once every 2 years. For this study, we identified 13,420 respondents with blood test and biomarker information. After removing respondents aged below 45 years and those individuals with missing values of dependent or independent variables, our final sample consisted of 11,377 respondents accounting for 84.8% of those without loss-to-follow-up.

Definition of the Metabolic Diseases

In this study, we counted the number of chronic diseases for each participant, identifying those with multimorbidity (19, 20). Hypertension was defined as systolic blood pressure $\geq$140 mmHg and/or diastolic blood pressure $\geq$90 mmHg, and/or being on antihypertensive medication for raised blood pressure (21). Diabetes was defined by (1) a fasting plasma glucose level of $\geq$126 mg/dL (7.0 mmol/L); and/or (2) HbA1c concentration of $\geq$6.5%; and/or (3) being insulin treatment and/or taking medication for raised blood sugar (22). Dyslipidaemia was defined by (1) total cholesterol (TC) $\geq$ 240 mg/dL (6.22 mmol/L); and/or (2) low-density lipoprotein cholesterol (LDL-C) $\geq$ 160 mg/dL (4.14 mmol/L); and/or (3) high-density lipoprotein cholesterol (HDL-C) $<$40 mg/dL (1.04 mmol/L); and/or (4) triglyceride (TG) $\geq$ 200 mg/dL (2.26 mmol/L); and/or (5) taking anti-dyslipidaemia medication (23). Hyperuricemia was defined as a blood uric acid concentration $>$ 7.0 mg/dL for men and 6.0 mg/dL for women (24). Central obesity was defined as a waist circumference $>$ 90 cm for men and 85 cm for women in participants with Body mass index (BMI) $\geq$ 30 kg/m^2 (25).

Outcome Variables

Respondents were asked about their utilization of healthcare services, including the frequency of outpatient visits and days of inpatient care: "How many times did you visit a general hospital, specialized hospital, clinic or other medical facilities for outpatient care in the past month? and How many days did you stay in hospital over the past year?" CHARLS also collected the information on how much respondents paid in total and how much out-of-pocket (deducting the reimbursed expenses) for their outpatient visits during the last month and inpatient care during the last year.

Functional health was assessed by activities of daily living (ADL) limitation and instrument activities of daily living (IADL) limitation (26). The ADL includes six activities: bathing, dressing, feeding oneself, using the toilet, getting in or out of bed, and controlling urination and defecation. Answers were categorized as: "can do it by myself," "have some difficulties," "need help," and "cannot do it." The IADL refers

to difficulty in doing household chores, cooking, shopping, making telephone calls, taking medications, and managing finances. Binary variables of ADL/IADL were constructed, and ADL/IADL disability was defined as having difficulty in one or more ADL/IADL items. This binary coding of ADL/IADL variables was also used as dependent variables in the multivariate regression analysis.

In terms of mental health, depression was assessed by the 10-item Center for Epidemiologic Studies Depression Scale (CES-D 10) (27), which has been identified as a valid, reliable, and useful mental health assessment tool for those aged 60 and above in China (28). The answers of the CES-D 10 include 4 options: (1) rarely, (2) some days (1–2 days per week), (3) occasionally (3–4 days per week), (4) most of the time (5–7 days per week). The participants' answers were recorded as 0 (rarely) to 3 (most of the time) for the negative questions in this study. For two positive questions, the items were reversed as 3 (rarely) to 0 (most of the time). The total scores of the CESD-10 range from 0 to 30. In this study, a binary variable of mental health was also constructed by defining an individual whose CESD-10 score was < 10 as having depression symptoms.

Statistical Analysis

The negative binomial regression models were applied to investigate the association of multimorbidity with the frequency of outpatient visits and inpatient care. Covariates included age, gender, marital status (married and partnered, unmarried and others), education (illiterate, primary school and below, secondary school, college and above), residence place (rural, urban), geographical region (east, central and west), economic status quartiles (yearly per capita household consumption expenditure), and health insurance status (yes, no). Linear regression models were used to examine the relationships between multimorbidity and outpatient and inpatient care

TABLE 1 | Characteristics of participants, the prevalence of single condition, and metabolic multimorbidity.

Variables	*N* (Percentage)[a]		Prevalence of single disease[b] (95% CI)			Prevalence of multimorbidity (95% CI)		
All	11,377	100.00	32.97	31.63	34.33	32.47	30.9	33.98
Age, years								
45–55	3,633	31.93	30.90	28.32	33.60	24.61	21.84	27.60
55–65	4,084	35.90	32.81	30.77	34.91	34.47	32.01	37.01
65–75	2,722	23.93	34.93	32.39	37.54	37.88	35.39	40.43
≥75	938	8.24	36.81	32.70	41.12	41.62	36.86	46.55
Gender								
Male	5,390	47.38	34.04	32.04	36.11	33.99	31.75	36.31
Female	5,987	52.62	31.94	30.19	33.75	31.01	29.09	33.00
Marital status								
Married and partnered	9,918	87.18	32.72	31.26	34.22	32.14	30.49	33.82
Unmarried and others	1,459	12.82	34.66	31.73	37.70	34.75	31.87	37.75
Education level								
Illiterate	4,903	43.10	33.32	31.72	34.95	32.01	30.12	33.97
Primary school	3,110	27.34	31.62	29.02	34.34	32.48	29.60	35.49
Secondary school	2,256	19.83	34.26	30.90	37.79	30.99	28.32	33.78
College and above	1,108	9.74	32.68	28.45	37.21	36.11	30.25	42.41
Residence place								
Urban	4,189	36.82	31.41	29.00	33.92	38.08	35.33	40.92
Rural	7,188	63.18	34.42	33.22	35.64	27.24	26.12	28.38
Region								
East	4,268	37.51	33.32	30.72	36.03	34.92	31.92	38.04
Central	4,370	38.41	33.25	31.54	35.01	32.01	30.30	33.76
West	2,739	24.07	31.83	29.87	33.86	28.63	26.70	30.64
PCE, RMB								
<5,000	4,554	40.03	32.44	30.50	34.44	30.48	28.12	32.94
≥5,000	3,462	30.43	33.37	30.96	35.86	34.93	32.43	37.52
Missing	3,361	29.54	33.18	30.60	35.86	32.24	29.43	35.19
Social health insurance								
No	2,022	17.77	32.82	29.24	36.60	26.90	23.72	30.33
Yes	9,355	82.23	33.00	31.60	34.43	33.82	32.18	35.50

[a]*N and percentages were based on study samples (unweighted);* [b]*Weighted prevalence of single disease and metabolic multimorbidity.*

TABLE 2 | The proportion of metabolic diseases and multimorbidity among Chinese adults by gender and age group.

Metabolic disease	Total		Male				Female			
	N	%	45–55	55–65	65–75	≥75	45–55	55–65	65–75	≥75
Single disorder										
Hypertension	4,269	36.90	26.10	40.25	48.18	49.41	21.50	35.16	49.24	63.73
Hyperlipidaemia	4,001	36.45	37.51	41.05	36.04	28.21	30.18	38.20	41.16	31.00
Diabetes	2,153	19.75	14.13	22.88	19.75	27.15	11.21	22.61	25.97	29.50
Hyperuricemia	1,299	13.70	18.14	15.37	14.50	20.78	10.15	8.87	12.75	19.49
Concentric obesity	588	4.92	4.56	3.36	2.64	2.84	7.63	6.41	4.89	2.82
Multimorbidity cluster										
Overall multimorbidity	3,470	32.47	28.38	36.77	35.92	38.52	21.32	32.31	39.97	44.89
Hypertension multimorbidity	2,600	22.95	17.09	25.34	29.37	25.03	11.61	23.49	32.84	37.75
Hyperlipidaemia multimorbidity	2,627	24.56	21.69	29.79	26.81	22.57	17.08	25.03	29.79	27.26
Diabetes multimorbidity	1,676	15.85	11.99	18.79	15.21	22.16	7.87	17.73	21.10	26.89
Hyperuricemia multimorbidity	1,037	10.99	13.05	12.11	11.68	18.63	8.12	7.55	11.29	15.38
Concentric obesity multimorbidity	519	4.40	4.21	3.01	2.64	2.84	6.38	5.62	4.58	2.82

Values are unweighted counts and weighted percentages unless otherwise indicated. Overall multimorbidity refers to any two or more metabolic conditions included in this study. Hypertension multimorbidity refers to hypertension with any one or more other metabolic conditions; Hyperlipidaemia multimorbidity refers to hyperlipidaemia with any one or more other metabolic conditions; Diabetes multimorbidity refers to diabetes with any one or more other metabolic conditions; Hyperuricemia multimorbidity refers to hyperuricemia with any one or more other metabolic conditions; Concentric obesity multimorbidity refers to concentric obesity with any one or more other metabolic conditions.

OOPE. Multivariable logistic regression models were used to estimate the association of multimorbidity with functional limitation and depression. We also performed sensitivity analyses for the impacts of multimorbidity on health service by using Poisson regression models and for the impacts on OOPE by using generalized linear models with a logarithm transfer.

For the negative binomial regression analysis, the incident rate ratio (IRR) were reported with results of 95% confidence intervals (CI) included in the **Appendix**. For linear regression models, we reported the coefficient (β) and 95% CI. For the logistic regression analysis, the adjusted odds ratio (AOR) and 95% CI were reported. Descriptive analysis of prevalence of multimorbidity and regression analysis were weighted to account for the multi-stage PPS design of CHARLS. All statistical analyses were conducted using STATA 15.0. $P < 0.05$ were considered as statistically significant.

RESULTS

Our analysis included data from 11,377 participants. The mean age of respondents was 60.29 years in 2015. Among the participants, 52.62% were women, 43.10% of the participants were illiterate, 63.18% were residing in rural areas and 82.23% were enrolled in social health insurance schemes. The prevalence of metabolic multimorbidity was 32.47% and increased with age, ranging from 24.61% in those aged 45–54 years, and 41.62% for those aged ≥ 75 years. People living in urban areas and those covered by social health insurance were suffering from a higher percentage of multimorbidity in China, compared with rural residents and individuals without health insurance (**Table 1**).

Table 2 showed the prevalence of main metabolic diseases and multimorbidity across gender and age group. Among the middle-aged and older population, more than a third of Chinese adults suffered from hypertension and hyperlipidaemia in 2015. The prevalence of diabetes, hyperuricemia and concentric obesity was 19.75, 13.70, and 4.92%, respectively. The prevalence of hypertension and metabolic multimorbidity increased with age among both males and females, but concentric obesity decreased with age in female populations. For diabetes and hyperuricemia, the senior older group (aged ≥ 75 years) suffered from the highest prevalence.

Table 3 indicated that multimorbidity was positively associated with health service use. Compared with people with single metabolic disease, patients with multimorbidity were likely to report more frequent outpatient visits (IRR = 1.30) and days of inpatient care (IRR = 1.52). The days of inpatient care increased substantially with age. Female patients used both outpatient and inpatient healthcare service more frequently than male patients. Individuals with a higher economic level and those patients in economically underdeveloped regions had more days of hospitalization compared with their counterparts.

Table 3 also showed that the prevalence of metabolic multimorbidity had a positive relationship with healthcare expenditure. The out-of-pocket spending on outpatient care was higher for patients with multimorbidity than those with a single disorder ($\beta = 82.99$). OOPE on outpatient care was significantly higher among female patients and those living in rural areas than spending among the male and urban citizens (**Figure 1**). The affluent population was likely to spend more out-of-pocket money on outpatient care ($\beta = 128.44$) and hospitalization care ($\beta = 1{,}218.2$) than those in a lower economic level. There was no statistically significant association between multimorbidity and OOPE for inpatient care. People enrolled in health insurance were likely to spend more on hospitalization care ($\beta = 526.56$) than those individuals without health insurance.

TABLE 3 | The association of metabolic multimorbidity with the frequency of healthcare utilization.

Variable (reference)	Number of outpatient visits		Days of inpatient care		OOPE for outpatient care		OOPE for inpatient care	
	IRR	*P*-value	IRR	*P*-value	*β*	*P*-value	*β*	*P*-value
Multimorbidity (single disorder)	1.30	0.017	1.52	<0.001	82.99	0.013	108.43	0.707
Age (45–59 years)								
55–65	0.97	0.818	1.55	<0.001	−15.82	0.682	556.90	0.069
65–75	1.09	0.484	1.99	<0.001	3.11	0.939	1,069.96	0.050
≥75	1.11	0.609	2.58	<0.001	−95.19	0.102	709.60	0.024
Gender (male)	1.48	<0.001	1.22	0.031	47.19	0.039	498.08	0.161
Marital status (married)	0.98	0.845	0.95	0.624	60.30	0.459	−631.38	0.006
Education level (Illiterate)								
Primary school	0.98	0.876	1.12	0.266	36.39	0.263	663.58	0.149
Secondary school	0.92	0.546	1.17	0.243	12.45	0.719	211.25	0.456
College and above	1.01	0.963	0.93	0.657	−21.02	0.529	224.85	0.746
Residence place (urban)	1.21	0.107	1.07	0.460	98.08	0.007	−238.30	0.313
Region (east)								
Central	1.06	0.608	1.43	0.004	−5.20	0.884	−321.03	0.383
West	1.22	0.146	1.81	<0.001	−34.89	0.421	−303.85	0.319
PCE (<5000 RMB)								
≥5000 RMB	1.10	0.401	1.52	<0.001	128.44	<0.001	1,218.25	0.001
Missing	1.10	0.448	1.34	0.003	84.70	0.020	166.34	0.348
Social health insurance (none)	1.13	0.449	1.15	0.268	10.89	0.762	526.56	0.039

Negative binomial regression models were used and adjusted for all socio-demographic covariates. IRR, incident rate ratio; CI, confidence interval; PCE, Per capita household annual consumption expenditure.

Table 4 showed that multimorbidity was associated with a higher likelihood of having functional difficulties. Compared with people with single metabolic disease, patients with multimorbidity were more likely to have an ADL limitation (AOR = 1.36). Older patients, females, those people with lower education status, and living in rural areas and undeveloped regions were reported higher levels of ADL limitation, IADL limitation and depression than their counterparts. No statistically significant association was found between multimorbidity and depression.

In terms of sensitivity analyses, we found similar associations between metabolic multimorbidity and frequency of outpatient and inpatient care as well as OOPE (**Supplementary Tables 1, 2**). The results were consistent with our original findings showing metabolic multimorbidity was associated with an increase in the number of outpatient visits (IRR = 1.30) and days of hospitalization (IRR = 1.52). Similarly, the days of hospitalization increased substantially with age. Female patients used both the outpatient and inpatient care service more frequently than male patients. People with a higher economic level and those patients in economically underdeveloped regions had more days in hospital compared with their counterparts.

DISCUSSION

This study used nationally representative data to assess the prevalence and impact of metabolic multimorbidity among middle-aged and elderly Chinese adults. It was found that metabolic multimorbidity was common, especially among elderly participants and those living in urban areas. We identified that metabolic multimorbidity was positively associated a greater use of both outpatient and inpatient care utilization, as well as greater health expenditure for outpatient care. Moreover, we found that metabolic multimorbidity was positively associated with a higher likelihood of having functional difficulties (ADL limitation). However, we did not identify a positive association between metabolic multimorbidity and depression.

This study showed that 30.5% of persons aged ≥45 years have metabolic multimorbidity in China. Based on previous studies, the overall prevalence of metabolic syndrome was 16.5% in 2000 (29) and 23.3% in 2009 (7) among the Chinese adults. A meta-analysis study in 2016 revealed that the pooled estimate of metabolic syndrome prevalence was 24.5% among subjects in Mainland China (30). It is indicated that China is experiencing an emerging epidemic of metabolic syndrome, which might be related to accelerating changes in lifestyle and nutrition caused by rapid economic development and urbanization (31). The increasing prevalence of metabolic multimorbidity in developing countries may eventually become similar to that in developed countries. Several studies have reported a high prevalence of metabolic syndrome in United States (35%), Turkey (44%), and Iran (37%) (32–34). Variations in the prevalence of metabolic syndrome from different studies might be either due to real disparities in different countries or regions, or because of potential differences in the definitions, methods of data collection, and sampling of study populations (34).

FIGURE 1 | Frequency of healthcare, health expenditure, and functional limitation by the number of disease and residence place.

Our results indicated that metabolic multimorbidity was positively associated with older age, urban area, and health insurance. Consistent with other studies (35, 36), the prevalence of metabolic multimorbidity increased with age, which can be attributed to the declining metabolic function during the aging process. Additionally, individuals living in urban areas are more likely to suffer from metabolic multimorbidity than those living in rural areas, which is in line with previous findings (30, 37). This may be attributable to the impact of urbanization, including unhealthy dietary patterns, decreased physical activity, uptake of a high caloric diet, excessive intake of fat and salt, all of which lead to the development of metabolic conditions (37–39). Notably, this study provides new evidence on the association between social health insurance

TABLE 4 | The association of metabolic multimorbidity with functional and mental health.

Variable (reference)	ADL limitation		IADL limitation		Depression	
	AOR	*P*-value	AOR	*P*-value	AOR	*P*-value
Multimorbidity (single disorder)	1.36	<0.001	1.16	0.051	0.99	0.871
Age (45–59 years)						
55–65	1.47	0.023	1.61	0.003	1.59	<0.001
65–75	2.15	<0.001	2.50	<0.001	1.87	<0.001
≥75	2.94	<0.001	4.80	<0.001	0.99	0.940
Gender (male)	1.45	<0.001	1.90	<0.001	2.03	<0.001
Marital status (married)	1.11	0.392	0.93	0.508	1.31	0.006
Education level (Illiterate)						
Primary school	0.72	0.008	0.49	<0.001	0.81	0.033
Secondary school	0.62	<0.001	0.48	<0.001	0.87	0.294
College and above	0.37	<0.001	0.21	<0.001	0.43	<0.001
Residence place (urban)	1.37	0.011	1.46	0.001	1.78	<0.001
Region (east)						
Central	1.81	<0.001	1.73	<0.001	1.49	<0.001
West	1.46	0.006	1.70	<0.001	1.86	<0.001
PCE (<5000 RMB)						
≥5000 RMB	1.03	0.800	0.90	0.314	0.92	0.369
Missing	1.23	0.043	1.18	0.076	0.88	0.182
Social health insurance (none)	1.21	0.103	1.16	0.145	2.47	<0.001

PCE, Per capita household annual consumption expenditure; AOR, Adjusted odds ratio; CI, confidence interval.

and metabolic multimorbidity in China. People covered by social health insurance were more likely to suffer from metabolic multimorbidity, compared with individuals without health insurance.

Previous studies have demonstrated that multimorbidity is significantly associated with greater healthcare utilization and higher level of health expenditure, which has been well-documented in developed countries (40, 41). Similarly, our study revealed that individuals with metabolic multimorbidity were more likely to have more frequent outpatient visits and more days of hospitalization, as well as to spend more out-of-pocket money on outpatient care. However, we found there was no significant association between metabolic multimorbidity and OOPE for inpatient care. The reason may be that individuals with metabolic multimorbidity have fewer complications than patients with other patterns of multimorbidity (e.g., cardiovascular diseases, musculoskeletal diseases, and respiratory diseases), so they require fewer health services and spend less money on inpatient care at the early stage of disease. Therefore, prioritizing health and medical resource allocation will be needed to prevent and control metabolic multimorbidity and the complications in China (37). Social health insurance should play a greater role in financial risk protection by reducing OOPE on healthcare. Expanded insurance coverage and improved benefits packages for individuals with metabolic multimorbidity are warranted.

Existing studies have revealed that multimorbidity has a significantly negative effect on physical and mental health outcomes (15–17). However, our findings indicated that individuals with co-existing metabolic diseases were more likely to have ADL limitation, but metabolic multimorbidity was not significantly associated with IADL limitation and depression. This may be explained by that metabolic multimorbidity is less likely to impair the instrumental activities and mental health of patients than other patterns of multimorbidity. Even so, metabolic diseases have been demonstrated to play a dominant role in multiple multimorbidity patterns (39). Among multimorbidity groups, the musculoskeletal group, as well as the cardiovascular and metabolic groups, were identified as having a significant risk of ADL limitation (16). It has been documented that the association between metabolic syndrome and negative cardiovascular outcomes or mortality (42). Our study provides new evidence that significant associations of metabolic multimorbidity with functional limitations are found among in rural areas rather than urban areas.

The literature on the impact of multimorbidity on healthcare utilization and spending among individuals with metabolic diseases is relatively limited in developing countries. This is the first nationally representative study that examined the effect of metabolic multimorbidity on health service use, costs and health outcomes in China, by using metabolic biomarkers for the disease diagnosis. However, our study has several limitations. First, we examined the effect of multimorbidity by simply counting the number of chronic conditions without accounting for the different clusters and severity of chronic diseases, hence the accuracy of the findings may be affected for the types of metabolic multimorbidity. Second, this study is a cross-sectional design, so it is difficult

to demonstrate the causal relationship between metabolic multimorbidity and healthcare utilization and spending. Third, this study only included middle-aged and older populations due to unavailable data of younger populations, which may exaggerate the prevalence of metabolic multimorbidity and its impacts.

In conclusion, metabolic multimorbidity has become a huge public health challenge to individuals and healthcare systems in China and other developing countries. There is a growing need to provide effective services to counter the impact of chronic metabolic multimorbidity. Targeting strategies and measures must be taken to control and reduce the increasing prevalence of metabolic multimorbidity. Healthcare systems need to shift from single-disease models to integrated care models to more effectively manage metabolic diseases and multimorbidity. Prioritizing health and medical resources allocation is needed to prevent, screen, and treat metabolic multimorbidity in the future.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: The datasets generated and analyzed during the current study are available in the China Health and Retirement Longitudinal Study repository. http://charls.pku.edu.cn/pages/data/111/en.html.

AUTHOR CONTRIBUTIONS

YZ and HW conceived, designed the study, and wrote the first draft of the paper. YZ did the initial analysis. HW supervised data analysis. PZ, BO, JL, AH, TH, and HW critically revised the first draft. All authors reviewed and approved the final manuscript submitted 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.2021.658706/full#supplementary-material

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Income, Relative Deprivation and the Self-Rated Health of Older People in Urban and Rural China

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Background: Substantial evidence indicated that absolute income is directly associated with health. Few studies have, however, examined if relative income may be equally associated with health. This study aimed to investigate the association between absolute income/relative deprivation (RD) and self-rated health (SRH). We also investigated whether the urban-rural difference was existing in these associations.

