Abstract: Few studies in China have focused on direct expenditures for cardiovascular diseases (CVDs), making cost trends for CVDs uncertain. Epidemic modeling and forecasting may be essential for health workers and policy makers to reduce the cost burden of CVDs.

To develop a time series model using Box–Jenkins methodology for a 15-year forecasting of CVD hospitalization costs in Shanghai. Daily visits and medical expenditures for CVD hospitalizations between January 1, 2008 and December 31, 2012 were analyzed. Data from 2012 were used for further analyses, including yearly total health expenditures and expenditures per visit for each disease, as well as per-visit-per-year medical costs of each service for CVD hospitalizations. Time series analyses were performed to determine the long-time trend of total direct medical expenditures for CVDs and specific expenditures for each disease, which were used to forecast expenditures until December 31, 2030.

From 2008 to 2012, there were increased yearly trends for both hospitalizations (from 250,354 to 322,676) and total costs (from US $388.52 to 721.58 million per year in 2014 currency) in Shanghai. Cost per CVD hospitalization in 2012 averaged US $2236.29, with the highest being for chronic rheumatic heart diseases (US $4710.78). Most direct medical costs were spent on medication. By the end of 2030, the average cost per visit per month for all CVDs was estimated to be US $4042.68 (95% CI: US $3795.04–4290.31) for all CVDs, and the total average cost per visit per year for all CVDs was estimated to be US $388.52 to 721.58 million per year in 2014 currency) in Shanghai. Cost per CVD hospitalization in 2012 averaged US $2236.29, with the highest being for chronic rheumatic heart diseases (US $4710.78). Most direct medical costs were spent on medication.

Total health expenditures for CVDs in Shanghai are estimated to be higher in the future. These results should be a valuable future resource for both researchers on the economic effects of CVDs and for policy makers.

INTRODUCTION

Cardiovascular diseases (CVDs) are a group of disorders of the heart and blood vessels, including coronary heart disease (CHD), cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis, and pulmonary embolism. The World Health Organization (WHO) has estimated that CVDs are the most common cause of death worldwide, occurring in men and women with almost equal incidence. An estimated 17.3 million people died from CVDs in 2008, representing 30% of all global deaths.

Cardiovascular and circulatory diseases were estimated to be responsible for almost 400 million disability-adjusted life years (DALYs) in 2010, accounting for 11.8% of global burden. By 2030, almost 25 million people will die from CVDs, which are projected to remain the single leading cause of death. The Global Burden of Disease Study has projected that the DALY loss attributable to CVD between 1990 and 2020 in developing countries would increase 55%, with 67% of the growing annual burden of CVD associated death and disability involving adults <65-years old. In contrast, developed nations will witness a 14.3% reduction in the proportion of DALY loss attributable to CVD during the same period. Thus, the increasing burden of CVD over the next 2 decades would be borne mostly by developing countries.

In China, an estimated 290 million people have CVDs, with 3.5 million people dying annually from these diseases, representing 41% of all deaths. In 2011, 12.89 million patients were hospitalized and discharged for CVDs, while total hospitalization expenditures were over Chinese Yuan (CNY) 40 billion, or an estimated 1.64% of national health expenditures. Optimal allocation of health resources requires an understanding of future costs for CVD health care. Previous projections have focused on disease states such as stroke or CHD, with most of these projections using data from developed countries, such as the USA. Systematic projections of costs for all major categories of CVD are currently unavailable in China, making the trend of costs for CVDs uncertain. The development of epidemic modeling makes possible the forecasting of the economic burden related to CVDs. Time series models have a greater ability to predict and a wider applicability than
nontemporal techniques, and have been used in disease management and expenditure prediction.\textsuperscript{9,10} Other studies used case-control methods and cross-sectional explanatory variables (e.g., age, sex, disease history, and comorbid conditions), and generalized linear models to develop cost prediction equations and estimate the costs of cardiovascular events.\textsuperscript{11} Time series autoregressive integrated moving average (ARIMA) modeling is accomplished in 3 stages. In the identification step, one selects a tentative model for development. The estimation step consists of using a computerized routine to calculate the parameters from the dataset using the chosen model. In the diagnostic step, one uses plots and statistic about the errors in prediction to evaluate the validity of the model. If the results in the diagnostic stage are poor, one then returns to the first step to attempt to find a better model.\textsuperscript{12} In epidemiology, ARIMA models have been successfully used to predict the incidence of infectious diseases\textsuperscript{13,14} and numbers of outpatients and emergency department visits.\textsuperscript{15,16} As well as the exponential smoothing method,\textsuperscript{17} an ARIMA model can also be used to predict average costs of hospitalization\textsuperscript{18} or costs of drug treatment.\textsuperscript{19}