Methods: Using cross-sectional data of 7,070 participants in the Shandong Family Health Service Survey of older people, this study applied binary logistic model and semi-parametric model to estimate the effect of absolute income and relative deprivation on SRH of older people. The Kakwani Index was used as a measure of relative deprivation at the individual level.

Results: Absolute income has a significant positive effect on the SRH among both urban and rural older people. When considered RD as a variable, both absolute income and RD have negative significant effects on SRH among all older people. In addition, the negative effect of RD on rural elderly is more pronounced than that of urban older populations. Semi-parametric regression results show that there was a complex non-linear relationship between income and SRH. Psychological distress substantially attenuated the association between relative deprivation and SRH.

Conclusions: Relative deprivation is negatively associated with self-rated health in both urban and rural older people after controlling the absolute income. RD may partly explain the association between income inequality and worse health status. Compared with the urban elderly, the effect of income-based relative deprivation on SRH was more pronounced among the rural elderly, and more care should be given to the lower income and rural older populations.

Keywords: income, relative deprivation, self-rated health, elderly, China

INTRODUCTION

The positive association of socioeconomic status with health has been well-established in the previous literature (1–3). As a main indicator of socioeconomic status, income has a strong impact on health. To a certain degree, the higher income people earn, the better their health (4). Two alternative hypotheses have been offered to explain the impact of income on individual's health. The absolute income hypothesis (AIH) suggested that absolute income has a direct effect on health (5, 6). Individuals with higher income are more likely to have good health than lower income individuals, because they have enough material resources that are conducive to good health. However, an individual' s health is not only determined by his own income, but also by relative income of others (7–9). Based on social comparison, the effect of relative income on health is referred to as the relative income hypothesis (RIH).

The RIH has several forms, such as income inequality, income rank and relative deprivation (RD) (10, 11). The impact of relative deprivation is one form of the RIH. Relative deprivation has been defined as "the difference between an individual's income and the income of individuals in their reference group" (12). Individuals tend to compare themselves with people whose income is higher than their own in the reference group. The greater the income gap, the stronger the perceived relative deprivation (13). Another form of the RIH is the income inequality which focuses on overall income deprivation. This measure is not considered in this study, although the findings are important for enriching our paper. There are two alternative pathways through which RD may affect one's health. One is material pathway, which suggested that RD increased the inequality of one's access to goods, services, and social activities such as employment or social networks and thereby adversely affects one's health (14). The other one is psychosocial pathway, which implies that those who feel relatively deprived will have some negative emotions, such as frustration or stress. The psychological stress may lead to directly negative effects on mental health or indirectly effects on physical well-being via health behaviors (e.g., smoking, alcoholism and substance use) (15, 16).

Previous studies which empirically tested the relative deprivation hypothesis have been presented the negative impacts of relative deprivation on various health outcomes. These negative effects are manifested in the increased prevalence of chronic diseases (17, 18), stress-related health behavior, such as smoking and drug abuse (19, 20) and poor self-rated health (21), functional disability (22) and mortality (23). However, the research results diverged, when considering different health outcomes. Studies utilizing self-rated health (SRH) as the outcome measure provided supportive evidence that RD has a strong association with SRH (24), findings from several studies focusing on other health outcomes (i.e., mortality and depression) did not (25, 26). In any case, almost all of these studies were conducted on developed countries, and few RIH related studies are conducted in low-income or middle-income countries.

China has witnessed rapid economic growth in the past 30 years, the per capita income of urban and rural residents in China has increased significantly. However, at the same time rapid economic growth has been accompanied by obvious income gap (27). Increasing income gap has brought negative impacts on the rapid increase in income inequality and individual quality of life, which ends to make vulnerable groups more vulnerable to adverse effects (28). Research and statistical data have shown that health and income levels have not increased simultaneously (29, 30). The unique dual structure of urban and rural areas makes income inequality present obvious regional differences (31). In contrast to the majority of the existing literature, which has been conducted in developed countries (15, 21, 24), the focus of this study is on a sample of older adults in China. This study focused on older people in urban and rural China for some reasons: First, China is rapidly transforming into an aging nation, and much attention has been paid to the health status of older adults (32). Secondly, it was hypothesized that relative deprivation based on income would be more pronounced in older populations. The incidence of poverty in this group is much higher than that of the general population (33). From a life course perspective, the impact of relative deprivation on health should be evidenced in older people because the influence of poverty on health may accumulate over time (34). In addition, there are obvious urban-rural differences in the living conditions and healthcare services of the older populations in China, and the relative deprivation is more prominent among them (35). Overall, this current study investigated the association between absolute income/relative deprivation and SRH. We also investigated whether the urban-rural difference was existing in the association between absolute income/relative deprivation and SRH.

METHODS

Study Population

Data were collected from the 2017 Survey of the Elderly Family Health Service. The survey was conducted in Shandong province, China. Stratified multi-stage random sampling was applied: in the first stage, according to the level of socioeconomic development (high, medium, and low) and geographical location (east, central and west), using probability proportionate to size sampling method (PPS), 3 cities were selected from 17 cities as the primary sampling units (PSUs). From each PSU, 1 district and 1 county were selected as the secondary sampling units (SSUs), and represented urban and rural areas separately (PPS). In the third stage, three towns and three sub-districts were selected randomly from each county and district separately (PPS). Then, from each town and sub-district, six villages and six committees were selected separately (PPS). Lastly, an average of 50 households were randomly selected and making up the total sample (Simple random sampling). Eligible participants were those aged 60 years or older with local household registrations. Finally, a total of 5,643 households consisting of 7,070 individuals were included in the sample. All data collection was performed by trained master students in the participant's home using a self-administered questionnaire (SAQ). The Myer's Index was estimated to be 2.19, and test of goodness for fit was not statistically significant, indicating a good quality of sampled data.

Self-Rated Health

SRH is an effective and reliable measure of health (36). In our survey, self-rated health was assessed using a single item: "Generally, how would you rate your current health status?" It has a 5-point Likert scale (very good, good, fair, poor, very poor). Scores were reverse coded and treated as a continuous measure ranging from 1 (very poor) to 5 (very good). There were relatively few respondents who provided extreme responses ("very good" or "very poor") to the health status question, in our analysis, SRH was dichotomized into two categories: 1 = good health, where SRH was either good or very good; 0 = poor health, where SRH was fair, poor or very poor. We modeled the probability of reporting good/very good (hereafter, good) health. Previous studies also divided SRH into two other categories: 1 = good health (very good/good/ fair); 0 = poor health (poor/very poor), and we carried out regression analysis according to this classification (see Tables C1, C2 of **Supplementary Material**).

Individual Income

Data on total individual income in the last 12 months was collected as continuous variable, which included farming income, fishing income, livestock income, retirement wages, pension, business income, children's support, investment income and other types of subsidies income. We make the assumption that an individual compares him/herself to others in his/her reference group based on their own income. When it comes to social comparisons, individuals are more likely to evaluate themselves in terms of their paychecks and other income and less likely to account for their household structure and the within household distribution of the total household income. Given that a considerable proportion of the participants are living in the same household, when it comes to possible common income (such as farming, fishing and livestock income. etc.), the individual income is determined by dividing the common income by the number of people surveyed in the family. The income structure for rural vs. urban participants was shown in Table A1 of **Supplementary Material**.

To ensure more accurate estimation of the non-linear relationship between absolute income and health, income was then transformed using logarithmic function, as suggested by previous work (37). Furthermore, logarithm of income also prevent bias on the coefficient on the relative income measures. Based on previous studies, the first hypothesis of our study is that actual income would be positively correlated with SRH.

Relative Deprivation

The Kakwani Index was used to measure RD. The Kakwani index is obtained on the basis of Yitzhaki index, which has the properties of dimensionless, normality and transfer invariance (38). Before measuring individual RD, it is necessary to give a reference group for individual comparison. Considering the urban-rural dual structure of China, we divided the total sample into rural and urban subgroups, and assume that individuals in each subgroup compare themselves with other individuals with higher income in the same group.

Formally, the Kakwani relative deprivation (KRD) index is defined as a function of the Yitzhaki index divided by the mean income of total sample in the reference group. The formula developed by Kakwani for measuring individual RD is:

$$KRD\,(x,x_i) = \frac{1}{n\mu_X}\sum_{j=i+1}^{n}\left(x_j - x_i\right) = \gamma_{x_i}^{+}\left[\frac{\left(\mu_{x_i}^{+} - x_i\right)}{\mu_X}\right]$$

where X represents a reference group and n was the total sample size in this group. $KRD\,(x, x_i)$ was the relative deprivation index for individual i, and x_i represents the income of individual i and x_j is the incomes of all individuals j whose incomes are higher than individual i's; μ_X is the average income of all samples in the reference group. $\mu_{x_i}^{+}$ is the average income of the sample whose income was higher than x_i in the reference group. $\gamma_{x_i}^{+}$ is the percentage of samples whose income was higher than x_i in the reference group. The greater the gap between x_i and x_j, individual i was hypothesized to feel more deprived. The second hypothesis of our study is that KRD is negatively correlated with SRH. The greater the degree of RD for an individual, the poorer their SRH status would be.

Covariates

According to previous empirical studies in China and other counties (1, 39, 40), we controlled age, gender, educational level, marital status, chronic disease, activities of daily living (ADL), psychological distress and personality trait at the individual level. Age was measured in chronological years; Education attainment was measured with the number of years spent in full time education. We divided education into three levels: no school (0 years), primary school (1–6 years), and junior school and above (at least 7 years); Marital status was categorized into married and others; chronic disease were dichotomized (yes or not) and self-reported, assessed by asking whether the participant was diagnosed with the following conditions: hypertension, diabetes, heart disease, stroke, COPD, cancer, and other. For measuring ADL of elderly, the Lawton and Brody Instrumental Activities of Daily Living Scale was used (41). The scale consists of 14 questions for evaluating self-maintenance, transportation utilization, medication behavior, housework activities and financial management among the elderly. Each question used 4-grade score with a range from 14 to 56, where higher scores indicate lower level of competence. The psychological was measured by The Kessler Psychological Distress Scale (K10 scale) (42). The scale consists of 10 questions and each question used a five-value response that was scored from five (all the time) through to one (none of the time). The maximum score is therefore 50, indicating severe distress, and the minimum score is 10, indicating no distress. Personality trait was measured using a single question: "how would you rate your personality traits?". Three options were provided: extraversion, introversion and in between.

Statistical Analysis

All analyses were stratified by urban-rural populations. We first present socio-demographic characteristics and self-rated health of our sample, and tested the statistical differences using the Chi square test for categorical variables and the Kruskal-Wallis test for abnormal distributed continuous variables. Second, the

binary logistic model and semiparametric regression model were applied to estimate the associations between absolute income and relative deprivation and SRH of older people, and the urban-rural difference in the coefficients was compared. Third, the sensitive analysis using different reference group was conducted to test the robustness of the estimates. All the statistical analyses were performed using Stata version 15.0. *P*-values were 2-sided, and statistical significance was set at $P = 0.05$.

RESULTS

Descriptive Analysis by Urban and Rural Populations

Table 1 shows the summary statistics of all participants stratified by prefecture of residence. Over 70% of the sample was in the young-old age group (60–74 years old). More than half was female. The majority of the individuals were married. Overall, the educational attainment was higher among urban respondents than rural ones.

Compared to urban participants, rural older people were more likely to have chronic disease and poorer ADL. The urban residents were more likely to report good/very good health compare with their rural counterparts (58.7 vs. 51.1%). Urban respondents had higher incomes than rural respondents, while the relative deprivation were more pronounced in rural elderly. The results indicated that the income gap was large within the rural area.

Association of Absolute Income and Relative Deprivation With SRH

The absolute income and RD were highly correlated in rural and urban populations ($r = -0.862$, $P < 0.001$; $r = -0.942$, $P < 0.001$, respectively), which indicated that the lower the absolute income, the more severe the relative deprivation of the older people (especially among urban population). There is no multicollinearity among covariates in these two samples (see Table B1 of **Supplementary Material**). The results of logistic regression and semiparametric regression after controlling for covariates were shown in **Tables 2**, **3**. We only reported a sub-set of the results, which focused on the impacts of absolute income and relative deprivation on SRH. The complete regression results are reported in the Tables B2, B3 of **Supplementary Material**. Before KRD index was included in the model, the regression coefficients of absolute income were positive and statistically significant for both urban and rural populations (Model 1 and Model 5). However, the association between absolute income and good SRH has reversed after including KRD index into the model, and the coefficients were statistically significant and negative (Model 2 and Model6). At the same time, there is also a significant negative correlation between KRD index and good SRH in both rural and urban samples (Model 2, Model 4, Model 6 and Model 8). This indicates that the huge negative association between RD and health pulls the coefficient of absolute income from positive to negative.

When comparing urban and rural populations, the absolute value of the regression coefficient of the KRD index on SRH among the rural older population was greater than that for the urban elderly, no matter in the logistic model or in the semiparametric model (−3.026 vs. −0.435; −0.504 vs. −0.294, respectively). This indicated that the impact of relative deprivation on SRH of rural elderly was more apparent than that of urban ones. To further test the psychosocial pathway that relative deprivation affecting SRH, we examined the changes of the regression coefficients of KRD index while controlling K10 scores in the models (Model 3 and Model 7). The findings showed that the coefficients of KRD index were attenuated in both urban and rural elderly, which indicated that psychological condition may play a mediating role in the relationship between relative deprivation and SRH. The models using alternative SRH categorization also showed similar results (see Tables C1, C2 of **Supplementary Material**).

In order to further explore the relationship between income and SRH, we obtained kernel regression figures of the relationship between absolute income and SRH under the semiparametric model (**Figure 1**). The two figures showed that there was a complex non-linear relationship between income and SRH. The link between health and income at different levels of income is not straightforward. At low income levels, the absolute income has a positive association with the SRH for both rural and urban elderly, and the increase in income brought a steady improvement in health. However, at high income level, the impact of income on the SRH of both urban and rural elderly has declined and fluctuated. Meanwhile, the urban-rural differences appeared. In rural elderly, the SRH level decreased slightly when the logarithmic income was about 4.8, while in urban elderly, the SRH level decreased significantly when the logarithmic income was about 5.2, and then increased rapidly.

In addition, to investigated the association between RD and SRH when the reference group was a more granular units, we conducted a sensitivity analysis after replacing the reference group from the all rural participants (all urban participants) to the town (sub-district) where the participants were located. The sub-sets of the results of sensitivity analysis were shown in **Tables 4**, **5**. The complete regression results are reported in the Online Appendix (see Tables B4, B5 of **Supplementary Material**). The results showed that there is still a negative correlation between KRD index and SRH in both rural and urban samples. The absolute value of the regression coefficient of the KRD index on SRH among the rural older population was still greater than that for the urban elderly, no matter in the logistic model or in the semiparametric model (−1.237 vs. −0.952; −0.252 vs. −0.179, respectively). As K10 scores was included in the model, the coefficients of KRD also decreased in both urban and rural elderly. The results of sensitivity analysis indicated that the association between RD and SRH was robust.

DISCUSSION

Utilizing a new relative deprivation measure, the Kakwani Index, this study explored the impacts of absolute and relative income on self-rated health among Chinese older people. Four

TABLE 1 | General characteristics of the older people according to residence.

Variables	Urban (n = 2,080)		Rural (n = 4,990)	
	n	%	*n*	%
Log income (mean, sd)	4.18	0.51	3.60	0.38
KRD (mean, sd)	0.39	0.27	0.54	0.21
K10 (mean, sd)	14.49	5.88	15.61	6.87
Self-rate health				
Fair/Poor/very poor	859	41.3	2,439	48.9
Good/very good	1,221	58.7	2,551	51.1
Age group				
60–74	1,609	77.4	3,883	77.8
75+	471	22.6	1,107	22.2
Gender				
Male	695	33.4	1,701	34.1
Female	1,385	66.6	3,289	65.9
Educational attainment				
No school	240	11.5	1,947	39
Primary school	905	43.5	2,069	41.5
Junior school and above	935	45	974	19.5
Marital status				
Married	1,734	83.4	4,040	81
Others	346	16.6	950	19
Chronic disease				
Yes	1,414	68	3,625	72.6
No	666	32	1,365	27.4
ADL, score				
14	1,786	85.9	3,681	73.8
15–21	246	11.8	1,037	20.7
≥22	48	2.3	272	5.5
Personality trait				
Extraversion	1,047	50.3	2,463	49.4
Introversion	570	27.4	1,548	31.0
In between	463	22.3	979	19.6

KRD, Kakwani relative deprivation; ADL, activities of daily living; K10, The Kessler Psychological Distress Scale.

TABLE 2 | Relationship between relative deprivation and SRH in urban older populations (select results)[a,b,c].

Variables	Model 1	Model 2	Model 3	Model 4
Log income	0.273*	−0.143*	−0.080*	
	(0.105)	(0.295)	(0.302)	
KRD		−0.435**	−0.339*	−0.294*
		(0.164)	(0.167)	(0.161)
K10, score			−0.078***	−0.017***
			(0.009)	(0.002)

KRD, Kakwani Relative Deprivation; K10, The Kessler Psychological Distress Scale.
[a]The coefficients in Model 1, 2, 3 were estimated by Binary logistic regression model and the coefficients in Model 4 was estimated by semiparametric regression model. Standard errors are in parentheses.
[b]The reference group was all the urban participants.
*[c]All models were adjusted for age, gender, marital status, education chronic disease, ADL score and personality trait. *P < 0.05; **P < 0.01; ***P < 0.001.*

TABLE 3 | Relationship between relative deprivation and SRH in rural older populations (select results)[a,b,c].

Variables	Model 5	Model 6	Model 7	Model 8
Log income	0.203*	−1.183***	−1.131***	
	(0.083)	(0.185)	(0.188)	
KRD		−3.026***	−2.736***	−0.504***
		(0.347)	(0.353)	(0.062)
K10, score			−0.073***	−0.013***
			(0.005)	(0.001)

KRD, Kakwani Relative Deprivation; K10, The Kessler Psychological Distress Scale.
[a]The coefficients in Model 5, 6, 7 were estimated by Binary logistic regression model and the coefficients in Model 8 was estimated by semiparametric regression model. Standard errors are in parentheses.
[b]The reference group was all the rural participants.
*[c]All models were adjusted for age, gender, marital status, education chronic disease, ADL score and personality trait. *P < 0.05; **P < 0.01; ***P < 0.001.*

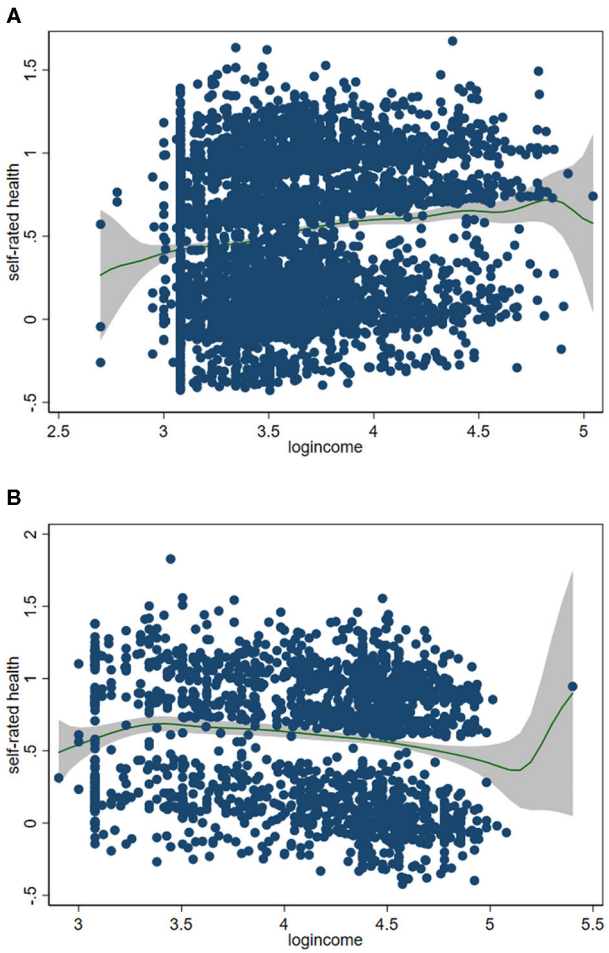

FIGURE 1 | Relationship between absolute income and self-rated health in urban older populations **(A)** and rural older populations **(B)**[a,b]. [a]Adjusted for age, gender, marital status, education, chronic disease, activities of daily living, personality trait, psychological distress and relative deprivation index. [b]The absolute income was transformed using logarithmic function.

TABLE 4 | Sensitive analysis in urban older population (select results)[a,b,c].

Variables	Model 2	Model 3	Model 4
Log income	−0.336	−0.276*	
	(0.235)	(0.239)	
KRD	−0.952*	−0.874*	−0.179**
	(0.396)	(0.403)	(0.161)
K10, score		−0.078***	−0.017***
		(0.009)	(0.002)

KRD, Kakwani Relative Deprivation; K10, The Kessler Psychological Distress Scale.
[a]The coefficients in Model 2, 3 were estimated by Binary logistic regression model and the coefficients in Model 4 was estimated by semiparametric regression model. Standard errors are in parentheses.
[b]The reference group was the urban older populations in the town/sub-district where the participant are located.
*[c]All models were adjusted for age, gender, marital status, education chronic disease, ADL score and personality trait. *P < 0.05; **P < 0.01; ***P < 0.001.*

TABLE 5 | Sensitive analysis in rural older population (select results)[a,b,c].

Variables	Model 6	Model 7	Model 8
Log income	−0.343**	−0.315*	
	(0.133)	(0.136)	
KRD	−1.237***	−0.992**	−0.252***
	(0.232)	(0.238)	(0.046)
K10, score		−0.074***	−0.014***
		(0.005)	(0.001)

KRD, Kakwani Relative Deprivation; K10, The Kessler Psychological Distress Scale.
[a]The coefficients in Model 6, 7 were estimated by Binary logistic regression model and the coefficients in Model 8 was estimated by semiparametric regression model. Standard errors are in parentheses.
[b]The reference group was the rural older populations in the town/sub-district where the participant are located.
*[c]All models were adjusted for age, gender, marital status, education chronic disease, ADL score and personality trait. *P < 0.05; **P < 0.01; ***P < 0.001.*

main findings were obtained: First, absolute income has a positive association with good SRH when relative income is not considered. Our study offered evidence to confirmed the AIH for both rural and urban older adults in China. Second, relative deprivation is associated with poor self-rated health. This result also demonstrates a support for the RIH in rural and urban Chinese elderly. Third, the magnitude of the correlation between relative income and SRH differed in rural and urban old populations. The impact of relative income on SRH was greater among the rural elderly compared to urban ones. Fourth, the present study shows that psychological distress substantially buffered the stronger negative impact of relative deprivation and SRH, suggesting that psychological condition may play a mediating role in the relationship between relative deprivation and SRH.

Empirical studies on the impact of absolute income on health have yielded mixed findings and there has been no consistent conclusion (43). However, the non-linear relationship between health and absolute income has often been reported (44, 45), and our results also offered evidence to confirm it. The result in our study that absolute income increased SRH at a decreasing rate was similar with previous research conducted in other countries and China (46, 47). People with higher household income, especially the older people, can increase access to healthcare by improving financial capacity to cover health-related expenses (48). In China, it seems that being poor can greatly reduce an individual's resilience to health shocks and lead to worse health (49). In addition, adequate finance will reduce future health vulnerability for the individual and the household by developing a balanced lifestyle, maintaining healthy living conditions and providing adequate resources for household dependents (50, 51). We only provided some possible explanations for the positive impact of absolute income on SRH, but considering the non-linear relationship between health and absolute income, the influential mechanism linking absolute income and health needs to be explored in future research.

This study also provided evidence to support the RIH in rural and urban Chinese older populations. The result reported a negative association between relative deprivation and SRH was in line with previous studies in China among adults and older populations (52, 53). An explanation of why relative deprivation in income may lead to poorer health status is the concept of allostatic load (54, 55). Invidious upward social comparisons often lead to perceived relative deprivation, and those who feel relatively deprived will have some negative emotions such as frustration and shame, thereby having a detrimental effect on mental health through the excessive secretion of the stress hormone, which leads to harmful health behaviors (56). Another explanation was the material pathway. Relative deprivation reduces the probability of individuals equally obtaining public goods, healthcare services and participating in social activities, thereby affecting the health of individuals (9).

The RIH in rural elderly was more pronounced than that in urban area. This urban-rural difference may be due to two reasons. First, the urban and rural elderly have different psychological perceptions of relative deprivation caused by income inequality. In China, income inequality in rural areas is higher than in urban areas, and income inequality aggravates the relative deprivation of rural populations (57). What's more, rural populations tend to be had lower socioeconomic status, which may lead to a strong sense of income inequality caused by income gap due to their living culture, and the idea of "suffering from poverty but not suffering from inequality" is more serious than urban residents. Second, differences in macro-structural characteristics of urban-rural segmentation makes the urban and rural elderly different in their tolerance for relative deprivation (58). Urban residents have relatively complete medical security, even if they are subject to greater income deprivation, they will suffer less psychological pressure. On the contrary, rural areas often lack medical resources, and the income deprivation suffered by rural residents will have a greater negative impact on their health. In addition, our results showed that the lower the absolute income, the more severe the relative deprivation of the older people, and low-income people in urban are more likely to feel relative deprivation. The lower the income of the elderly, the more difficult it is to meet their own needs, and they are more likely to be in a disadvantaged position when making social comparisons with others, resulting in relative deprivation.

What's more, urban older people differ greatly in occupational levels, and there are obviously more high-educated and high-income groups than in rural areas. Therefore, when making social comparisons, urban low-income older people are more likely to have relative deprivation.

This study has a number of limitations. First, we lacked information on the actual reference groups people use to make social comparisons. Alternative reference groups based on age or education may have formed the basis for interpersonal comparisons. However, as a special group, the elderly gradually withdraws from the labor market, and the family income will reach the maximum at this time. The impact of age and education on income is no longer significant. Therefore, we assume that individuals in each subgroup (urban or rural) compare themselves with other individuals who have higher income in the same group. Second, we may have omitted some potential variables, such as individual variations in ability, temperament, and personality, which could also reflect the association between relative deprivation and health. We used an extensive range of control variables based on those used in previous literature, thereby reducing the chance of possible omitted variable bias. Third, the KRD Index is an objective measure of relative deprivation. It is not known whether those who had a higher KRD Index in fact perceived themselves as deprived compared to others. Previous studies have found that subjective feelings of deprivation or self-reported inequality was more important than objective measures (16). Fourth, a considerable proportion of the participants are living in the same household, and these people likely had a correlation in terms of SRH and income. Fifth, the data in our study is cross-sectional data, which can only reflect the current associations between income and relative deprivation and health, while delayed and cumulative effects cannot be reflected. Meanwhile, we are unable to demonstrate a causal relationship between relative deprivation and self-rated health because of the cross-sectional design.

CONCLUSION

In conclusion, the present study supported the AIH and BIH in Chinese older adults. Relative deprivation is negatively associated with self-rated health in both urban and rural older people after controlling the absolute income. Furthermore, the correlation between relative income and SRH was more pronounced among the rural older populations than among the urban ones. Our findings have some potentially important policy implications. The first policy option is to improve the financial security by increasing income of older people, especially for the rural elderly. Second, the negative impact of relative deprivation could be addressed by reduce income inequality, such as via income transfers to reduce the gap between rich and poor. Third, when considering the impact of income on health, in addition to considering absolute income, the income-based relative deprivation should also be concerned.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

LX and SW contributed to the conception and design of the study. WQ performed the statistical analysis and wrote the first draft of the manuscript. HS contributed to revise the paper. All authors contributed to the study design, critically reviewed draft versions and provided important intellectual content during revisions, and accept accountability for the overall 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.2021.658649/full#supplementary-material

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Prevalence, Association Relation, and Dynamic Evolution Analysis of Critical Values in Health Checkup in China: A Retrospective Study

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Objective: The critical values in health checkup play a key role in preventing chronic diseases and different types of cancer. This study aimed to analyze the prevalence, association relation, and dynamic evolution of critical values in health checkups at a large physical examination center in China.

Methods: Herein, we chose 33,639 samples of physical examiners from January 2017 to December 2019. After strict exclusion processes, combined with the critical values in health checkup reporting data, 4,721 participants with at least one critical value were included. We first defined a critical value list for laboratory test, imaging, cervical cancer screening, electrocardiogram, and health checkup informed on site, and then performed a cross-sectional study to analyze the distribution and significance of critical values of 4,721 participants from different views and the association relation of 628 participants with more than one critical value and a retrospective cohort study to analyze the incidence and dynamic evolution of critical values based on 2,813 participants attending the physical examination from 2017 to 2019.

Results: A total of 4,721 participants were included in the retrospective study. The prevalence of 10 critical values from 33,639 participants was over 0.6%. The critical values of obesity, hypertension, Glucose_T, Liver_T, Kidney_T, Lipid_T, Urine_T, and Head_CT were significantly increased in men ($P < 0.05$), whereas the results were the opposite for the Blood_T and Thyroid_US ($P < 0.01$). The prevalence trend of critical values increased along with age, where the prevalence of men was higher than that of women under 60 years old ($P < 0.01$), while the prevalence of women increased by four times and exceeded the prevalence of men above 70 years old. Association relation analysis identified 16 and 6 effective rules for men and women, respectively, where the critical values of Urine_T and Glucose_T played the central roles. Furthermore, a retrospective dynamic evolution analysis found that the incidence of new critical values was about 10%, the incidence of persistent critical values was about 50%, and that most of the effective evolution paths tended to no critical values for men and women.

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Conclusion: In conclusion, this study provides a new perspective to explore the population health status using the critical value reporting data in a physical examination center, which can assist in decision-making by health management at the population level and in the prevention and treatment of various types of cancer and chronic diseases at the individual level.

Keywords: critical values in health checkup, prevalence analysis, association relation analysis, dynamic evolution analysis, health managament

INTRODUCTION

In clinical activity, the term "critical value" was defined first by George D. Lundberg in 1972 as a laboratory test result that represents a pathophysiologic state at such variance with normal as to be life-threatening unless something is done promptly and for which some corrective action could be taken (1–4) and then plays an important role in ensuring patient safety and supporting effective clinical decision-making (5). Similarly, in health management and examination activity, there exist critical values in health checkup, which is represented as the important abnormal results of a certain system or an organ that is found by the physical examinee without symptoms and signs, including clinical critical values, major diseases and their clues, acute and chronic lesions, and abnormal examination results requiring dynamic observation (6). Thus, compared with clinical critical values, the critical value in health checkup has a much wider definition scope and a lower population ratio in the healthy population.

Recently, critical value research mainly involves two aspects: critical value reporting policies and practices and critical value data analysis. The critical value reporting is a key component to improve total healthcare system by encouraging health care providers for effective treatment of the patients; thus, many studies examine critical value reporting policies and practices and identify critical value ranges for different hospitals using a national survey (7–10). For the second aspect, many studies mainly analyze the occurrence and distribution of critical values and the relationship between the frequency of such values and patient outcome and can provide information for hospitals on improving reporting policies (11–15). In summary, most of these studies focus on laboratory critical values and also the lack of the association relation and dynamic evolution analysis over time for critical values.

In addition, few studies have formally analyzed and discussed the critical values in health checkup. In China, the malignant tumor has become one of the major public health problems. According to the latest statistics, the death rate of malignant tumor accounts for 23.91% of the total death causes of residents, and the incidence and the mortality have been increasing in the recent decade; thus, early prevention, early screening, early diagnosis, and early treatment of malignant tumors are very important. Critical values in health checkup are the early symptoms and an inevitable process of malignant tumors, and the analysis of critical values is a crucial task in a health management center (16). Hence, in this study, our objectives are to (1) examine the prevalence of the critical values in health checkup at the healthy population level to find the possible relationship with the incidence of malignant tumors, (2) explore the association relation among the critical values to find the core critical values, and (3) carry out the retrospective cohort analysis to acquire the incidence of new and persistent critical values and a dynamic evolution trend of critical values in health checkup over time.

METHODS

Participant Information

This study was conducted in accordance with the Helsinki Declaration and Rules of Good Clinical Practice. The study was approved by the Institutional Review Board of the First Affiliated Hospital of Zhengzhou University (2018-KY-56). From January 2017 to December 2019, there were a total of 33,639 physical examiners with the same physical examination items from the Health Management Center, the First Affiliated Hospital of Zhengzhou University in Central China. The same items are the basis of the critical value analysis in health checkup because it is difficult to make sure whether the participants have this critical value if they do not take this examination. The physical examination items mainly include a laboratory test (blood routine test, urine routine test, liver function, renal function, blood lipid, and blood glucose) by a Roche cobas 8000 automatic biochemical analyzer, ultrasound examination items (breast, thyroid, abdominal ultrasonography, etc.) by a Philips Affiniti 50 color Doppler ultrasound system with a linear array probe and a frequency of 5–12 MHz, cervical cancer screening items [Thinprep Cytologic Test (TCT) by cytological diagnosis based on Bethesda systematic classification, Human Papillomavirus (HPV) by a Roche cobas HPV detection kit], electrocardiogram by Electrocardiograph (MedEx, MECG-300, China), CT by a spectral CT scanner (Discovery CT, GE Healthcare), height and weight measurement for body mass index (BMI) by an ultrasonic height and weight meter with SK-X80 (SONKA, China), and blood pressure measurement by a medical electronic sphygmomanometer (OMRON, China). The same physical examination items used the same devices and equipment from 2017 to 2019. After removing 28,918 participants without critical values, the remaining 4,721 participants were used for statistical analysis, including the prevalence and significance analysis, association relation, and dynamic evolution analysis (**Figure 1**).

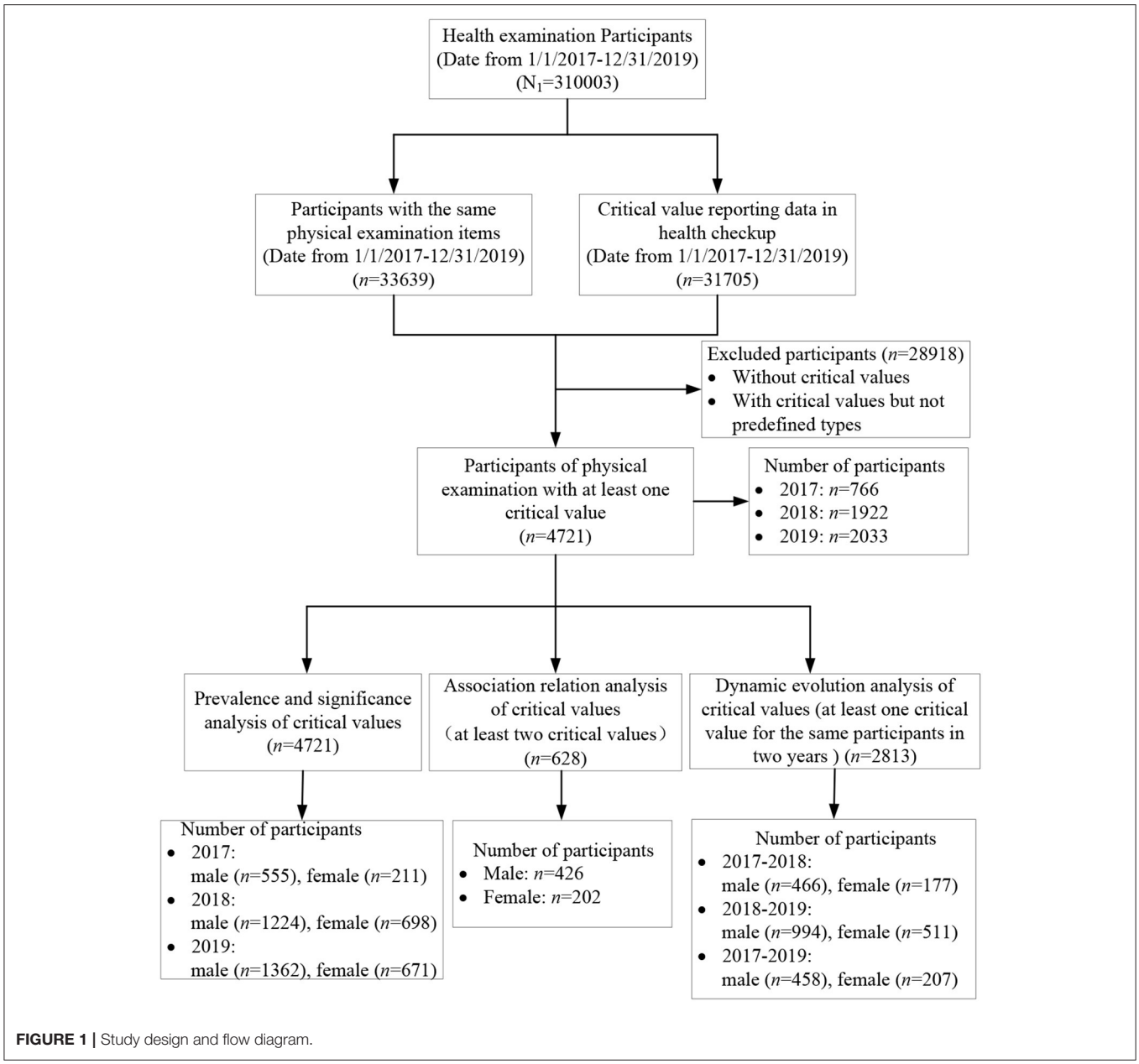


FIGURE 1 | Study design and flow diagram.

Definition of the Critical Values in Health Checkup

According to the expert consensus on the management of important results with abnormal values in physical examination, the clinical experts from the health management center and relevant departments jointly study and determine the critical value lists and submit them to the medical quality committee of the hospital for approval. The critical value list includes two categories: one is highly abnormal and endangering the life safety of the physical examinees and the other is some important positive findings that may affect the life and health of the physical examinees, although they will not endanger the life and health in a short time. The critical value lists include the test items, analytes, and ranges (**Tables 1**–**4**).

An Effective Association Rule and Dynamic Evolution Path Identification

In this study, an association rule ($X \geq Y$) refers to the occurrence of a critical value (Y) based on another critical value X, while an effective and strong association rule must meet three conditions, including the support, confidence, and lift. The support [p (X, Y)] is the co-occurrence frequency of the critical values X and Y, the confidence [p (Y/X)] measures the possibility that the critical value Y occurs after suffering from the critical value X, and the lift

TABLE 1 | The critical value list in health checkup for a laboratory test.

Test items	Analytes	Critical value range
Routine Blood Test (Blood_T)	WBC count	$\leq 2 \times 10^9$/L, $\geq 20 \times 10^9$/L
	Platelet count	$\leq 30 \times 10^9$/L, $\geq 1000 \times 10^9$/L
	Hemoglobin	≤60 g/L
Blood Glucose Test (Glucose_T)	Glucose	≥16.7 mmol/L and ≥13.9 mmol/L with strong positive urine ketone body
	Glycosylated hemoglobin	≥15%
Liver Function Test (Liver_T)	Alanine aminotransferase	≥100 U/L
	Aspartate aminotransferase	≥100 U/L
	Glutamyl transpeptidase	≥200 U/L
	Total bilirubin	≥85.5 μmol/L
Kidney Function Test (Kindney_T)	Creatinine	>115 μmol/L
Blood Lipid Test (Lipid_T)	Triglyceride	≥15 mmol/L
Thyroid Function Test (Thyroid_T)	Free triiodothyronine	≥2 × maximum reference value
	Free thyroxine	
	Thyroid stimulating hormone	
Routine Urine Test (Urine_T)	Occult blood	≥3 +
	Pathological cast	≥1/μL
	Transparent tube type	≥2/μL
	Ketone body	≥2 +
	Glucose	≥4 +
	Protein	≥3 +
Tumor Marker Test (Tumor_T)	Alpha fetoprotein, Carcinoembryonic antigen	≥2 × maximum reference value
	Ca72-4, Ferritin	≥3 × maximum reference value
	Ca125, Ca19-9	≥maximum reference value
	Tumor abnormal protein	≥160 μm^2
	Total prostate specific antigen	≥4 ng/ml

TABLE 2 | The critical value list in health checkup for imaging.

Examination items	Critical value list
Thyroid Ultrasound (Thyroid_US)	TI-RADS ≥ category 4; Parathyroid adenoma; Cervical lymph nodes enlargement; Considering lymph node metastasis.
Cardiac Ultrasound and Computed Tomography (Cardiac_US&CT)	Ventricular aneurysm; Severe reflux; Ascending aorta widening (widening > 45 mm); Pericardial effusion (large amount); Moderate-severe stenosis (moderate-severe incomplete closure); Aortic aneurysm; Coronary artery stenosis degree > 75%.
Abdominal Ultrasound (Abdominal_US)	Liver cirrhosis; Ascites; Severe fatty liver; Liver cyst; Solid space occupying lesions (retroperitoneal space occupying lesions); Solid nodules (further examination); Intrarenal hyperechogenicity (further examination); Intrahepatic and extrahepatic bile ducts Widening (or high limit); Pancreatic lesions (any lesions); Separation of collecting system; Massive pleural effusion; Intrahepatic low-density shadow.
Neck Vascular Ultrasound (Neck_US)	Carotid artery stenosis > 50; Moderate-severe stenosis; Internal carotid artery occlusion; Left cervical lymph node enlargement.
Urinary System Ultrasound (Urinary_US)	Hydronephrosis (moderate-severe); Small renal volume; Localized thickening of bladder wall; Ureteral dilatation; Separation of renal collecting system; Prostate.
Pelvic Ultrasound (Pelvic_US)	Ectopic pregnancy.
Breast Ultrasound and Mammography (Breast_US&MG)	BI-RADS category 0 and ≥ category 4A; Space occupying; Shadow.
Lung Computed Tomography and Chest X-Ray (Lung_CT&X)	Space occupying; Mediastinum widened; Hilar widened (slightly larger plus data); Pleural effusion (medium and large amount); Suspicious small nodules; Abnormal density shadow; Ground glass nodules.
Head Computed Tomography (Head_CT)	High pathological changes >80%; Cerebral vascular stenosis; Cerebral hemorrhage; Aneurysms; Subacute cerebral infarction; Arachnoid cyst; Cerebral hemorrhage; New cerebral infarction; Brain abscess and other signs of canceration.

TABLE 3 | The critical value list in health checkup for cervical cancer screening and electrocardiogram.

Test or Examination items	Critical value list
Thinprep Cytologic Test and Human Papilloma Virus (TCT&HPV)	TCT: Non benign/reactive lesions; Malignant cells; Low-grade and high-grade intraepithelial lesions; Atypical squamous cells; HPV-16/18 positive.
Electrocardiogram (ECG)	Ventricular premature beats (biphasic, triplet, quadruple, multifocal, frequent, ventricular tachycardia, arrest); Atrioventricular block, ventricular arrest and occasional sinus arrest were more than type 2; High potassium, low potassium, low blood calcium, visible atrial escape rate; High and sharpT wave, ST segment elevation (arch back upward) or significantly depressed with T wave inversion; Sinus bradycardia<45, accompanied by long interval of 3S, QT prolongation; Acute myocardial infarction/Brugada wave.

TABLE 4 | The critical value list in health checkup informed on site.

Measurements items	Critical value list
Measurement of height and weight (Obesity)	Body mass index (BMI) = weight/(height)^2: BMI≥30(Kg/m^2)
Blood pressure measurement (Hypertension)	Systolic blood pressure (SBP)≥180(mmHg) or Diastolic blood pressure (DBP)≥110(mmHg)

[p (Y/X)/p(Y)] measures the promotion function of critical value Y after the critical value X, reflecting the effectiveness of relation between the critical value X and the critical value Y. Hence, an effective association rule can be identified when the support and the confidence exceed the minimum values defined beforehand, and also the lift is >1.

A dynamic evolution path (Y→ Z) refers to the transition of the critical value Z after the critical value Y in two consecutive years, reflecting the persistence and variability of the critical values. Thus, an effective evolution path can be identified when the transition probability of the critical value Y in 1 year and Z in the next year exceeds the minimum values defined beforehand.

Statistical Analysis

Statistical analysis were performed using R software. R software was used to analyze the prevalence and significance, construct the association rule model (R 4.0.2; an arules and arulesViz package), and identify the dynamic evolution path of critical values in health checkups from 2017 to 2019. A cross-sectional study was performed for the single participant to determine the prevalence and association among critical values in health checkups. A retrospective cohort study was performed for the incidence of emerging and persistent critical values for the participants with follow-up physical examination. The age value is presented as the mean ± SD. The Student's t-test was used to evaluate the differences between the sets of continuous variables, the chi-square test was used to evaluate the differences between the sets of categorical variables, and there were significant differences between observation groups with and without critical values in health checkup when P is < 0.05.