This study was performed to develop a time series model for a 15-year forecast of CVD hospitalization costs in Shanghai. The projections assumed no change in policy but did reflect changing population size overtime. The projections serve as an illustration of what is likely to occur to CVD prevalence and costs if no change to current policy is made and no further action is taken to reduce the health and economic burden of CVDs. These projections provide a useful baseline to gauge the success of current and future CVD policy.

\section*{METHODS}

\subsection*{Study Population}

The study population consisted of the 14 million working individuals who were registered residents living in 9 urban districts (279 square kilometers) of Shanghai who participated in workers’ basic medical insurance; and nonworking individuals including children, students, and unemployed adults who participated in the urban residents’ basic medical insurance and excluded those with new rural cooperative medical insurance. In China, commercial health insurance is supplementary to basic health insurance, and commercial health insurance plan covered only approximately 7.6% of the population,\textsuperscript{20} most of which were also covered with basic health insurance. Residents only covered with commercial insurance were not included in this study.

\subsection*{Data Collections and Measures}

Daily visits and medical expenditures for CVD hospitalizations between January 1, 2008 and December 31, 2012 were obtained from the Shanghai Health Insurance Bureau (SHIB). The SHIB is a government agency that administers the Shanghai Health Insurance System, which provides compulsory universal health insurance covering more than 97% of all registered residents. Of the nonworking group, over 80% were children and students, and other 9% were the residents who were above 70 years of age. All public hospitals, including 1061 public hospitals (767 primary hospitals, 221 secondary hospitals, and 73 tertiary hospitals) in this city are under contract with this system. It is estimated that until the end of 2011, the proportion of private hospitals in Shanghai was about 42.52%, and the beds of private hospitals accounted for approximately 7.20% of all beds.\textsuperscript{21} Since most of the private hospitals were not included in the social health insurance, they were not included in our analysis; computerized records of hospital visits are maintained at each contracted hospital and sent to the SHIB through an internal computer network. The health insurance is monitored and supervised by the Shanghai Medical Insurance Supervision and Inspection Institute.

The numbers of CVD hospitalizations were aggregated by sex and age, as were direct medical expenditures by materials. CVDs were classified by their International Classification of Diseases Revision 10 (ICD 10) codes as acute rheumatic fever (I00-I02), chronic rheumatic heart diseases (I05-I09), hypertensive diseases (I10-I15), ischemic heart diseases (I20-I25), cerebrovascular diseases (I60-I69), and stroke (I64). In this study, medical expenditures were defined as the direct medical costs for treating CVD and any related complications during hospitalization, including diagnostic testing, treatment, prescription drugs, and medical supplies. The costs of treatment and the proportions of the different categories were assumed to remain unchanged between 2008 and 2012.

Patient records were de-identified prior to analysis; only the daily aggregated admissions to each hospital and costs of CVD hospitalizations were calculated and used for analysis. The authors did not access to individual patient information prior to personal privacy protection and data aggregation, and none had any interactions with the patients involved in this study, so personal IDs were not available. Neither ethics review nor informed consent was required for the current analysis. An exemption from ethical review has been approved by the Ethics Committee of School of Public Health, Fudan University. We could only describe the characteristics of the study groups.