RESULTS

Participant Demographics

A total of 33,639 participants (19,185 males and 14,454 females) were extracted in this study from January 2017 to December 2019. Then, 28,918 participants without critical values were excluded, and the remaining 4,721 participants were identified for further data analysis. Among 4,721 participants, 4,093 participants have only one critical value, 539 participants have two critical values, 72 participants have three critical values, 15 participants have four critical values, and 2 participants have five critical values. All the 4,721 participants are affiliated with 107 units, such as universities, banks, enterprises, and institutions, as well as other social organizations. The mean age was 49.32 ± 13.87 years old, where the youngest and the oldest were 21 and 96 years old, respectively. Specifically, the numbers of male and female participants were 3,141 and 1,580, respectively, the mean ages were 48.50 ± 13.50 and 50.95 ± 14.43 years old, respectively, and there was a significant difference in years ($P < 0.05$). In addition, the number of participants gradually increased from 766 in 2017 and 1,922 in 2018 to 2,033 in 2019, since the total amount of physical examinees in 2017 is far less than that in 2018 and 2019.

After analyzing the critical value data of 4,721 participants, the prevalence and significance of critical values in health checkups were shown in **Table 5** and **Figure 2**. In summary, the prevalence of critical values was 14.03, 16.37% for men and 10.93% for women. Among the prevalence of all the critical values over 0.6%, obesity accounted for the highest percentage with the prevalence of 6.40% for all the participants, 9.18% for men and 2.71% for women, followed by thyroid_US (1.69%), hypertension (1.54%), ECG (0.95%), lung_CT and X (0.83%), tumor_T (0.81%), liver_T (0.74%), TCT and HPV (0.67%), Breast_US and MG (0.64%), and urine_T (0.61%) for all the participants; hypertension (1.94%), thyroid_US (1.25%), liver_T (1.02%), ECG (0.99%), urine_T (0.91%), lung_CT and X (0.88%), and liver_T (0.74%) for male participants; thyroid_US (2.28%), hypertension (1.01%), ECG (0.91%), tumor_T (0.89%), lung_CT and X (0.76%), TCT and HPV (0.67%), and breast_US and MG (0.64%) for female participants.

Moreover, in **Table 5** and **Figure 2**, the total number and prevalence of critical values in men were higher than that in women ($P < 0.01$), hinting that men were prone to present abnormal items. More specifically, compared with women, the prevalence of obesity, hypertension, glucose_T, liver_T, kidney_T, lipid_T, urine_T, and head_CT were significantly increased in the male population ($P < 0.05$), whereas for blood_T and thyroid_US, the female population presented an increased percentage compared with the male population ($P < 0.01$). In addition, the prevalence of tumor_T, cardiac_US and CT, abdominal_US, neck_US, urinary_US, ECG, and lung_CT and X in men and women had no significant difference, indicating that both suffered from these abnormal items with the same risk.

TABLE 5 | The prevalence and significance analysis of critical values in health checkup.

Critical value	Total (N = 33,639)	Male (n = 19,185)	Female (n = 14,454)	x^2	P-Value
Obesity	2154 (6.40%)	1762 (9.18%)	392 (2.71%)	576.17	**<0.01****
Hypertension	519 (1.54%)	373 (1.94%)	146 (1.01%)	47.35	**<0.01****
Blood_T	75 (0.22%)	18 (0.09%)	57 (0.39%)	33.47	**<0.01****
Glucose_T	86 (0.26%)	65 (0.34%)	21 (0.15%)	12.11	**<0.01****
Liver_T	248 (0.74%)	196 (1.02%)	52 (0.36%)	49.35	**<0.01****
Kindney_T	81 (0.24%)	68 (0.35%)	13 (0.09%)	24.01	**<0.01****
Lipid_T	18 (0.05%)	15 (0.08%)	3 (0.02%)	5.08	**0.024***
Thyroid_T	20 (0.06%)	9 (0.05%)	11 (0.08%)	1.18	0.277
Urine_T	205 (0.61%)	174 (0.91%)	31 (0.21%)	65.26	**<0.01****
Tumor_T	274 (0.81%)	146 (0.76%)	128 (0.89%)	1.58	0.208
Thyroid_US	570 (1.69%)	240 (1.25%)	330 (2.28%)	52.72	**<0.01****
Cardiac_US&CT	31 (0.09%)	23 (0.12%)	8 (0.06%)	3.73	0.053
Abdominal_US	117 (0.35%)	70 (0.36%)	47 (0.33%)	0.38	0.54
Neck_US	44 (0.13%)	30 (0.16%)	14 (0.1%)	2.24	0.135
Urinary_US	71 (0.21%)	39 (0.2%)	32 (0.22%)	0.13	0.72
Pelvic_US†	46 (0.3%)	2 (0.01%)	44 (0.3%)		
Breast_US&MG†	93 (0.64%)		93 (0.64%)		
TCT&HPV†	97 (0.67%)		97 (0.67%)		
ECG	321 (0.95%)	189 (0.99%)	132 (0.91%)	0.45	0.502
Lung_CT&X	278 (0.83%)	168 (0.88%)	110 (0.76%)	1.32	0.25
Head_CT	109 (0.32%)	73 (0.38%)	36 (0.25%)	4.41	**0.036***
All	4721 (14.03%)	3141 (16.37%)	1580 (10.93%)	206.16	**<0.01****

*****Denotes a statistically significant difference (P <0.05).*

******Denotes a statistically significant difference (P <0.01).*

† *Only for the female.*

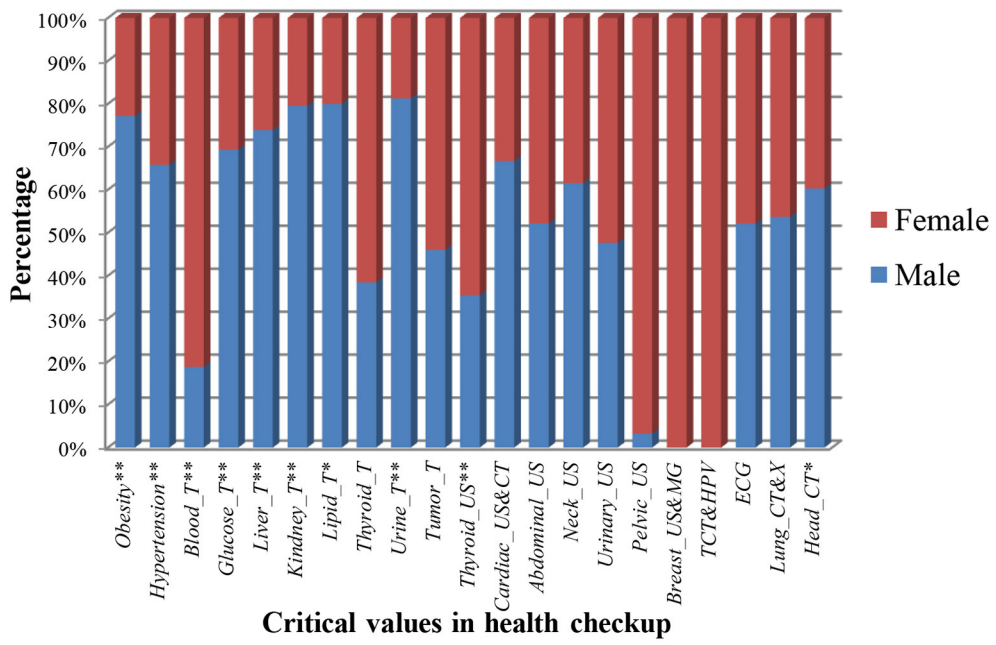


FIGURE 2 | The prevalence of critical values in health checkup for different genders. * and ** denote the statistically significant difference in the 0.05 and 0.01 tested levels.

TABLE 6 | The significance analysis of critical values for different ages and genders.

Age group		Obesity	Hypertension	Thyroid _US	Urine _T	ECG	Lung _CT&X	Total
18–30	Male (1,090)	106	2	8	11	6	5	153 (14.04%)
	Female (951)	12	1	17	15	8	8	58 (6.10%)
	X^2	66.53		4.66	1.27	0.63	1.17	34.52
	P-Value	**<0.01****		**0.03***	0.25	0.43	0.279	**<0.01****
31–40	Male (5,676)	640	58	53	38	28	23	894 (15.75%)
	Female (4,673)	103	9	93	43	28	27	380 (8.13%)
	X^2	316.49	27.40	20.56	2.07	0.53	1.59	137.81
	P-Value	**<0.01****	**<0.01****	**<0.01****	0.15	0.47	0.21	**<0.01****
41–50	Male (5,331)	505	126	63	45	41	43	847 (15.89%)
	Female (3,811)	82	23	93	43	28	27	410 (10.76%)
	X^2	198.24	42.94	20.99	1.88	0.04	0.28	149.31
	P-Value	**<0.01****	**<0.01****	**<0.01****	0.17	0.85	0.6	**<0.01****
51–60	Male (4,432)	327	81	72	32	59	46	716 (16.16%)
	Female (2,945)	76	26	85	14	26	18	330 (11.21%)
	X^2	78.85	11.05	13.52	1.74	3.12	3.75	35.62
	P-Value	**<0.01****	**<0.01****	**<0.01****	0.19	0.08	0.05	**<0.01****
61–70	Male (1,681)	116	59	24	14	25	26	296 (17.61%)
	Female (1397)	66	29	46	8	18	24	225 (16.11%)
	X^2	6.50	5.65	11.94	0.73	0.22	0.14	1.23
	P-Value	**0.011***	**0.017***	**<0.01****	0.39	0.64	0.71	0.268
>70	Male (969)	68	47	20	6	30	25	235 (24.25%)
	Female (668)	53	58	14	0	23	16	177 (26.50%)
	X^2	0.485	9.67	0		0.15	0.06	1.06
	P-Value	0.486	**<0.01****	0.97		0.70	0.81	0.304

*****Denotes a statistically significant difference (P <0.05).*

******Denotes a statistically significant difference (P <0.01).*

Lastly, pelvic_US, BCDU and M, and TCT and HPV only existed in women.

Furthermore, we analyzed the difference analysis of critical values for different genders and ages, acquired the results of the top six with the highest prevalence (**Table 6**), and the prevalence trend of critical values along with age (**Figure 3**). The prevalence of obesity and hypertension in men was higher than that in women under 70 years old, while the opposite was true for thyroid_US. The prevalence of urine_T, ECG, and lung_CT and X had no significant difference in men and women. More importantly, the prevalence of all critical values increased to about 25% along with age, where the prevalence of men was higher than that of women under 60 years old ($P < 0.01$), while the prevalence of women increased by four times and exceeded the prevalence of men above 70 years old.

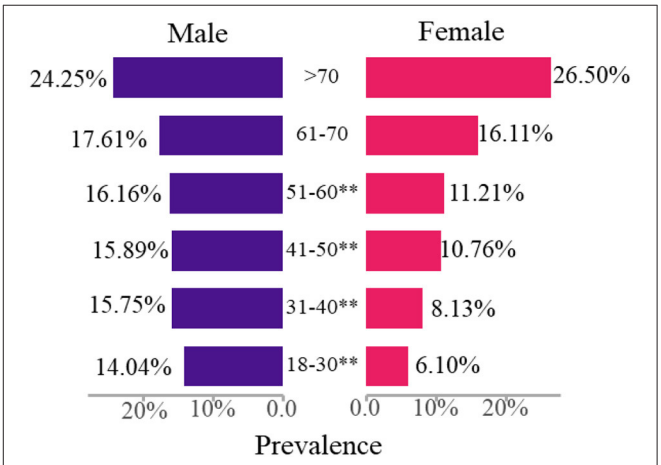


FIGURE 3 | The prevalence trend of critical values along with age for the male and female. **Denotes a statistically significant difference ($P < 0.01$).

Association Relation Analysis

A total of 629 participants with more than one critical value were selected to analyze the association relation, including 426 males and 203 females. After adopting the Apriori algorithm (17) and defining the minimum support, confidence, and lift as 0.01, 0.4, and 1, we finally identified 16 and seven effective rules for the male and the female participants (**Table 7**, **Figure 4**). An effective rule can be represented by a group of critical values from the left hand side (LHS) to the right hand side (RHS).

Specifically, men identified 16 rules with 11 critical values, and the core critical values were urine_T and glucose_T. The rule

TABLE 7 | The detailed results of the identified effective and strong rules.

Gender	No.	Rule (LHS ≥ RHS)	Support	Confidence	Lift	Count
Male	1	{Glucose_T,Tumor_T} ≥ {Urine_T}	0.01	1	4.44	6
	2	{Glucose_T,Hypertension} ≥ {Urine_T}	0.01	1	4.44	5
	3	{Liver_T,Urine_T} ≥ {Glucose_T}	0.02	0.88	5.82	7
	4	{Tumor_T,Urine_T} ≥ {Glucose_T}	0.01	0.86	5.71	6
	5	{Glucose_T} ≥ {Urine_T}	0.13	0.84	3.74	54
	6	{Glucose_T,Liver_T} ≥ {Urine_T}	0.02	0.78	3.45	7
	7	{Hypertension} ≥ {Obesity}	0.19	0.71	1.34	83
	8	{Glucose_T,Thyroid_US} ≥ {Urine_T}	0.01	0.63	2.77	5
	9	{Liver_T} ≥ {Obesity}	0.08	0.56	1.07	36
	10	{Urine_T} ≥ {Glucose_T}	0.13	0.56	3.74	54
	11	{Thyroid_US,Urine_T} ≥ {Glucose_T}	0.01	0.56	3.7	5
	12	{Glucose_T,Obesity} ≥ {Urine_T}	0.01	0.56	2.47	5
	13	{Hypertension,Urine_T} ≥ {Glucose_T}	0.01	0.5	3.33	5
	14	{Thyroid_US} ≥ {Obesity}	0.06	0.44	0.82	27
	15	{Abdominal_US} ≥ {Lung_CT&X}	0.04	0.43	3.23	17
	16	{Cardiac_US&CT} ≥ {ECG}	0.01	0.42	3.35	5
Female	1	{Urine_T} ≥ {Glucose_T}	0.07	0.75	7.58	15
	2	{Glucose_T} ≥ {Urine_T}	0.07	0.75	7.58	15
	3	{Hypertension} ≥ {Obesity}	0.13	0.6	1.92	27
	4	{Neck_US} ≥ {Thyroid_US}	0.01	0.43	1.31	3
	5	{Obesity} ≥ {Hypertension}	0.13	0.43	1.92	27
	6	{Urinary_US} ≥ {Thyroid_US}	0.02	0.42	1.28	5

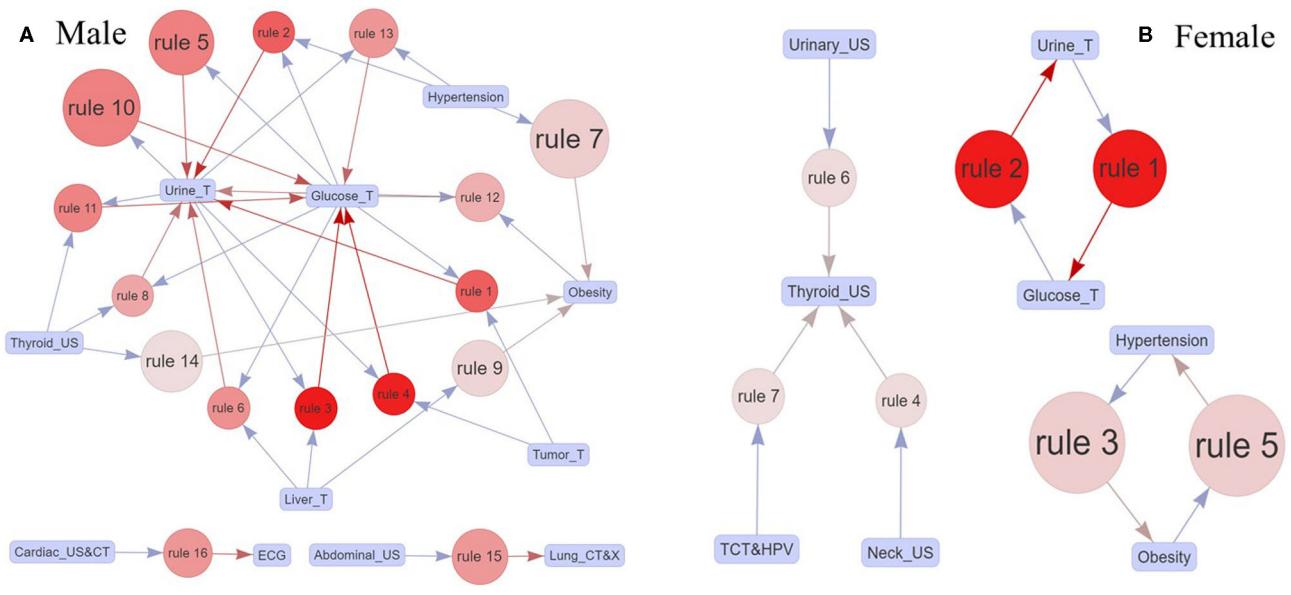
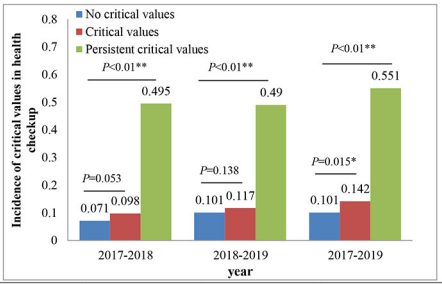


FIGURE 4 | (A,B) The effective association rules for the male and the female participants. A rule was composed of boxes, arrows, and a circle; the blue and red arrows were the critical values on LHS and RHS; and the size and the color of the circle showed the support of the critical value on LHS and the lift of the rule, respectively.

{hypertension} ≥ {obesity} (rule 7) had the maximum support with 0.19, indicating that the combination of hypertension and obesity was particularly prevalent in men. Then, the rules with the second largest support were {glucose_T} ≥ {urine_T} (rule 5) and {urine_T} ≥ {glucose_T} (rule 10), where the confidence of the former is larger than that of the latter. Also, the confidence values of the first two rules ({glucose_T, tumor_T} ≥ {urine_T}, {glucose_T, hypertension} ≥ {urine_T}) were 1, showing the critical values on the RHS appeared certainly along with the critical values on the LHS. While for



		2017-2018	2018-2019	2017-2019
No critical value†	Total number	3131	6195	2890
	New cases	223	623	291
Critical value‡	Total number	420	882	374
	New cases	41	103	53
Persistent critical value♀	Total number	420	882	374
	Persistent cases	208	432	206

FIGURE 5 | The incidence of emerging and persistent critical values for the participants with follow-up physical examination. † Denotes no critical value in the previous year but new critical values in the next year, ‡denotes critical values in the previous year and new critical values in the next year, and ♀denotes critical values in the previous year and the next year. *Denotes a statistically significant difference ($P < 0.05$), **denotes a statistically significant difference ($P < 0.01$).

women, there were only six rules with seven critical values and three decentralized association networks, including urine_T, glucose_T, hypertension, obesity, thyroid_US, urinary_US, and neck_US. Similarly, the combination of hypertension and obesity was prevalent in women, since rules 1 and 5 had the maximum support. Meanwhile, the rules {urine_T} ≥ {glucose_T} (rule 1) and {glucose_T} ≥ {urine_T} (rule 2) had the same support, confidence, and lift.

Dynamic Evolution Analysis

A total of 2,813 participants with more than one critical value attending the physical examination in 2 years from 2017 to 2019 were selected to analyze the dynamic evolution, including 643 participants (466 males and 177 females) in 2017 and 2018, 1,505 participants (994 males and 511 females) in 2018 and 2019, and 665 participants (458 males and 207 females) in 2017 and 2019. **Figure 5** shows the incidence of emerging and persistent critical values for the participants with follow-up physical examination, and **Figure 6** shows the effective evolution paths for men and women from 2017 to 2019, after defining the minimum transition probability as 0.2.

In **Figure 5**, we found that the incidence of new critical values was from 7 to 14%, whereas the incidence of persistent critical values was about 50%. In addition, whether there was a critical value in 2017 and 2018 or not, the incidence of new critical values in 2018 and 2019 had no significant difference ($P = 0.053$, $P = 0.183$). Interestingly, if there exist critical values in 2017, the incidence of new critical values in 2019 was significantly higher than that without critical values in 2017 ($P = 0.015$). Also, the incidence of persistent critical values had a significantly higher than the incidence of new critical values in 2017→2018 ($P < 0.01$), 2018→2019 ($P < 0.01$), and 2017→2019 ($P < 0.01$).

In **Figure 6**, 20 and 23 effective evolution paths were identified in 2017→2018 and 2018→2019 for men, while 15 and 28 effective evolution paths were identified in 2017→2018 and 2018→2019 for the women, respectively. An effective evolution path can be represented by a critical value in 1 year to a critical value in the next year, that is, A → B, which reflects the persistence and variability of critical values. The path of critical values → 0 was the most popular, indicating the participants paid attention to the critical value and timely prevented, intervened, and treated these diseases after the physical examination; thus, no critical values were found in the next year. In addition, there existed larger persistence for many critical values, especially obesity and thyroid_US. Also, the variability among critical values in different years existed, such as abdominal_US → obesity, hinting at the mutual influence relationship among diseases.

DISCUSSION

Health management is a process of comprehensive management of individual or population health risk factors. Its characteristics determine that the critical value in health checkup covers a wider range than that of the clinical critical value. We first defined the critical value list in health checkup according to the clinical practice, including 19 abnormal items and the corresponding critical value types and the range, such as for the WBC count and the platelet count in the routine blood test, the clinical critical value ranges were "$\leq 1.5 \times 10^9$/L" and "$\geq 50 \times 10^9$/L," "≤20 (a non-hematological ward) or 10 (a hematological ward)" and "$\geq 1{,}000 \times 10^9$/L" (14), while the critical values in health checkup were "$\leq 2 \times 10^9$/L" and "$\geq 20 \times 10^9$/L," "$\leq 30 \times 10^9$/L" and "$\geq 1{,}000 \times 10^9$/L," respectively. Moreover, for radiology and ultrasound examination, the number of clinical critical values was far less than that of the critical value in health checkup (12, 18).

In health examination report interpretation, critical value report, and follow-up practice, the clinician usually treated the critical value in health checkup as the high-risk factors of serious diseases to develop health intervention regimens. Also, critical values are the early symptoms of various types of cancer and the most direct reflection of the non-infectious chronic diseases (NCDs). Our results identified 10 critical values over.6% in 33,639 participants, that is, obesity (6.4%), thyroid_US (1.69%), hypertension (1.54%), ECG (0.95%), lung_CT and X (0.83%), tumor_T (0.81%), liver_T (0.74%), TCT and HPV (0.67%), breast_US and MG (0.64%), and urine_T (0.61%) for all the participants. The prevalence of many critical values in men was significantly higher than that in women, such as obesity, hypertension, glucose_T, liver_T, kidney_T, lipid_T, urine_T, and head_CT, while blood_T and thyroid_US are the opposite. Furthermore, for different age groups, men under 70 years old have a higher prevalence of obesity and hypertension than that of women, while thyroid_US is the opposite. Interestingly, the prevalence of the total critical values increased to about 25% along with age, which was always higher in men than in women under 60 years old ($P < 0.01$), while the opposite is true for those above 70 years old. According to the new report of cancer epidemiology in China (2015), there were about 3.929 million people who suffered from cancer and 2.338 million people died,

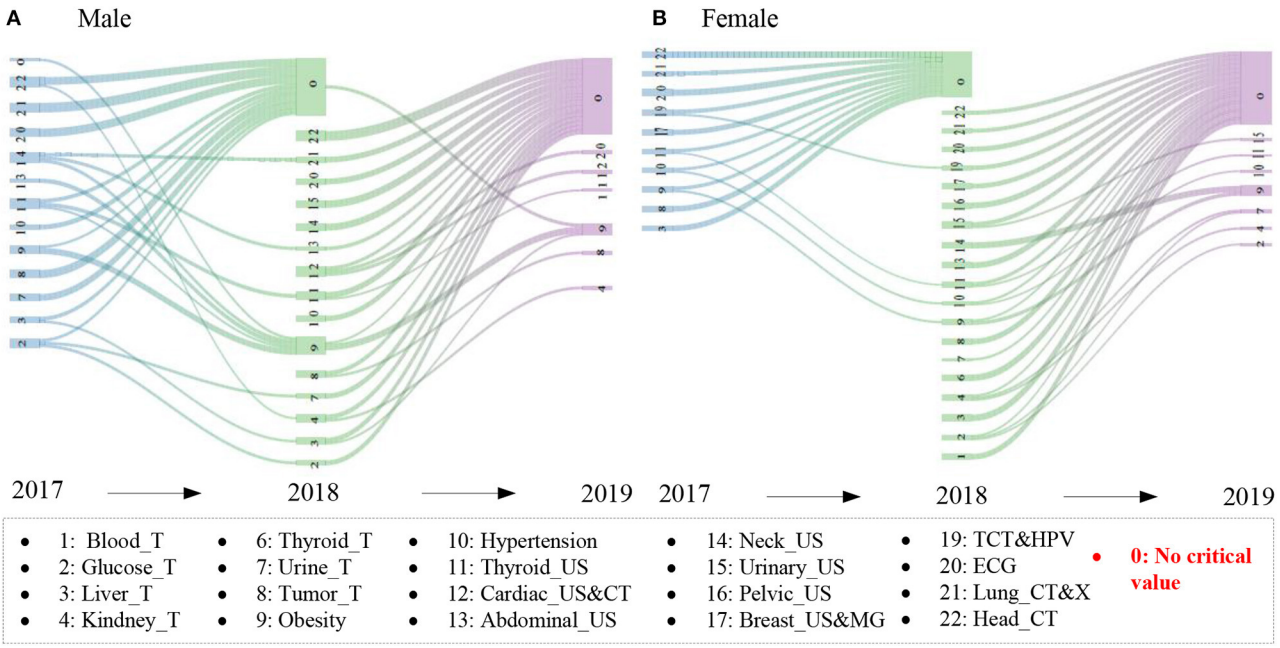


FIGURE 6 | The effective evolution paths for men and women. 2017→ 2018 and 2018→ 2019 denote the same participants with at least one critical value in 2017 and 2018 and 2018 and 2019, respectively. The critical values were shown when the transition probability exceeded 0.2.

and the incidence rate and the mortality rate of cancer continued to rise (19, 20). Also, NCDs, such as cardiovascular disease (CVD), diabetes, cancers, and osteoporosis, are the leading causes of death and health costs. According to the 2020 Report on Chinese Resident's Chronic Disease and Nutrition, NCDs account for 88.5% of the disease burden of China in 2019, more than all other causes combined (21). Thus, according to the relationship between NCDs and critical values, we summarized the incidence, prevalence, and mortality of malignant tumors, some common NCDs, and the corresponding critical values (**Table 8**).

More concretely, lung cancer, upper digestive system tumor, liver cancer, colorectal cancer, and female breast cancer are still the main malignant tumors in China. The incidence and the mortality of lung cancer, stomach cancer, colorectum cancer, liver cancer, and esophagus in men are higher than that of in women, which is consistent with the prevalence of the critical values in **Table 5** (male:female = 16.37:10.93%, $P < 0.01$). Furthermore, from the age distribution, the incidence of malignant tumors increases with age. It is below the level of young people under 40 years old, increases rapidly from 40 years old, mainly concentrates over 60 years old, and reaches the peak in the 80-year-old group (22). Similarly, our results also showed that the prevalence of critical values increased along with age and reached the maximum value above 70 years old, as shown in **Table 6** and **Figure 3**. The incidence of thyroid cancer ranks fourth in women (22.56/100,000) and is significantly higher than that in men (23, 24). Also, our results found that the prevalence of thyroid_US in women (2.28%) was two times as many as that in men (1.25%) with a significant difference in the 0.01 tested levels in **Table 5**. Interestingly, the prevalence of thyroid_US in men was about 100 times more than the incidence of thyroid cancer in women, indicating that 1% of women with a critical value of thyroid_US (mainly TI-RADS 4A) was likely to develop thyroid cancer. Tumor markers are playing an increasingly important role in cancer screening and management, which can be specific for a certain type of cancer or may be present in different types of cancers (25). We found that the prevalence of abnormal tumor markers (810/100,000) was three times as much as the incidence of the total malignant tumors (285.83/100,000), hinting that one-third of abnormal tumor markers was likely to develop into malignant tumors. Thus, the critical values in health checkup could be regarded as an important warning of early malignant tumors (cancers).

In China, about 290 million people have suffered from CVD, and the main forms are hypertension, stroke, and coronary heart disease (26). According to the 2020 edition of the guideline of China for the prevention and treatment of type 2 diabetes, the prevalence of diabetes in China is increasing and now ranks first in the world, from 9.7 in 2010, 10.4 in 2013, and 11.2% in 2017 for people over 18 (27). However, our results showed that the prevalence of critical values is far lower than that of NCDs in **Table 8**, mainly including two reasons. One is the higher standard of critical values in health checkup than chronic diseases, such as hypertension III [SBP $\geq$ 180 (mmHg) or DBP $\geq$ 110 (mmHg)], indicating that the participants have suffered from very serious hypertension, and the blood pressure of many patients with hypertension cannot reach the defined critical value. The other reason is that many patients with chronic diseases have taken antihypertensive, hypoglycemic, and lipid-lowering drugs before

TABLE 8 | The incidence and the mortality of malignant tumors and NCDs with partial critical values.

Top 10 malignant tumors	Incidence (1/100,000)			Mortality (1/100,000)			Critival values in health checkup	Prevalence (1/100,000)		
	All	Male	Female	All	Male	Female		All	Male	Female
Lung	57.26	73.9	39.78	45.87	61.52	29.43	Lung_CT&X	830	880	760
Stomach	29.31	39.95	18.15	21.16	28.59	13.37				
Colorectum	28.2	31.96	24.25	13.61	15.56	11.58				
Liver	26.92	38.98	14.26	23.72	34.31	12.6	Liver_T; Abdominal_US	740; 350	1,020; 360	360; 330
Breast†	45.29		45.29	10.5		10.5	Breast_US&MG	640		640
Esophagus	17.87	25.13	10.25	13.68	19.45	7.62				
Thyroid	14.6		22.56				Thyroid_T; Thyroid_US	60; 1,690	50; 1,250	80; 2,280
Cervix	16.56		16.56			5.04	TCT&HPV; Pelvic_US	670; 300		670; 300
Brain,CNS	7.72	7.04	8.43	4.1	3.1	3.77	Head_CT	320	380	250
Pancreas	6.92	7.67		6.16	4.8	5.41	Abdominal_US	350	360	330
Prostate		10.23			4.36		Urinary_US	210	200	220
Bladder		8.83					Urinary_US	210	200	220
Lymphoma		7.43		3.62	4.38		Lung_CT&X	830	880	760
Uterus			10.28				Pelvic_US	300	10	300
Leukemia				3.96	3.2		Blood_T	220	90	390
Ovary						3.73				
Total	285.83	305.47	265.21	170.05	210.1	128	Tumor_T	810	760	890
NCDs	**Prevalence (1/100,000)**			**Mortality (1/100,000)**			**Critival values in health checkup**	**Prevalence (1/100,000)**		
	All	Male	Female	All	Male	Female		All	Male	Female
Hypertension and cardiovascular disease‡	25,200	26,200	24,100	271.8	296.4	264.4	Hypertension; Cardiac_US&CT; Head_CT	1,540; 90; 320	1,940; 120; 380	1,010; 60; 250
Diabetes‡	11,200						Glucose_T; Urine_T; Kindney_T	260; 610; 240	340; 910; 350	150; 210; 90
Dyslipidemia‡	40,400	47,000	33,500				Lipid_T	50	80	20
Total	23,000			533	611.2	452.6	Total‡‡	14,030	13,770	10,930

†Only for the female; ‡aged 18 and above in China; ♀aged 40 and above in China; ‡‡the total of critical values in health checkup.

the physical examination so that the measurement results cannot reach the defined critical value.

The results of association relation analysis showed that glucose_T and urine_T were the most typical abnormal items with the highest frequency for the male participants in **Table 7** and **Figure 4**. More concretely, glucose_T and urine_T had a strong relation with most of the identified abnormal items, such as liver_T, lipid_T, thyroid_US, tumor_T, kidney_T, and ECG. First, for the abnormal glucose_T, the definition of critical values in health checkup indicated that the participants may have suffered from diabetes mellitus, where the glucose values were >16.7 mmol/L and 13.9 mmol/L with strong positive urine ketone body, or the glycosylated hemoglobin was >15% (28, 29). Diabetes mellitus was one of the most important public health challenges of the 21st century, which could lead to chronic damage, idiopathic pulmonary fibrosis, and dysfunction of various tissues, especially eyes, kidneys, heart, blood vessels, and nerves (30, 31). For the abnormal urine_T, the critical values in health checkup included the abnormal occult blood, pathological cast, transparent tube type, ketone body, glucose, and protein. Similarly, the urine_T is a basic indicator reflecting the health status of the body, which could directly and quickly reflect the situation of the urinary system and kidney metabolism and indirectly reflect some systemic diseases that affect the urine changes, such as diabetes mellitus, blood diseases, and hepatobiliary diseases (32, 33).

Furthermore, we found {hypertension} and {obesity} to be the most pervasive health problems in the Chinese population, since the rules had the highest support [male:{hypertension} $\geq$ {obesity}(rule 7, 19%), female:{hypertension} $\geq$ {obesity} and {obesity} $\geq$ {hypertension} (rules 3 and 5, 13%)]. The result of women participants showed that obesity also coexisted in 60% of the participants if they had suffered from hypertension, while the percentage was up to 71% in men. Also, the result of women participants showed the confidence of {hypertension} $\geq$ {obesity} (rule 3, 60%) was higher than {obesity} $\geq$ {hypertension} (rule 5, 43%), indicating that the emerging percentage of the obesity after hypertension exceeded that of hypertension after

obesity. Thus, our results also indirectly proved the obesity is an important risk factor for hypertension (34). Besides, the results also identified two isolated rules in men, i.e., rule 15 ({abdominal_US} $\geq$ {lung_CT and X}) and rule 16 [(Cardiac_US&CT) $\geq$ (ECG)]. For rule 15, the reason may be that partial critical value of abdominal_US would be also found in the lung_CT and X, since the lower part of the lung is next to the liver, so, after scanning all the lungs by lung-CT, there must be "part" of the liver in the image (35). For rule 16, the abnormal cardiac_US and CT indicated that the participants had a high risk of heart diseases, for instance, coronary heart disease and cardiomyopathy, which are often accompanied by the abnormal ECG (e.g., ST segment elevation and Brugada wave) (36, 37). Hence, the abnormal lung_CT and X had a strong relation with tumor_T (38), possibly along with the abnormal head_CT.

A retrospective dynamic evolution analysis found that the incidence of new critical values was about 10%, the incidence of persistent critical values was about 50%, and most of the effective evolution paths tended to have no critical values for men and women. Also, for some specific critical values, persistence and variability existed. Physical examination aims to screen the early diseases and provide the intervention regimen, while the critical values are the most important. Our results showed that the incidence of new critical values (10%) is about 30 times as much as that of the malignant tumors (285.83/100,000), hinting that 1 in 30 with abnormal critical values was likely to develop malignant tumors. In addition, critical values in health checkup mainly include clinical critical values, major diseases, and their clues, acute, and chronic lesions, and abnormal examination results require timely handling, and the participants possibly adopted some effective ways to intervene in progress of critical value after being informed, such as the changes of healthy lifestyle, surgical treatment, or drug intervention; thus, these participants were not detected by the critical values in the next year (39, 40).

STUDY LIMITATIONS

The present study is the first to analyzes the critical values in health checkup at a large physical examination center in China. The limitations for the present study are the inclusion of a short-term retrospective cohort (only from 2017 to 2019) and the lack of comprehensive follow-up information, making the accurate incidence between critical values in health checkup and a participant cancer outcome unclear. Thus, with the recent trends of perfecting the whole process quality control in health checkup, further research should be conducted to develop personalized intervention regimens, combined with critical values in health checkup in the big data environment.

CONCLUSIONS

Health management becomes more and more important in controlling risk factors, designing prevention regimens, and further improving health quality, whereas critical value management in health checkup is a crucial step. This study conducts a cross-sectional and retrospective survey to analyze the prevalence, association relation, and dynamic evolution of critical values at a large physical examination center in Central China from 2017 to 2019. The findings of this study provide historical data supporting further research to explore health management decision-making at the population level and the prevention and treatment of various types of cancer and NCDs at the individual level.

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 Institutional Review Board of the First Affiliated Hospital of Zhengzhou University (2018-KY-56). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JC and SD designed the experiments. JC and ZW analyzed the data. YL, LW, TL, YD, and QQ provided the data. JC wrote the paper. SD and ZW reviewed and edited the paper. All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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Functional and Cognitive Impairments Increased Risks of Outcomes of Healthcare Utilization in Patients With Stroke Receiving Home and Community-Based Care in Taiwan

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Aim: Stroke is a leading cause of disability; however, little is known about the outcomes of the utilization of long-term care (LTC) recipients in Taiwan. This study aimed to quantify the burdens of disease of stroke survivors receiving LTC by evaluating the outcomes of their utilization including mortality, readmissions, and re-emergency within 1 year after diagnoses of strokes.

Methods: By interlinkages among the national mortality registry, LTC dataset (LTC-CM), and the National Health Insurance Research Dataset (NHIRD), the outcomes and the factors associated with receiving LTC up to 1 year were explored. Patients were aged 50 years and over with an inpatient claim of the first diagnosis of stroke of intracerebral hemorrhage (ICH) and ischemic stroke during 2011–2016. Outcomes of the healthcare utilization include rehospitalization and re-emergency.

Results: There were 15,662 patients with stroke who utilized the LTC services in the dataset among the stroke population in NHIRD. Stroke survivors receiving LTC showed no difference in clinical characteristics and their expected years of life loss (EYLL = 7.4 years) among those encountered in NHIRD. The LTC recipients showed high possibilities to be rehospitalized and resent to emergency service within 1 year after diagnosis. Apart from the comorbidity and stroke severity, both the physical and mental functional disabilities and caregiving resources predicted the outcomes of the utilization.

Conclusions: For stroke survivors, both severe functional impairments and cognitive impairments were found as important factors for healthcare utilizations. These results regarding reserving functional abilities deserve our consideration in making the decision on the ongoing LTC policy reform in the aged society of Taiwan.

Keywords: long-term care, mortality, rehospitalization, re-emergency, stroke survivors

INTRODUCTION

Stroke is a leading cause of disability and morbidity associated with increased economic burden related to acute treatment, poststroke care (PSC), and rehabilitation. Although notable therapeutic advances have contributed to reducing brain damage and disability in patients with stroke (1), many of them are still left with a functional impairment that prevents them from performing basic activities of daily living. Thus, stroke survivors would still face challenges of long-term care (LTC) and continued rehabilitation, which usually result in a tremendous burden.

The Taiwan government launched the LTC 1.0 policy in 2007, which aimed at assisting frail elderly people with LTC needs. The initial objective was to develop a system of home and community-based services (HCBS), including home services, adult day care, home nursing care, home and community-based rehabilitation, home meal delivery, palliative care for caregivers, and transportation services. To facilitate service delivery, the government began to transform the LTC 1.0 into a new reform of the LTC 2.0 policy system in 2016 (2). Under LTC 2.0 policy, more transitional care linking with LTC has been provided, such as planning for home discharge in the hospitals and home healthcare. However, little has been evaluated about the outcomes of the utilization of LTC recipients under the LTC 1.0 policy. By interlinkages among the national mortality registry, LTC dataset (LTC-CM), and the National Health Insurance Research Dataset (NHIRD), this study aimed to quantify the burdens of disease of patients with different subtypes of strokes under LTC by evaluating their mortality and outcomes of the utilization including readmissions and re-emergency within 1 year after the diagnoses of strokes under the National Health Insurance (NHI). The results of these real-world data could provide additional evidence for improving service delivery and reform of the LTC policy 2.0 in Taiwan.

Literature Review

The risk of stroke increases with age, is more common among women, and is a major contributor to long-term disability, especially among the elderly (3). Previous studies in the US indicated that nearly 90% of strokes are ischemic, which are caused by a blockage in the cerebral artery, which restricts blood flow (4). Based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), the incidence of stroke admissions was high among the acute ischemic stroke (AIS) and intracerebral hemorrhage (ICH).

Caring for stroke survivors imposes a substantial economic burden on society (3). The activities of daily living (basic and instrumental) are reliable indicators of the functional status of patients affected by stroke for the initial evaluation (5). An Australian study showed that among 3-month stroke survivors, 74% required assistance with activities of daily living and received informal care from family or friends (6). In the U.S., 75 % of survivors returned home 1 year after index stroke admission (7). In Taiwan, an earlier study showed that about 15.2% were institutionalized after 6 months of stroke (8).

Stroke survivors also suffered from the heavy burden of disease. In the US, stroke is one of the top ten contributors to Medicare costs (4). Taiwan has had a well-established NHI system with over a 99% coverage rate for acute care since 1995. It is estimated that in Taiwan, nearly 75% of those who need LTC are aged 65 years and over (9). Although the recipients of such LTC program must be reassessed every 6 months under the regulations of 1.0 LTC policy, to the best of our knowledge, the outcomes of the utilization have not been systematically evaluated for continued quality assurance, improvement of the care plan, and possible development into an insurance system.

Therefore, from the perspective of LTC, this study explored the profile of stroke survivors who utilized formal HCBS in Taiwan and examined their 1-year outcomes and the predicting factors after index stroke admission and receiving LTC. In this study, we summarized the profile (sociodemographics and functional disabilities) of the LTC recipients with stroke during 2011–2016 among those encountered in NHI of Taiwan, including their life expectancy (LE) and expected years of life loss (EYLL). Then, LTC recipients were enrolled for the analyses of the outcomes related to healthcare utilizations, such as rehospitalization and re-emergency up, to 1 year after index stroke admission and the associated predicting factors. With evidence coming from these real-world data, we hope to add information regarding health outcomes of stroke care in HCBS and hope to be useful to sustain stroke care under the LTC system in Taiwan.

MATERIALS AND METHODS

The study protocol (no: A-ER-106-183) was approved by the Institution Review Board before commencement, and no conflicts of interest exist between the authors and the goals of this study.

Long-Term Care Data Set

The data were obtained from the national LTC-CM in Taiwan. This dataset has been maintained by the LTC center in each county, in which the health and functional indicators of care recipients are recorded in an initial needs assessment and are reassessed by care managers during the follow-up process (10, 11). This study is designed to interlink records of the LTC-CM during 2011–2016 with NHIRD and to explore the outcome of healthcare utilization and the factors associated with receiving HCBS up to 1 year.

Case Selection

The inclusion criteria were patients aged 50 years and over with an inpatient claim of the first diagnosis of stroke defined as follows: confirming principal diagnosis codes for primary or secondary ICD-9 codes of ICH (431.x) and ischemic stroke (433.x and 434.x) from January 2011 to December 2016, in any position by ICD-9-CM and its matched codes in ICD-10 since 2016. The flowchart of the study population is shown in **Figure 1**.

To identify the LTC recipients with diagnoses of strokes mentioned above, cases were further identified by linking the LTC dataset with NHIRD. In total, there were 249,233 cases identified, and among them 15,662 persons received HCBS in the LTC system of Taiwan after discharge from hospitals.

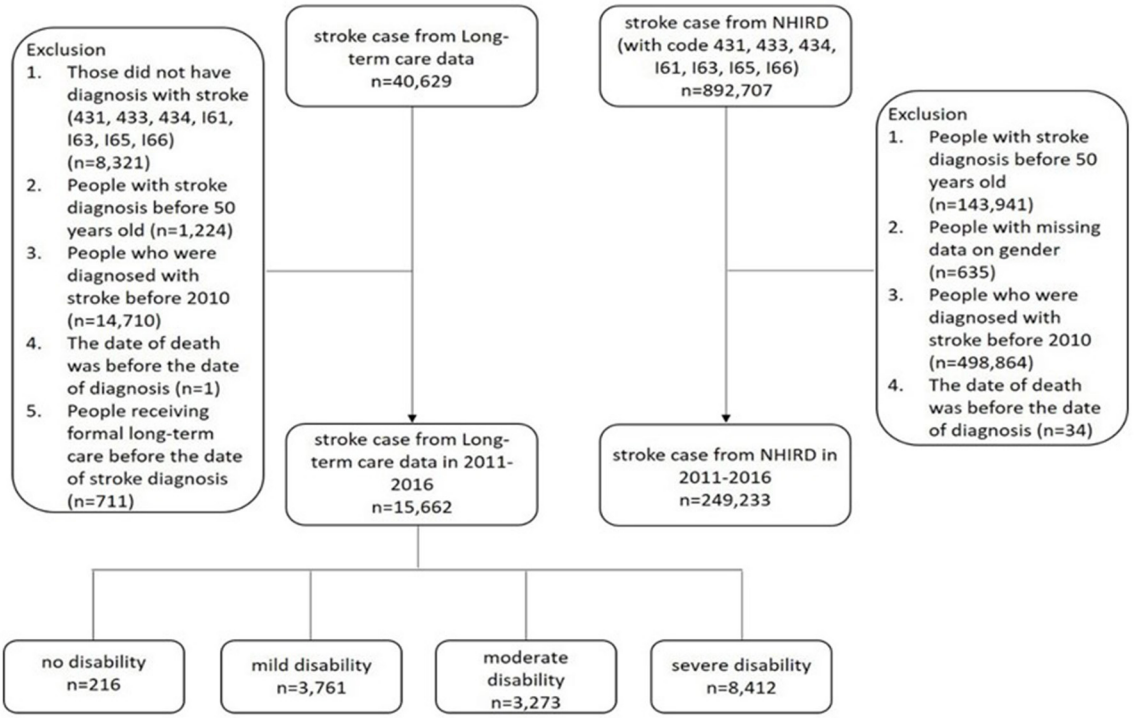

FIGURE 1 | Flow chart of the study samples.

Statistical Analysis

For the analyses of the predictors of healthcare utilizations (rehospitalization and re-emergency) up to 1 year, the negative binomial regression models were constructed and the dependent variables are a count of events by controlling the time periods staying in the HCBS system. The analyses were performed using Statistical Analysis System (SAS) version 9.4.

After verifying the survival status of all cases through cross-referencing with the national mortality registry at the end of the follow-up period (December 31, 2016), the Kaplan-Meier method was used to estimate the survival function based on the 2011–2016 follow-up data. Extrapolation of survival to lifetime for the stroke cohort after the termination of the follow-up period was conducted. Because the LE is the summation of the area under the lifetime survival curve, we would be able to obtain the EYLL by comparing the LEs between the stroke cohort and that of the correspondingly matched referents (12, 13). The approach was mathematically proved valid for predicting the LE under the assumption of constant excess hazard earlier (14–16). Moreover, the software has been updated in the iSQoL 2 with a new algorithm of "rolling over" month by month and only assumes constant hazard within the extrapolated 1 month to accommodate diseases with versatile courses, such as stroke (12).

Measures of Stroke Severity and Comorbidities

In this study, stroke severity index (SSI) and modified Charlson comorbidity index (modified CCI) were used to identify stroke severity and comorbidities. A claims-based SSI is found to be a valid proxy for the National Institutes of Health Stroke Scale (NIHSS) and an effective adjustment for stroke severity in studies of AIS or ICH outcome with administrative claims data (17–19).

The severity of comorbidities was summarized using a modified version of the CCI that excluded cerebrovascular disease and hemiplegia (20). The modified CCI was dichotomized into low comorbidity ($\leq$1) or high comorbidity ($>$1) for analyses.

RESULTS

There were 15,662 patients with stroke who utilized the HCBS after the selection process of patients. The detailed profiles of the LTC recipients with stroke from 2011 to 2016 are summarized in **Table 1**. It showed that the average age of women was higher than men. The ratio of ischemic stroke vs. hemorrhagic stroke was slightly higher than 4:1, and the mean age of those with a higher SSI was younger. More than half (53.1%) of them entered into the LTC system $<$6 months after stroke admission. Approximately 19.1% of the LTC recipients were from mid-low/low-income households, and more than 90% of them were accompanied by caregivers at own home at the first entry to LTC.

In terms of self-care functions, more than half of them (53.7%) were suffering from severe difficulties in activities of daily living (ADLs $<$30). About 63.9% of the LTC recipients showed a score of instrumental activities of daily living (IADL) lower than 8. Based on the thresholds of the Center for Epidemiologic Studies Depression (CESD), 31.8% of them seemed depressive and about

TABLE 1 | The profile (sociodemographics and functional disabilities) of the long-term care (LTC) recipients with stroke from 2011 to 2016.

	N (%)	Age	*p*-value
Age (years)	15,662 (100%)	73.7 ± 9.4	
Gender			
Male	8,702 (55.6%)	72.0 ± 9.7	<0.001
Female	6,960 (44.4%)	75.1 ± 8.6	
Stroke subtype			
Hemorrhagic Stroke	2,921 (18.6%)	69.3 ± 10.3	<0.001
Ischemic Stroke	12,741 (81.4%)	74.3 ± 8.9	
Stroke severity index			
Mild ≤5	5,611 (35.8%)	73.6 ± 8.8	<0.001
Moderate 5–13	4,660 (29.8%)	74.0 ± 9.1	
Severe >13	5,391 (34.4%)	72.5 ± 10.1	
Time to long-term care			
0–6	8,311 (53.1%)	75.5 ± 8.4	<0.001
6–12	2,244 (14.3%)	71.2 ± 10.1	
12–24	2,234 (14.3%)	71.0 ± 10.1	
24+	2,873 (18.3%)	70.8 ± 9.5	
Welfare status			
Non-low-income households	12,673 (80.9%)	74.7 ± 8.7	<0.001
Mid-low/low incomes households	2,989 (19.1%)	67.8 ± 10.2	
Caregivers			
Yes	14,403 (92.0%)	73.4 ± 9.4	0.005
No	1,259 (8.0%)	72.6 ± 9.6	
ADL[†] difficulties			
Severe (score 0–30)	8,412 (53.7%)	75.2 ± 8.9	<0.001
Moderate (score 31–60)	3,273 (20.9%)	72.8 ± 9.4	
Mild (score 61–100)	3,977 (25.4%)	70.7 ± 9.5	
IADL[‡] difficulties			
Severe (score <8)	10,010 (63.9%)	74.3 ± 9.1	<0.001
Mild (score ≥ 8)	5,652 (36.1%)	71.7 ± 9.6	
CESD[§]			
No depressive symptoms	10,684 (68.2%)	72.5 ± 9.4	<0.001
Depressive	4,978 (31.8%)	75.2 ± 9.1	
MDAI[¶] cognition			
Severe impairment	5,446 (34.8%)	75.8 ± 8.9	<0.001
Moderate impairment	2,399 (15.3%)	74.7 ± 8.7	
Mild impairment	1,972 (12.6%)	73.4 ± 9.1	
No impairment	5,848 (37.3%)	70.5 ± 9.4	

[†]*ADL, activity of daily living.*
[‡]*IADL, Instrumental activity of daily living.*
[§]*CESD, Center for Epidemiologic Studies Depression, the thresholds of depressive tendency: male ≥12, female ≥10.*
[¶]*MDAI, multi-dimensional assessment instrument for cognition.*

34.8% of the LTC recipients showed severe cognitive impairment (**Table 1**).

Table 2 shows the clinical characteristics of stroke patients receiving LTC among those encountered in NHI of Taiwan. The mean age of the LTC recipients with stroke was significantly older than their counterparts in NHIRD [73.7 ± 9.4 vs. 70.7 ± 10.6, standardized difference (SD) = 0.3]. Alternatively, all the calculated SDs of comorbidities and severity between patients

TABLE 2 | The prevalence and means of clinical characteristics *at baseline* of patients with stroke receiving LTC among those hospitalized through National Health Insurance (NHI) of Taiwan during 2011–2016.

Clinical characteristic	LTC recipients (*n* = 15,662)	NHI (*n* = 249,233)	SMD
Age (years), Mean (SD)	73.7 ± 9.4	70.7 ± 10.6	0.30*
Sex (Female), *N* (%)	6,960 (44.4)	103,703 (41.6)	0.06
Stroke subtype			
Hemorrhagic, *N* (%)	2,921 (18.6)	43,962 (17.6)	0.03
Ischemic, *N* (%)	12,741 (81.4)	205,271 (82.4)	
Modified CCI[†]			
0 or 1, *N* (%)	9,885 (63.1)	157,050 (63.0)	<0.01
>1, *N* (%)	5,777 (36.9)	92,183 (37.0)	
Hypertension, *N* (%)	12,212 (78.0)	185,410 (74.4)	0.08
Diabetes mellitus, *N* (%)	6,287 (40.1)	94,626 (38.0)	0.04
Hyperlipidemia, *N* (%)	5,300 (33.8)	89,668 (36.0)	0.04
Prior stroke, *N* (%)	3,518 (22.5)	64,392 (25.8)	0.08
Atrial fibrillation, *N* (%)	2,324 (14.8)	28,563 (11.5)	0.10
Coronary heart disease, *N* (%)	1,689 (10.8)	26,952 (10.8)	<0.01
Chronic kidney disease, *N* (%)	1,312 (8.4)	24,393 (9.8)	0.05
SSI[‡] score	10.2 ± 6.2	9.1 ± 6.2	0.18
Hemorrhagic Stroke	15.6 ± 5.2	14.8 ± 5.9	0.14
Ischemic stroke	9.0 ± 5.7	7.9 ± 5.6	0.19
Life expectancy (in year)	6.12 ± 0.12	8.08 ± 0.10	17.74*
Expected years of life loss (in year)	7.38 ± 0.14	7.36 ± 0.10	0.17

[†]*CCI, Charlson comorbidity index.*
[‡]*SSI, stroke severity index.*
[*]*SMD, standardized mean difference is usually considered statistically significant if >0.2.*

with stroke receiving LTC and those encountered in the NHI were below 0.2. For example, the two groups looked similar. Although the LE of those receiving LTC was 1.96 years lower than that of the NHI patients with stroke, there was no difference in their EYLL, or both cohorts lost about 7.4 years of LE. It indicates that the difference of their LE would be from a different age of onset.

Table 3 summarizes the 1-year mortality, rehospitalization, and re-emergency among the LTC recipients. We found that the mortality rate of the LTC cohort seemed to be generally low (8.4%) during the first year. However, the proportion of rehospitalization seemed high. It showed the proportion of about 30.7% within 1 month and 63.2% within 1 year among LTC recipients. The 1-year average times of rehospitalization were also significantly higher than the nationwide cohort (1.69 ± 2.21 vs. 1.02 ± 1.76), especially among those with hemorrhagic stroke. The proportion of re-emergency within 1 month appeared similar between the two cohorts (14.6 vs. 12.8%), the difference increased gradually along time, and the average frequency of re-emergency at the end of 1 year for LTC recipients was significantly higher than that of the nationwide cohort (1.65 ± 2.46 vs. 1.01 ± 2.09).

Table 4 presents the inferential analyses for predictors of rehospitalization and re-emergency up to 1 year among the LTC

TABLE 3 | The mortality and follow-up indices (rehospitalization and re-emergency) of patients with stroke receiving LTC among the National Health Insurance Research Dataset (NHIRD) in Taiwan during 2011–2016.

Characteristic	LTC recipients (n = 15,662) N (%)	NHIRD (n = 249,233) N (%)	p-value	SMD
Age (years)	73.7 ± 9.4	70.7 ± 10.6		0.30*
Mortality				
<1 month	44 (0.3)	21,611 (8.7)	<0.001	0.41*
1–3 months	238 (1.5)	9,976 (4.0)	<0.001	0.15
3–6 months	365 (2.3)	7,290 (2.9)	<0.001	0.04
6–12 months	673 (4.3)	9,833 (4.0)	<0.001	0.02
Total (0–12 months)	1,320 (8.4)	48,710 (19.5)	<0.001	0.02
Re-hosp.				
<1 month	4,795 (30.7)	36,359 (15.9)	<0.001	0.35*
1–3 months	4,812 (30.7)	48,268 (19.4)	<0.001	0.26*
3–6 months	4,413 (28.2)	42,108 (16.9)	<0.001	0.27*
6–12 months	4,897 (31.3)	48,547 (19.5)	<0.001	0.27*
Total (0–12 months)	9,902 (63.2)	110,182 (44.2)	<0.001	0.39*
1-year average	1.69 ± 2.21	1.02 ± 1.76		0.34*
Hemorrhagic Stroke	2.21 ± 2.68	1.19 ± 2.08	<0.001	0.43*
Ischemic stroke	1.58 ± 2.07	0.98 ± 1.68	<0.001	0.32*
Re-ER				
<1 month	2,276 (14.6)	29,040 (12.8)	<0.001	0.05
1–3 months	3,802 (24.3)	39,737 (15.9)	<0.001	0.21*
3–6 months	4,034 (25.8)	40,649 (16.3)	<0.001	0.23*
6–12 months	5,497 (35.1)	54,736 (22.0)	<0.001	0.29*
Total (0–12 months)	9,067 (57.9)	109,145 (43.8)	<0.001	0.28*
1-year average	1.65 ± 2.46	1.01 ± 2.09	<0.001	0.28*
Hemorrhagic Stroke	1.54 ± 2.32	0.80 ± 1.73	<0.001	0.36*
Ischemic stroke	1.67 ± 2.48	1.06 ± 2.16	<0.001	0.26*

Standardized mean difference (SMD) is usually considered statistically significant if >0.2.

recipients with stroke (n = 12,789). Based on the construction of negative binomial regression models, we found that men, high severity, more comorbidity, and those without caregivers were more likely to be readmitted, even after adjustment for multiple functional disabilities. Functional disabilities including ADLs, IADLs, and cognitive impairments were significant predictors for rehospitalization in the follow-up of 1 year. For the re-emergency rates (**Table 4**), the results again showed that functional disabilities including severe dependence on ADLs, CESD, and severe cognitive impairments were significant predictors for re-emergency in the follow-up of 1 year. That is, subjects with severe functional disabilities of self-care, daily activities, cognition, and depression would be more likely to be rehospitalized or sent to the emergency by the end of the follow-up of 1 year.

DISCUSSIONS

Stroke is a major contributor to long-term functional disability, especially among the elderly (3, 21). For stroke survivors, the need for LTC seems inevitable. The study explored the profile of stroke survivors who utilized formal HCBS of Taiwan and followed their utilization outcomes up to 1 year. The influencing factors of utilization outcomes after index stroke admission were also examined.

The LTC policy in Taiwan has been launched by the central government since 2007 aiming at developing the HCBS. For stroke survivors, apart from institutional care, home nursing and home services remained the primary LTC services during the time period of the study. However, among stroke survivors with LTC needs, how many received the help from the HCBS and how were their healthcare utilization outcomes and predictors have not yet been explored and somehow ignored due to the integrating gap between acute care and LTC. Although the post-acute care plan has been launched in a few local hospitals during the follow-up time since 2014, the outcomes of the utilization of stroke survivors receiving the HCBS afterward and the predictors would be important to effort improvement on clinical interventions and the ongoing LTC policymaking. To the best of our knowledge, the outcomes of the utilization of stroke survivors in receiving the HCBS up to 1 year and the predictors were first analyzed in Taiwan.

Previous studies showed that <9% of patients with AIS received long-term home care after hospitalization in the US (21). Our results found that for the patients with ICH and AIS, there was about 6.3% of the stroke survivors who used the HCBS after

TABLE 4 | Estimates of incidence rate ratio (IRR) with 95% CI for risk factors of 1-year outcomes (rehospitalization, re-emergency) among the LTC recipients with stroke based on negative binomial regressions.

Risk factors	Times of Re-hospitalization in 1 year IRR (95% CI)	Times of Re-emergency in 1 year IRR (95% CI)
Age	0.98 (0.98, 0.98)***	1.01 (1.00, 1.01)***
Female (vs. Male)	0.81 (0.78, 0.81)***	0.85 (0.81, 0.89)***
Mid/low vs. non-low incomes	0.92 (0.87, 0.97)**	1.00 (0.94, 1.06)
No Caregivers (vs. with caregivers)	1.14 (1.06, 1.24)***	1.16 (1.06, 1.26)***
Hemorrhagic Stroke (vs. Ischemic Stroke)	1.01 (0.96, 1.07)	0.95 (0.89, 1.01)
Charlson comorbidity index	1.05 (1.04, 1.07)***	1.09 (1.08, 1.11)***
Stroke severity index	1.03 (1.03, 1.03)***	1.00 (0.99, 1.00)
Functional disability		
ADL† severe (vs. ADL† mild)	1.54 (1.45, 1.65)***	1.47 (1.36, 1.57)***
ADL† moderate (vs. ADL† mild)	1.24 (1.16, 1.32)***	1.07 (0.99, 1.15)
IADL severe (vs. IADL‡ mild)	1.05 (1.00, 1.10)*	1.05 (0.99, 1.10)
CESD§ depression (vs. no depression)	1.02 (0.97, 1.08)	1.08 (1.02, 1.14)**
Cognition impairment mild (vs. no imp.)	0.98 (0.92, 1.05)	1.05 (0.98, 1.13)
Cognition impairment moderate (vs. no. imp.)	1.02 (0.96, 1.09)	1.07 (0.99, 1.15)
Cognition impairment severe (vs. no imp.)	1.12 (1.05, 1.20)***	1.19 (1.11, 1.28)***

†*ADL, activity of daily living.*
‡*IADL, Instrumental activity of daily living.*
§*CESD, Center for Epidemiologic Studies Depression, the thresholds of depressive tendency: male ≥12, female ≥10.*
*$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.*

index stroke admission during the study period. The utilization rate could be influenced by many contextual factors in various countries. In Taiwan, the development of LTC infrastructure and lack of workforce may cause the low utilization rates during the study period. Some other factors from the demand side may be also influential, such as in Taiwan, preference of families of hiring foreign care workers at own homes to support informal caregiving instead of using formal HCBS subsidized by the central government (10, 22).

In general, we found no difference between stroke survivors at baseline among who utilized LTC or not after index stroke admission in NHIRD. Regarding LE and EYLL, the LTC recipients were found to be those with shorter LE that may be partly explained by their higher mean age. However, there were no differences in EYLL between the two groups in long term.

For the mortality rates, the result showed that the LTC recipients were those stroke survivors with lower percentages of mortality, especially within 1 month of occurring stroke. The mortality rates among the LTC recipients had increased gradually after index stroke admission, however, showing no statistical difference with their counterparts nationwide after 1 month. Therefore, it seems not surprised that those who utilized LTC or not showed no influence in terms of EYLL and mortality.

Regarding the utilizations, all-cause readmission rates and re-emergency rates within 1 year of utilizations of HCBS had been focused on and analyzed in this study. The higher rehospitalization and re-emergency rates and the 1-year average of utilizations among the LTC recipients were, however, significantly higher than their counterparts nationwide. A previous study on poststroke in Singapore showed that the highest utilization occurred in the first quarter poststroke across all service types and decreased with time since stroke (23). This study found that the percentage of rehospitalization and re-emergency among patients with stroke has increased within 1-year follow-up. If the results mean worse outcomes or because of higher accessibilities of healthcare utilizations after receiving HCBS was not examined in this study and needs to be further addressed. However, these results deserve our notice and consideration in making the decision on national health and LTC policy, especially on prevention.

Few studies have systematically evaluated predictors of readmission after stroke, a measure of inpatient quality of care (24). The previous study indicated that the use of care after hospitalization for AIS was greatest for individuals with more severe strokes, lower functioning at hospital discharge, older age, unmarried, and black in the US (21). This study has shown some key predictors for outcomes of the utilization up to 1 year after index stroke admission. For the rehospitalization, apart from the sociodemographic factors of the LTC recipients, the modified CCI and SSI predicted the utilization. For the re-emergency, the result showed that hemorrhagic stroke has less incidence rate ratio (IRR) than ischemic stroke for re-emergency in the study. The findings also showed the consistency that the modified CCI was a significant predictor for subsequent rehospitalization and re-emergency within 1-year follow-up.

Moreover, the levels on functional disabilities including both physical (ADLs and IADLs) and mental (CESD and cognition status) were found to be key predictors in the outcomes of the utilization (rehospitalization and re-emergency). The study indicated that functional impairment is associated with increased risk of 30-day, all-cause hospital readmission in Medicare seniors, especially those admitted for heart failure, myocardial infarction, or pneumonia (25). Our study found that the influence exists after the follow-up up to 1 year after index stroke admission. Both the physical and the mental functional impairments were influential for the rehospitalization and re-emergency, especially for those in severe conditions. For senior stroke survivors in Taiwan, functional impairment and severe cognitive impairment were found as important factors in preventing readmissions, and severe functional impairment, depression, and severe cognitive impairment were found as important factors in preventing re-emergency.

Our results reflect the notion proposed by the WHO that the composite of all the physical and mental capacities of an individual at any point in time, or intrinsic capacity, is important. Both the health and social care services should be targeted toward preventing and managing declines in intrinsic capacity and improving functional ability in the elderly (26, 27). For

example, LTC would be a means to ensure and facilitate the elderly with a significant loss of capacity for healthy aging through reengineering and reconstructing their functional ability and intrinsic capacity.

As part of the learning process, this study examined the outcomes of services of patients with stroke receiving the HCBS and hoped to be useful to facilitate the policy to provide closer continuity of LTC services with quality.

Limitations

Some limitations in the study need to be addressed. First, to narrow down stroke survivors, only patients with ICH and AIS with admission index from NHIRD with or without LTC use were identified in the study by linking the LTC dataset. Patients with stroke who were not hospitalized or treated at outpatient clinics were not included in the study. Because patients with a definite diagnosis of stroke can be waived from copayment for the first month in the NHI system of Taiwan, our collection would include almost all patients with stroke except those with minimal transient ischemic attack and would be relatively representative. Second, only the LTC dataset was available with information of functional disabilities of patients and no such data collected in NHIRD. Thus, our regression models could only present those ever-received services from LTC. Finally, we chose to follow up on 1-year outcomes of the healthcare utilization in the study instead of a lifelong perspective. Future studies of a more comprehensive evaluation of outcome, including long-term survival and dynamic changes of functional disabilities, would be warranted to assess the cost-effectiveness of such services.

CONCLUSIONS

In Taiwan, stroke survivors receiving HCBS showed no difference in clinical characteristics from NHIRD nationwide. For them, in addition to the risk factors of comorbidity and stroke severity, both severe functional impairments and cognitive impairments were found as important factors for healthcare utilizations including readmissions and re-emergency. These results regarding reserving functional abilities among stroke survivors were reckoned to be useful information for the ongoing LTC policy reform and the burden of disease for the aged society in Taiwan.

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 Institution Review Board (No: A-ER-106-183). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

L-FL: study design, resource gathering, study implementation, and writing up of the manuscript. W-MW: data cleaning and statistical analyses. J-DW: consultation of the research method and resource gathering. All authors contributed to the article and approved the submitted version.

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Chronic Diseases and Labor Force Participation Among Presenile and Senile Chinese

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Background: The incidence of chronic diseases has increased dramatically due to rapid aging and lifestyle changes of China in recent decades. The population aged more than 45 years is an important participant in the labor force market, and the health status directly affects their labor force participation decision. This study aims to explore the relationship between chronic diseases and the labor force participation among the elderly Chinese population aged more than 45 years.

Method: We employ a multivariate probit (MVP) model to construct five structural equations for an analysis. The advantage of this model is that it can deal with the endogeneity of chronic diseases.

Results: Firstly, compared with the elderly, younger people are more likely to participate in the labor force market; the influence of chronic diseases is the largest for presenile women in the decision-making of labor force participation; the impact of psychological problems on labor force participation cannot be ignored, especially for men aged more than 45 years. In addition, sociodemographic factors such as geographical location and marital status also have direct effects on the probability of labor force participation while the impact of both family wealth and family number is much smaller. Finally, unhealthy lifestyles through chronic diseases have negative and indirect marginal effects on labor force participation.

Conclusions: This article proves that chronic diseases have a negative impact on the labor force participation for Chinese aged more than 45 years. The public should give more tolerance and opportunities to these groups. The population aged more than 45 years are more vulnerable and face more psychological problems, which will lead to a decline in labor force participation. Psychological health counseling and services are urgently needed. As the urban areas enjoy more social welfare, Chinese welfare policy needs to be tilted toward the rural elderly. For individuals, maintaining healthy lifestyles can help you stay away from chronic diseases and stay in the labor force market.

Keywords: chronic diseases, labor force participation, mental problem, multivariate probit model, presenile and senile chinese

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INTRODUCTION

The global aging problem has become increasingly prominent, and the growth rate of the aging population of China ranks first in the world. In 2020, the population aged more than 40 years accounted for ∼17.8% of the total population in China. It is expected that a quarter of the population will be more than 60 years old by 2,035 (WHO). The aging of population has led to the changes in disease patterns dominated by chronic diseases, which put tremendous pressure on the society and the economy (1). Chronic diseases have been described as a non-negligible problem accompanying the aging society. According to the Global Cancer Research Center, the number of chronic diseases in the global elderly population will boost from 12.7 million in 2008 to 21.5 million in 2030 (2). The epidemic of chronic diseases will provoke long-term and huge problems such as labor shortage, increasing dependency ratio, and crisis of social security system.

The relaxation of the one-child policy indicates that the demographic structure of China is unbalanced and skewing toward the elderly. Meanwhile, the prevalence of chronic diseases in the presenile and senile population poses a huge health challenge to the health targets of Millennium Development Goals. Under the current national conditions of China, presenile and senile workers occupy a vital position in the labor force market. However, the reality is that the labor force participation of these groups is quite low. The key reason lies on the ill-health and subhealth conditions caused by chronic diseases.

Chronic diseases will lead to subhealthy status, thereby affecting the labor force participation of an individuals. The relationship between chronic health conditions and the work status stems from the theoretical concepts of human resources and health production model, and health can be treated as an endowment of human capital (3). Poor health has a negative impact on labor force participation. Bloom et al. (4) summarized how health affects the economy: people with good health take a longer time to work and are more productive, healthy people have a longer life expectancy, so they have more motivation to invest in human capital that will also provide more investment to the economy. However, it is difficult for the elderly with chronic diseases to continue a remunerated work, and they tend to exit the labor force market earlier. On the other hand, when older people have no sources of income, they need the support from the labor population that will become a huge burden for social welfare (5).

However, there is no systematic research on the relationship between the health status and the labor force participation in China. Current literature studies mainly focus on developed labor markets such as Australia with adequate welfare and pension systems while there is a general lack of research on developing countries especially China, which is facing severe aging problem. In addition, traditional empirical studies of health status often use self-assessed health indicators, which will lead to an unobservable deviation and inaccuracy (6). Another problem is that current literature studies on health human capital focus on physical health rather than psychological health (7). There are no profound studies about the mental health impact on labor force participation (8, 9). Nevertheless, in a stressful contemporary society, mental problems such as presenile depression are emerging constantly. Measuring the impact of mental problems is obligatory (10). In this article, psychological problems are included in the research scope as a kind of chronic disease, which can enrich the existing human capital theory to a certain extent. Furthermore, it is necessary to analyze the joint pathology of chronic diseases. Most scholars only pay attention to the impact of certain health conditions or specific chronic diseases on labor force participation (11, 12). A few studies on the impact of multiple chronic diseases and comorbidity are limited. However, different chronic diseases may interact with each other, they will have a direct impact on labor force participation and an indirect impact through other chronic diseases (13). For example, as a diabetic complication, the prevalence of cardiovascular diseases in patients with diabetes is very high, about 72.2% in our data. As a consequence, we select the four representative chronic diseases with a high incidence among presenile and senile Chinese residents as our research objects, and estimate their unique and mutual influence on labor force participation using the multivariate probit (MVP) model (14). The four kinds of chronic diseases include cardiovascular diseases, diabetes, mental problems, and other chronic diseases such as cancer, asthma, and digestive diseases. The exogenous MVP model is a generalization of the probit model and is used to jointly estimate multiple correlated binary outcomes (15).

This article contains four main sections. section Materials and Methods introduces the method—MVP model, section Results presents the model results including various probabilities, treatment effects, and marginal effects, and section Discussion and Conclusion.

MATERIALS AND METHODS

MVP Model

Chronic diseases possessing the characteristics of comorbidity, different chronic diseases may have similar influencing factors, and a separate analysis of each chronic disease cannot reflect the real impact on labor force participation. To solve this problem, our article chooses the MVP model to evaluate the impact of the four chronic diseases on the labor force participation of presenile and senile Chinese residents. The MVP model is suitable for analyzing both observable and unobservable effects on the labor force participation and the morbidity of chronic diseases. This model can identify the key factors affecting labor force participation and presume chronic diseases as endogenous (16). Most studies in this field suggest that chronic diseases are endogenous, but scholars do not have a perfect method to measure endogeneity, our model builds five simultaneous equations and chooses lifestyles and personal characteristics to control the endogeneity of chronic diseases. The MVP model is based on the multivariate normal distribution and is recommended when the relevant alternatives are independent of each other. This model is suitable for studying the impact of chronic diseases, which are closely related and tend to be affected by the same factors (17).

The impact of chronic diseases on labor force participation is indirectly replicated through human capital, where health is regarded as a form of human capital. The mechanism is that

non-communication diseases affect the health of an individual, and the health status affects the labor supply. If the expected utility is >0, the individual chooses to participate in the labor market (18). We define a binary variable to model the outcome: $L = 1$ in case of participation in the labor force, and 0 in case of no participation. In addition, we set $Ch = 1$ if an individual suffers from a certain kind of chronic disease h and 0 if not. Individual choice is affected by the two ways: the observable factors and the unobservable factors of personal preference (19). The choice function can be described as follows:

$$Y = \left\{ \begin{array}{l} 1 \text{ if } Y^* > 0 \\ 0 \text{ if } Y^* \leq 0 \end{array} \right\} \quad (1)$$

The multiple-choice probability of an individual i in the MVP model can be described as:

$$\begin{aligned} \Pr ob(y_{i1} &= 1, y_{i2} = 1, y_{i3} = 1, y_{i4} = 1, y_{i5} = 1 \left| x_{ij}, \rho \right.) \\ &= \Pr ob(y_{i1}^* > 0, y_{i2}^* > 0, y_{i3}^* > 0, y_{i4}^* > 0, y_{i5}^* > 0 \left| x_{ij}, \rho \right.) \end{aligned} \quad (2)$$

The discrete stochastic model is presented as the following equations

$$\begin{aligned} L^* &= x_L' \beta_L + \gamma_H c_H + \gamma_D c_D + \gamma_M c_M + \gamma_O c_O + \varepsilon_L \\ c_H^* &= x_H' \beta_H + \varepsilon_H \\ c_D^* &= x_D' \beta_D + \varepsilon_D \\ c_M^* &= x_M' \beta_M + \varepsilon_M \\ c_O^* &= x_O' \beta_O + \varepsilon_O \end{aligned} \quad (3)$$

where the stochastic error terms ε_i follow the multivariate normal distribution with mean 0 and variance Σ, that is $(\varepsilon_L, \varepsilon_H, \varepsilon_D, \varepsilon_M, \varepsilon_O) \sim \text{MVN}[0, \Sigma]$.

This article studies the impact of chronic diseases on the decision-making of presenile and senile Chinese about whether to participate in the labor force market. The MVP model in this article contains five seemingly unrelated equations. The multivariate normal cdf and conditional probabilities can be described as Equations (4) and (5), respectively.

$$\begin{aligned} \Pr\ ob\,(X_1 < x_1, X_2 < x_2, X_3 < x_3, X_4 < x_4, X_5 < x_5) &= \int_{-\infty}^{x_5} \int_{-\infty}^{x_4} \int_{-\infty}^{x_3} \int_{-\infty}^{x_2} \int_{-\infty}^{x_1} \phi_5\,(Z_5, Z_4, Z_3, Z_2, Z_1, \rho)\, dz_1 dz_2 dz_3 dz_4 dz_5 \\ &= \Pr\ ob\left(X_1 = 1, X_2 = h, X_3 = d, X_4 = m, X_5 = 0\right) \end{aligned} \quad (4)$$

$$\Pr\ ob\left(X_1 = 1 | X_2 = h, X_3 = d, X_4 = m, X_5 = 0\right) = \frac{\Pr\ ob\left(X_1 = 1, X_2 = h, X_3 = d, X_4 = m, X_5 = 0\right)}{\Pr\ ob\left(X_2 = h, X_3 = d, X_4 = m, X_5 = 0\right)} \quad (5)$$

The joint probabilities of the observed events [L, C_H, C_D, C_M, C_O] that form the basis of the log-likelihood function are the five-variate normal probabilities, and the log-likelihood equation is defined as:

$$\begin{aligned} L_i &= \Phi_5\left(q_{iL} x'_{iL} \beta_L, q_{iH} x'_{iH} \beta_H, q_{iD} x'_{iD} \beta_D, q_{iM} x'_{iM} \beta_M, q_{i0} x'_{i0} \beta_0, R^*\right) \\ &\text{where} \\ q_{im} &= 2 y_{im} - 1 \\ R_{jm}^* &= q_{ij} q_{im} \rho_{jm} \\ \text{m} &\in (\text{L,H,D,M,O}) \\ \text{q}_{ij} &= 1 \text{ if } \text{y}_{ij=1} \text{ and } -1 \text{ if } \text{y}_{ij} = 0 \text{ for j} = 1, 2, 3, 4, 5 \end{aligned} \quad (6)$$

In addition, we also calculate the treatment effects of having certain chronic diseases on labor force participation, it can be described as the difference between the conditional probabilities of labor force participation with and without that kind of chronic disease.

Data and Sample

Our sample comes from the China Health and Retirement Longitudinal Study (CHARLS 2015) funded by the World Bank, Peking University, and the National Institute of Aging in China. The study uses a longitudinal questionnaire and collected the individual and household information of representative samples of Chinese residents aged more than 45 years. Recent CHARLS data were conducted in 28 provinces, 150 districts, and 450 villages across the country. It is the most reliable national source of information on aging, health conditions, and work status (4). For the purpose of comparison, the incidence of chronic diseases of residents aged more than 60 years is 55.1% in our sample, it is very close to the estimation of 51.2% in the Chinese Health Statistics Yearbook (CHSY).

We select the three waves from the CHARLS data set to conduct our analysis: (1) demographic background wave, (2) health status and functioning wave, and (3) healthcare and insurance wave. The sample in this article involves over 11,300 Chinese individuals aged more than 45 years (20). In this article, we define "presenile" as people aged more than 45 years and before retirement, "senile" as those who have retired. Based on this, we further define women between 45 and 55 years as the "presenile women" group, women more than 55 years as the "senile-women" group, and men between 45 and 60 years as the "presenile men" group, and men more than 60 years as the "senile men" group. After data cleansing, our sample includes the four groups of cross-sectional data.

The binary variable of the labor force participation derives from the "working status" of respondents. Our clarification of chronic diseases is based on the two questions of the CHARLS questionnaire—"Have you been diagnosed with the following chronic disease by a doctor (DA007)" and "Do you know if you have certain kind of chronic disease (DA008)." There are 14 kinds of chronic diseases included in the questionnaire. We define cardiovascular diseases as "hypertension; dyslipidemia; heart attack, coronary heart disease, angina, congestive heart failure, or other heart problems; stroke"; diabetes as "diabetes or high blood sugar"; mental problems as "emotional, nervous, or psychiatric problems"; other diseases include "cancer or malignant tumor; chronic lung diseases; liver disease; kidney; stomach; or other digestive disease; memory-related disease; and arthritis or rheumatism; Asthma." The answers to these two questions only include "yes or no," thus we can only know whether the respondent suffers from certain chronic disease or not. It is difficult to classify the level of each chronic disease and is impossible for us to use a dummy variable to define the different

levels of chronic diseases in our analysis. All the definition of the abbreviations used in the model and later empirical analysis are listed in the **Appendix** at the end of the paper.

RESULTS

Probabilities and Correlations

Before estimation, we first present a brief description of the variables used in the analysis. As shown in panel A of **Table 1**, the mean of labor force participation is 0.67 with a positive skewness. Most of the respondents are more than 45 years old with an average age of around 60 years; the sample is balanced in terms of gender and region, with little more women than men, and little more rural respondents than the urban ones. Most of the respondents are married, the mean is 0.87 with a negative skewness. The average household total wealth is 0.11 million, and the average number of each household is 3.4. In the sample, only a minority of respondents are highly educated, the mean of middle- and low-level education is 0.31 and 0.11, respectively, indicating that more than half of the sample respondents have no educational background. Regarding lifestyle variables, the mean of moderate drinking (MIDDRK) is 0.11, and the mean of heavy drinking (HVYDRK) is much lower, indicating that most of the respondents have no drinking habits; the same is true for smoking habits, the mean of current smoking (CURSMK), and historical smoking (BEFSMK) is 0.28 and 0.12, respectively, more than half of the respondents do not smoke. In terms of exercise, about 47% of the sample have high-intensity exercise, 37% have moderate-level exercise, and 7% have low-intensity exercise, and only a small number of respondents do not take exercise.

In panel B of **Table 1**, we give the simple pairwise correlations among labor force participation and the four kinds of chronic diseases. All four chronic diseases have significant negative correlations with labor force participation, the coefficients of two physical diseases are −0.206 and −0.108, and the coefficient of mental problems is smaller but unneglectable. The correlations of various chronic diseases are also significant among which the coefficient of cardiovascular diseases and diabetes is the highest, that is, 0.198, it indicates that a univariate analysis of each chronic disease is inaccurate and the consideration of comorbidity is necessary.

We also give a detailed analysis of the unconditional and some conditional probabilities of each chronic condition, which reflects the intangible heterogeneity of the observations in **Table 2**. From this table, we can see that the conditioning on other kinds of chronic diseases and the probability of certain chronic disease increase significantly. For instance, the unconditional probability of cardiovascular diseases (Ch) is 34.5% while the probability increases to 72.8% conditioning on diabetes. The conditional probabilities of diabetes (Cd) range from 6.2 to 16.9%, all higher than the unconditional probability of 5.7%. The same is true for the probability of mental problems and other chronic diseases. Significant correlations and high conditional probabilities of the four chronic diseases indicate that it is necessary to establish simultaneous equations and estimate the cross-equation error terms. Considering the high comorbidity, we choose a system function to calculate the correlated errors, which make it possible to estimate an unobservable impact after controlling the observable factors (21).

Our concern is to analyze the impact of chronic diseases on the labor force participation of Chinese workers in the context of aging, thus we split our sample into four groups—presenile men (age $\leq$ 60), senile men (age $>$ 60), presenile women (age $\leq$ 55), and senile women (age $>$ 55). In **Table 3**, we list the percentages of labor force participation under different chronic conditions for the four age-gender groups. Consistent with common sense,

TABLE 1 | Summary description.

Variable	Mean	Median	std	Skewness	Kurtosis
A: DESCRIPTION OF CHARACTERISTICS					
Labor	0.67	0	0.47	0.74	1.55
MALE	0.48	0	0.50	0.08	1.01
AGE	59.77	59	10.20	0.57	2.91
URBAN	0.41	0	0.49	0.39	1.15
MARRIED	0.87	1	0.33	−2.23	5.97
TOTWTH	11.31	11.47	1.44	−0.67	4.62
NUMBER	3.40	3	1.74	1.25	5.79
EDUHIG	0.03	0	0.17	5.55	31.85
EDUMID	0.31	0	0.46	0.85	1.72
MIDDRK	0.11	0	0.31	2.54	7.43
HVYDRK	0.07	0	0.26	3.36	12.28
CURSMK	0.28	0	0.45	0.99	1.99
BEFSMK	0.12	0	0.32	2.37	6.62
EXH	0.47	0	0.50	0.11	1.01
EXM	0.37	0	0.48	0.53	1.29
EXL	0.07	0	0.26	3.38	12.42

	Labor	Card	Diab	Mental	Othdis
B: CORRELATION					
Labor	1				
Card	−0.206***	1			
Diab	−0.108***	0.198***	1		
Mental	−0.045***	0.032***	0.013*	1	
Othdis	−0.017**	0.105***	0.022***	0.057***	1

**means significant at the 10% level; **means significant at the 5% level; ***means significant at the 1% level.*

TABLE 2 | Probability of chronic diseases.

	C_h	C_d	C_m	C_o
P(.)	34.5	5.7	2	53.1
P(.|C_h=1)	100	12	2.7	60.2
P(.|C_d=1)	72.8	100	2.8	57.4
P(.|C_m=1)	45.3	7.9	100	72.7
P(.|C_o=1)	39.3	6.2	2.8	100
P(.|C_h=1, C_d=1)	100	100	3.7	59.5
P(.|C_h=1, C_m=1)	100	16.9	100	84.6
P(.|C_d=1, C_m=1)	96.4	100	100	85.7

TABLE 3 | The labor force participation of each chronic disease (%).

	Ch = 1	Ch = 0	Cd = 1	Cd = 0	Cm = 1	Cm = 0	Co = 1	Co = 0
Male	61.03	80.33	55.00	75.10	54.29	74.42	73.55	74.73
Presenile Male (60–)	81.55	90.14	76.21	88.37	57.97	88.27	87.62	88.04
Senile Male (60+)	45.17	65.14	36.32	58.36	50.70	57.13	59.07	54.46
Female	47.88	67.93	39.82	61.88	50.71	60.70	59.99	61.02
Presenile Female (55–)	68.63	79.75	60.45	77.51	64.18	76.92	76.54	76.92
Senile Female (55+)	40.07	58.59	33.09	51.95	44.44	50.72	51.66	48.90

when one gets any chronic disease, the labor force participation rate will drop. For example, the labor force participation of men decreases from 80.33 to 61.03% when getting cardiovascular diseases. In the similar age groups, the labor force participation rate of men is higher than that of women in all age and chronic cases, taking the labor force participation with diabetes as an example, the rate for presenile men is 76.21%, higher than 60.45% of presenile women, the rate for senile men is 36.32%, also higher than 33.09% of senile women. On the other side, in the same gender groups, the labor force participation rate of preseniles is much higher than that of seniles regardless of chronic conditions. Such as the percentage for presenile men with diabetes, the value of 76.21% is more than two times of 36.32%—the percentage for senile men with diabetes.

Coefficients of MVP Model

In this subsection, we carry out the MVP model. Our model contains five independent equations, and the estimated correlation coefficients among the error terms of each equation are presented in **Table 4**. Most correlations between the error terms of the labor equation and chronic disease equations are statistically significant except the cases of labor force participation with diabetes in the presenile men group and with mental problems in the presenile women group. For example, the correlation coefficient between labor force participation and mental problems is significant at 0.58. Considering the significant correlations, a study on the relationship between chronic diseases and labor force participation is necessary for the aging problem of China. In terms of the correlation among the error terms of the four chronic diseases, cardiovascular diseases have a strong positive correlation with diabetes at 1% level, around 0.36 in all the four groups. Diabetes also has significant coefficients with mental problems, which demonstrates the existence of mutual interactions among different chronic diseases. The strong correlations among error terms indicate that the exogenous hypothesis of chronic diseases is not acceptable when studying their impact on labor force participation, and a separate analysis of labor force participation and chronic diseases is not applicable, that is why we choose the MVP model with simultaneous equations.

The advantage of our MVP model is that we treate chronic diseases as endogenous, and we also consider the comorbidity of all chronic diseases by using five structural equations. In **Table 5**, we compare the MVP model with the bivariate probit (BVP) model, which does not consider the comorbidity and the univariate probit (UVP) model taking chronic diseases as exogenous. As presented in **Table 5**, the coefficients of the BVP model are much higher than the MVP model, that is, because of the existence of noise terms when ignoring the interaction of each chronic disease. When using five simultaneous equations and considering comorbidity, the coefficients turn smaller and reflect the real effect of chronic diseases. The coefficients of the UVP model are smaller than those of our MVP model, for example, the UVP coefficient of diabetes of the presenile women group is −0.44, which is smaller than the MVP coefficient of diabetes (−1.13). That is the case when chronic diseases are exogenous, however, the significant correlations in **Tables 1**, **4** indicate that taking chronic diseases as exogenous is unreasonable, thus our MVP model takes into account the endogeneity of chronic diseases.

TABLE 4 | Estimated correlation coefficients of a multivariate probit (MVP) model.

	Presenile men	Presenile women	Senile men	Senile women
ρ_{lh}	0.1**	0.13**	0.35***	0.28***
ρ_{ld}	0.09	0.24**	0.17**	0.25***
ρ_{lm}	0.58***	0.09	0.53***	0.37***
ρ_{lo}	0.25***	0.27***	0.19***	0.11**
ρ_{hd}	0.37***	0.36***	0.35***	0.37***
ρ_{hm}	−0.07	0.05	0.05	0.11**
ρ_{ho}	0.02	0.11*	0.07*	0.04
ρ_{dm}	0.11***	0.16***	0.08***	0.11***
ρ_{do}	0.02	0.1***	0.03	0.06**
ρ_{mo}	0.09**	0.14***	0.18***	0.07**

*means significant at the 10% level; **means significant at the 5% level; ***means significant at the 1% level.

TABLE 5 | Estimated coefficients comparation of probit models.

	Presenile Men			Presenile Women		
	MVP	**BVP**	**UVP**	**MVP**	**BVP**	**UVP**
Card	−0.71***	−1.67***	−0.36***	−0.63***	−1.58***	−0.32***
Diab	−0.59**	−1.96***	−0.11**	−1.13***	−1.86***	−0.44**
Mental	−1.66***	−2.44***	−0.96***	−0.04	−2.22***	−0.44***
Othdis	−0.23**	−1.49***	−0.01	−0.06	−1.33***	−0.04
	Senile Men			**Senile Women**		
	MVP	**BVP**	**UVP**	**MVP**	**BVP**	**UVP**
Card	−0.85***	−1.64***	−0.50***	−0.61***	−1.64***	−0.44***
Diab	−0.40**	−1.71***	−0.32**	−0.39**	−2.03***	−0.33***
Mental	−1.08***	−2.35***	−0.18	−0.95***	−2.06***	−0.11
Othdis	−0.33***	−1.36***	−0.14**	−0.11	−1.33***	−0.12***

*means significant at the 10% level; **means significant at the 5% level; ***means significant at the 1% level.

Based on the abovementioned analysis, we have two conjectures: firstly, senile respondents have lower labor force participation than the presenile ones in both gender groups. Secondly, respondents with chronic diseases have lower labor force participation than the ones without chronic diseases. We check these conjectures in **Table 6**, where we present some conditional probabilities and treatment effects of each group. When considering only one chronic disease, consistent with our conjecture, both senile groups have lower labor force participation than presenile counterparts. For example, the labor force probability of presenile women conditioning on mental problems is 42.83%, which is lower than the probability without mental problems (52.43%). However, there are a few exceptions for cardiovascular diseases, the probabilities of labor force participation with cardiovascular diseases are higher compared to the probabilities without that kind of disease for both presenile groups and senile men. It also leads to the higher labor force participation probabilities with more than two chronic diseases including cardiovascular diseases. For example, for the presenile men group, the probability conditioning on cardiovascular diseases is 54.24%, much higher than 42.84%—the probability without cardiovascular diseases, meanwhile, the probability conditioning on cardiovascular diseases and mental problems is 52.94%, also higher than the probability without two kinds of chronic diseases (42.86%). One explanation is that for cardiovascular diseases, to pay for the diseases, respondents have to continue working. But for other diseases, the health conditions are too poor to continue working. This also causes the treatment effects of cardiovascular diseases to be quite different from other diseases, which are positive except for senile women.

As for diabetes, mental problems, and other diseases, the treatment effects are consistent. Among the four age-gender groups, presenile women are most vulnerable in face of chronic diseases when making working decisions, especially in the case of mental problems, the treatment effect of mental problems is −9.6, which is the highest among all the univariate treatment effects. As a comparison, the influence of chronic diseases on presenile men is the smallest among the four groups, indicating that presenile men face a higher burden of raising the family and cannot quit working even when they suffer from chronic diseases. As for the two senile groups, men are more influenced by physical conditions such as diabetes on their labor force participation decision, whereas women are easy to get affected by psychological problems. For instance, the treatment effect of diabetes for men is −4.74, higher than −2.27 of women and the treatment effect of mental problems for women is −4.95, higher than −2.57 of senile men. Furthermore, when suffering from more than one chronic disease, the labor force participation probability of women decreases dramatically compared with the case of only one chronic disease. Taking the presenile women as an example, compared to −7.45 of diabetes, the treatment effect increases to −15.96 when the respondent has both diabetes and mental problems. However, cases are different when it comes to men and cardiovascular diseases, there are two opposite effects of cardiovascular diseases on the labor force participation decision: on one hand, when suffering from cardiovascular diseases, men may reduce working intensity considering their poor-health conditions; on the other hand, as a Chinese tradition, men have a greater pressure of supporting the family, and the cost of cardiovascular diseases is in a long range, the expenses and family burden force men to continue working. We cannot define which side of the effects is more important, thus the treatment effect of cardiovascular diseases is uncertain.

TABLE 6 | Predicted labor force participation probabilities (%).

	Presenile women	Presenile men	Senile women	Senile men
Marginal probabilities				
P (L=1)	52.14	53.17	41.19	43.64
Conditional probabilities				
P(L=1|Ch=0)	45.16	42.84	42.16	40.14
P(L=1|Ch=1)	53.75	54.24	40.28	45.89
P(L=1|Cd=0)	54.00	53.53	42.15	45.49
P(L=1|Cd=1)	46.55	52.02	39.89	40.75
P(L=1|Cm=0)	52.43	53.23	41.51	43.78
P(L=1|Cm=1)	42.83	51.40	36.56	41.22
P(L=1|Co=0)	52.37	53.23	41.32	43.83
P(L=1|Co=1)	38.73	42.72	35.00	25.53
Treatment effects				
P(L=1|Ch=1)–P(L=1|Ch=0)	8.59	11.41	−1.88	5.75
P(L=1|Cd=1)–P(L=1|Cd=0)	−7.45	−1.52	−2.27	−4.74
P(L=1|Cm=1)–P(L=1|Cm=0)	−9.60	−1.83	−4.95	−2.57
P(L=1|Co=1)–P(L=1|Co=0)	−13.64	−10.51	−6.31	−18.29
P(L=1|Cd=1,Cm=1)–P(L=1|Cd=0,Cm=0)	−15.96	−2.30	−6.04	−4.97
P(L=1|Ch=1,Cm=1)–P(L=1|Ch=0,Cm=0)	−0.36	10.08	−7.14	3.89
P(L=1|Ch=1,Cd=1,Cm=1)–P(L=1|Ch=0,Cd=0,Cm=0)	−6.81	9.86	−8.71	1.15
P(L=1|Ch=1,Cd=1,Cm=1,Co=1)–P(L=1|Ch=0,Cd=0,Cm=0,Co=0)	−15.38	4.10	−14.50	−13.05

Marginal Effects of Exogenous Variables

In addition to the MVP coefficients and probabilities of conditioning on chronic diseases, we also calculate the marginal effects of all explanatory variables on the univariate probability of labor force participation. To analyze the exact impact of each exogenous variable, we divide it into two parts: direct marginal effects on the probability of labor force participation and indirect marginal effects through four chronic diseases. The socioeconomic variables, such as marital status and education conditions, have both direct and indirect effects on the probability of labor force participation, and the lifestyle variables, such as smoking, drinking habits, and exercise, only have indirect marginal effects *via* chronic diseases.

Tables 7A,B present the direct and indirect marginal effects for two presenile and senile groups, respectively. As for the effect of age and for all age-gender groups, the probability of labor force participation decreases with age. For example, taking men aged between 55 and 60 years as a reference, men aged between 50 and 54 years are 3.6% and more likely to join the labor force market, and men aged between 45 and 49 years are 4.9% and

TABLE 7A | Marginal effects on the labor force participation of presenile groups.

	Direct	Indirect				Total
		Card	Diab	Mental	Othdis	
Male						
AGE44	0.0824	−0.0107	0.0175	−0.0044	0.0001	0.085
AGE49	0.0411	0.0060	0.0005	−0.0009	0.0020	0.049**
AGE54	0.0362	−0.0003	−0.0004	0.0001	0.0004	0.036**
URBAN	−0.1042	−0.0098	−0.0017	−0.0008	0.0023	−0.114
MARRIED	0.0826	−0.0032	−0.0003	0.0052	0.0000	0.084
TOTWTH	0.0047	−0.0015	−0.0003	0.0009	0.0011	0.005**
NUMBER	−0.0009			0.0000		−0.001**
EDUHIG	−0.0160			0.0213		0.005
EDUMID	−0.0079			0.0003		−0.008**
MIDDRK		−0.0045	−0.0004	−0.0012	0.0010	−0.005**
HVYDRK		−0.0026	0.0001	−0.0011	0.0004	−0.003**
CURSMK		0.0048	0.0007	0.0012	−0.0021	0.005**
BEFSMK		−0.0046	−0.0005	−0.0003	−0.0018	−0.007**
EXH		0.0276	0.0032	0.0076	0.0101	0.049
EXM		0.0117	0.0015	0.0051	0.0038	0.022
EXL		0.0028	−0.0008	0.0051	0.0017	0.009
Female						
AGE44	0.0748	0.0188	0.0147	0.0001	0.0008	0.109**
AGE49	0.0786	0.0073	0.0029	0.0001	0.0005	0.089**
URBAN	−0.1708	−0.0066	−0.0051	−0.0001	0.0007	−0.182**
MARRIED	−0.0120	0.0143	−0.0035	0.0001	0.0004	−0.001**
TOTWTH	−0.0096	0.0026	0.0011	0.0001	0.0005	−0.005**
NUMBER	0.0063			0.0000		0.006**
EDUHIG	0.1245			0.0001		0.125**
EDUMID	−0.0447			0.0000		−0.045**
MIDDRK		−0.0144	0.0077	0.0000	−0.0007	−0.007**
HVYDRK		0.0119	0.0040	−0.0001	0.0005	0.016**
CURSMK		−0.0065	−0.0048	0.0003	0.0003	−0.011**
BEFSMK		−0.0057	−0.0007	−0.0001	−0.0039	−0.01**
EXH		0.0463	0.0164	0.0002	0.0064	0.069**
EXM		0.0258	0.0080	0.0001	0.0038	0.038**
EXL		0.0020	0.0044	0.0001	0.0000	0.007**

**means significant at the 10% level; **means significant at the 5% level; ***means significant at the 1% level.*

TABLE 7B | Marginal effects on the labor force participation of senile groups.

	Direct	Indirect				Total
		Card	Diab	Mental	Othdis	
Male						
AGE64	0.4799	−0.0088	−0.0016	−0.0061	−0.0061	0.457**
AGE69	0.3790	−0.0117	−0.0014	−0.0058	−0.0123	0.348**
AGE74	0.2580	−0.0211	−0.0009	−0.0030	−0.0057	0.227**
URBAN	−0.2778	−0.0378	−0.0056	0.0004	0.0069	−0.314**
MARRIED	0.1490	−0.0067	−0.0025	−0.0002	−0.0061	0.133**
TOTWTH	−0.0225	−0.0069	−0.0006	0.0005	0.0005	−0.029**
NUMBER	−0.0017			0.0006		−0.001**
EDUHIG	−0.3166			0.0068		−0.31**
EDUMID	−0.1168			−0.0010		−0.118**
MIDDRK		0.0042	0.0011	0.0003	0.0039	0.01**
HVYDRK		0.0219	0.0035	0.0012	0.0024	0.029**
CURSMK		0.0218	0.0035	−0.0032	−0.0080	0.014**
BEFSMK		−0.0111	0.0003	−0.0066	−0.0132	−0.031**
EXH		0.0971	0.0053	0.0128	0.0341	0.149**
EXM		0.0530	0.0026	0.0100	0.0155	0.081**
EXL		0.0257	0.0048	0.0084	−0.0020	0.037**
Female						
AGE59	0.5681	0.0068	−0.0062	−0.0064	−0.0035	0.559**
AGE64	0.4905	−0.0032	−0.0101	−0.0069	−0.0050	0.465**
AGE69	0.4078	−0.0164	−0.0078	−0.0039	−0.0050	0.375**
AGE74	0.2283	−0.0121	−0.0088	−0.0044	−0.0030	0.200**
URBAN	−0.2752	−0.0266	−0.0074	0.0017	0.0022	−0.305**
MARRIED	0.1236	−0.0002	−0.0021	0.0013	−0.0006	0.122**
TOTWTH	−0.0326	−0.0027	−0.0005	0.0009	0.0003	−0.035**
NUMBER	0.0055			−0.0003		0.005**
EDUHIG	−0.2559			−0.0071		−0.263*
EDUMID	−0.2212			0.0017		−0.22**
MIDDRK		0.0453	0.0028	−0.0006	−0.0013	0.046**
HVYDRK		0.0081	0.0139	0.0016	−0.0019	0.022**
CURSMK		−0.0027	0.0046	−0.0070	−0.0017	−0.007**
BEFSMK		−0.0208	−0.0040	−0.0100	−0.0089	−0.044**
EXH		0.0701	0.0115	0.0109	0.0111	0.104**
EXM		0.0357	0.0067	0.0092	0.0046	0.056**
EXL		0.0247	0.0038	0.0064	−0.0007	0.034**

**means significant at the 10% level; **means significant at the 5% level; ***means significant at the 1% level.*

more likely to join the labor force market. The positive marginal effect of age mainly comes from the direct effect in the labor equation. The younger the age, the higher the probability of labor force participation.

Geographical location also has a significant effect on the probability of labor force participation. As can be seen for all groups, living in urban areas reduces the probability of labor force participation, and the effect is stronger for seniles. For instance, the probability of labor force participation decreases by 30.5% for senile women who live in urban areas and decreases by 18.2% for presenile women, taking living in the rural as a reference. That is reasonable under the background of Chinese national conditions, the urban areas have relatively a complete welfare and pension system, which will guarantee the basic life of aging population, but in rural areas, one needs to worry about livelihood even when he gets old and has to make money through work. Most of the indirect effects *via* chronic diseases are negative, indicating that in urban areas, people tend to reduce labor force participation when they suffer from chronic diseases. However, the case is different in rural areasas the welfare system is not sound, and aging people have to continue working even when they are suffering from chronic problems. That is also an urgent problem to be solved.

For a marginal effect of marriage conditions and for the two senile groups, the total effects are significantly positive and mainly come from direct effects in the labor equation,

and the negative indirect effects *via* chronic equations offset a part of the positive direct effects. Compared with unmarried respondents, married men (women) have a 13.3% (12.2%) higher probability of labor force participation. As for the presenile groups, marriage has a different effect on labor force participation for men and women. Married men have a 8.4% high probability of participating in the labor force market, but the effect is not significant; married women have a 0.1% low probability of labor force participation, the direct effect is 1.2%, but mostly offset by an indirect effect from cardiovascular diseases. As the old saying goes "Men's work centers around outside, women's work centers around the home," after getting married, women spend more time in taking care of the family and act as a housewife while men continue working to support the family.

As for income-related variables, we tried individual income, household total income, household per capita income, household wealth per capita, and the total household wealth (TOTWTH). The results show that the TOTWTH has a most significant impact on the labor force participation of aging Chinese. There is no doubt that senile respondents with higher household wealth have a low probability of labor force participation, the decrease ranges from 2.9% for men to 3.5% for women. For senile groups, there is a reasonable decline in the probability of labor force participation of women while the probability for men increases. However, the magnitude of both effects is smaller and only 0.5%, indicating that for preseniles, the impact of family wealth is not as important as the selection of other exogenous variables when making a labor force participation decision. Interestingly, the household number has a positive marginal effect for men and a negative marginal effect for women, a reasonable explanation is that women tend to join the labor force market to release the burden when the family number is large. The magnitude of household number is also as small as the total wealth, indicating that a marginal effect of number is not a main concern.

Regarding a marginal effect of education conditions, we divide the education conditions of respondents into three levels: low education (reference), mid-level education (EDUMID), and high education (EDUHIG). The data comes from the question "What is the highest level of education you have attained?" we define the education level as "low" if the answer of a respondent is lower than "elementary school," as "mid-level" if the answer is "middle school, high school or vocational school," as "high" if the answer is "college associate, bachelor, master, or doctoral degree." As shown in the tables, compared with the low-level education, senile groups with middle/high-level education tend to have a low labor force participation, and the probability for men is high. For instance, the labor force participation dropped by 31% for high-educated men. That is the same for mid-educated preseniles, but the magnitude is much small, dropped only by 4.5% for women and 0.8% for men. The most different is high-educated presenile men. The higher the level of education, and the higher the probability of labor force participation. This is identical with the policy of reasonable utilization of talented human resources.

As for the marginal effect of lifestyles, we test the three kinds of lifestyles, which have a significant influence on the incidence of chronic diseases—drinking, smoking, and exercise habits. Lifestyles only show indirect effects through chronic diseases as they are not considered in the labor equation. For drinking habit, the alcohol in the CHARLS questionnaire include spirits, beer, and wine, and we clarify drinking levels using the international standard drink. Based on the questionnaire, we define the drinking level as MIDDRK if the weekly standard drink is <7 or the daily standard drink is <3; as HVYDRK if the weekly standard drink is more than seven or the daily standard drink more than three. In **Table 7B**, compared with no drinking, moderate, and HVYDRK, both increase the probability of the labor force participation of seniles, which range from 1 to 4.6%, the effects mainly come from indirect effects *via* physical conditions. As for the presenile groups in **Table 7A**, the marginal effects of moderate and HVYDRK for men are negative. The results are consistent with Balsa and French (22) who proposed that intemperance is a thorny problem for presenile men, which can lead to a host of social issues. As for women, MIDDRK will reduce their probability of labor force participation by 0.7%, whereas HVYDRK will increase the probability by 1.6%, they need working to get money for their bad habits and the consequent expenses for chronic diseases (23).

As for smoking habits, our data comes from the two questions "Have you ever chewed tobacco, smoked a pipe, smoked self-rolled cigarettes, or smoked cigarettes/cigars" and "Do you still have the habit or have you totally quit." According to the answers, we clarify smoking to the three levels: no smoking, BEFSMK, and CURSMK. For women, both smoking habits have negative marginal effects on the probability of labor force participation and the effects range from 0.7 to 4.4%, the mechanism is that bad smoking habits lead to the invasion of chronic diseases, which indirectly affect the labor force participation. For men, CURSMK and BEFSMK have the opposite effect. Smoking history has a negative marginal effect on the probability for both presenile and senile men; CURSMK has a positive effect on labor force participation, one explanation is that smoking can be seen as a way to relieve pressure as men may feel stressful in raising the family (24).

For the marginal effects of exercise, we clarify exercise to the three levels based on exercise hours and the question "Do you have any difficulty running/walking about…km"—low-level exercise (EXL), mid-level exercise (EXM), and high-level exercise (EXH) and taking no exercise as a reference. As shown in the table, all exercise levels have a positive effect on the probability of labor force participation, but the effect for presenile men is not significant. The higher the exercise level, the higher the increase of labor force participation probability. Taking presenile men as an example, respondents with EXL have a 0.7% high probability to join the labor force market, the increase improves to 3.8% for the middle-level exercise respondents, and 6.9% for the EXH respondents. Furthermore, the positive exercise effect is more beneficial to senile groups, especially senile men.

DISCUSSION AND CONCLUSION

Our article aims to study the impact of chronic diseases on the labor force participation among presenile and senile Chinese. By comparing the different models, we find that the MVP

model is the most effective one when considering the significant correlations and the endogeneity of chronic diseases (25). We use a system equation method and estimate the five equations, including the labor force participation and four kinds of chronic diseases. Most of our estimated correlations are statistically significant. Our sample is derived from the CHARLS database, and the empirical results include various probabilities, treatment effects, and the marginal effects of exogenous variables on the probability of labor force participation separated by age and gender (presenile men, presenile women, senile men, and senile women). The prevalence of chronic diseases especially among the aging population has profound a negative impact on the labor force participation in China. This article helps to identify the risk factors for labor force participation and to measure the impact level of chronic diseases on labor force participation.

The analysis reveals some useful results. Firstly, in general, when suffering from epidemic chronic diseases, the labor force participation of the population aged more than 45 years shows a downward trend, the impact of chronic diseases on labor force participation is most obvious for presenile women with the treatment effect as high as 15.96 under the conditions of diabetes and mental problems. In addition, living under high pressure nowadays, mental problems have become a prevailing chronic disease affecting the aging Chinese. As can be seen from the MVP-estimated coefficients, the impact of mental problems is much severe than the physical problems especially for men, psychological health consulting and services are in urgent need. Generally speaking, the prevention of chronic diseases is necessary, the government needs to make their people aware of the adverse effects of chronic diseases both on themselves and on the social economy.

Sociodemographic exogenous variables also have direct and indirect effects on the probability of labor force participation. The age bonus of labor force participation disappears as one gets elder. The population in urban areas enjoys more social welfare while the rural elderly is suffering, the developing strategy of Chinese urbanization needs to be adjusted and tilted to rural areas and aging people. Family wealth and family number are not the main concerns when making a labor force participation decision for Chinese aged more than 45 years. Regarding the lifestyles that have direct effects on chronic diseases and indirect effects on labor force participation, we also get some intuitive conclusions—a good way of maintaining a healthy lifestyle for aging people to be immune to chronic diseases and stay in the labor force market.

This article selects the sample of China—a developing country to study the relationship between the labor force participation and four kinds of chronic diseases. It is an important supplement to current literature studies on labor force participation as most studies of this area focus on advanced economies such as Australia. Based on our empirical results, we also give some practical suggestions, which are helpful for the aging problem of China.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: http://charls.pku.edu.cn/.

AUTHOR CONTRIBUTIONS

XQ analyzed questionaire, carried out the experiments, interpreted the results, and prepared the manuscript. BW supervised and reviewed the final version. HG edited the final paper and is in charge of project administration and funding acquisition. All authors read and approved the final manuscript.

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APPENDIX

Acronym	Definition
L/Labor	1 if in labor force, 0 otherwise
Ch/card	1 if having cardiovascular diseases now, 0 otherwise
Cd/diab	1 if having diabetes now, 0 otherwise
Cm/mental	1 if having mental problems, 0 other wise
Co/othdis	1 if having other chronic diseases, 0 otherwise
AGE44	1 if age younger than 45, 0 otherwise
AGE49	1 if age between 45 and 49, 0 otherwise
AGE54	1 if age between 50 and 54, 0 otherwise
AGE59	1 if age between 55 and 60, 0 otherwise(referenced group)
URBAN	1 if in urban area, 0 if in rural area
MARRIED	1 if married, 0 otherwise
TOTWTH	Total wealth of household
NUMBER	Fanily numbers of household
EDUHIG	1 if had high level education, 0 otherwise
EDUMID	1 if had middle level education, 0 otherwise
CURSMK	1 if currently smoking, 0 otherwise
BEFSMK	1 if before smoking, 0 otherwise
MIDDRK	1 if male$\leq$14 per week(4 per day), female$\leq$7 per week(3 per day), 0 otherwise
HVYDRK	1 if heavy level drink, 0 otherwise
EXH	1 if high level exercise, 0 otherwise
EXM	1 if middle level exercise, 0 otherwise
EXL	1 if low level exercise, 0 otherwise

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