\subsection*{Statistical Analysis}

All statistical analyses were performed using IBM SPSS Statistics 20. Categorical variables were presented as numbers and percentages. Descriptive data analyses were performed to explain the demographic and clinical characteristics of the study population, including sex distribution, age group, and type of insurance. Total visits and expenditures per year during the study period were calculated to determine the temporal pattern of CVD hospitalizations. And all the expenditures were transferred to US dollars according to the exchange rate data from the World Bank Database.\textsuperscript{22}

\subsection*{Prevalence-Based Cost Estimation}

Data from 2012 were used to estimate prevalence-based costs, including yearly total health expenditures and expenditures per visit for each disease, as well as per-visit-per-year medical costs of each service for CVD hospitalizations in 2012.

\subsection*{Projections of Direct Medical Costs}

Time series analyses were performed to determine the long-term trend of total direct medical expenditures for CVDs and specific expenditures for each disease. Costs for all CVDs and for each specific disease from 2008 to 2012 were adjusted to the CNY value in 2014, based on the Medical Care Consumer Price Indices data from the National Bureau of Statistics of China\textsuperscript{23} and then transferred to US dollars according to World Bank Official exchange rate. To determine the temporal patterns of total costs and costs by major ICD 10 category, the average hospitalization costs per visit per month were calculated by dividing the monthly costs by the number of visits that month, repeated for each of the 60 months of the study. ARIMA time series models were first used to fit the data according to similar
The data were assorted to detrend the time series and fit with AR and MA terms based on autocorrelation function and partial autocorrelation function plots. Identification of the correct fit for each time series model was based on the results of parameter estimates, and the best model was based on the normalized Bayesian Information Criterions (BIC) value. Since the ARIMA model did not fit the data for ischemic heart diseases, an exponential smoothing model was used as a substitute. The time series models were then used to forecast the average expenditures per month per visit until December 31, 2030, with the total expenditure calculated by multiplying average costs by estimated visits.

In projecting the average costs per visit per month for CVDs, we assumed the same changes in rates of population increase and treatment patterns (medicines and treatment) before and after 2012, thus reflecting the increases in hospitalization visits and direct medical costs. In addition, as there were few adjustments to the basic payment patterns and populations covered by medical insurance from 2008 to 2012, we assumed no change in policy or health insurance coverage over the period to 2030. We multiplied the estimated total hospitalization visits by the costs per visit to estimate the yearly total expenditure, and calculate the total hospitalization visits according to the estimated population size. We assumed that hospitalization rates would remain the same (24.5%) as that determined by the National Health Services Survey of 2008; so, the total hospitalization visits would be determined by the population in Shanghai.

Sensitivity Analysis
Population size and structure can both affect predictions of expenditures for CVDs. Thus, this study included a one-way sensitivity analysis to determine the effects of increased population and of aging of the population. The Shanghai Population and Family Planning Yearbook has estimated that the population of Shanghai will increase steadily over the next decade and then decrease slightly, and another report released by Shanghai Municipal Health and Family Planning Commission predicted the yearly population of Shanghai with 3 schemes. The low scheme presumed that the policy was kept strictly till 2030; the middle scheme presumed that every couple will have 2 children only after 2025; and the high scheme presumed that couples who were the only child in the family could have a second child from 2003 since Shanghai issued a regulation in 2003 which allowed couples who were the only child in the family to have a second child, and after 2010 every couple will have 2 children. The middle scheme was used as the main scenario for estimating the total expenditure, while the other two were used for sensitivity analysis. We also used confidence intervals of the predicted cost per month per visit to estimate the range of total expenditure based on the different scenarios.

RESULTS
General Characteristics of the Study Population
Yearly cumulative hospital admissions and direct medical expenditures from 2008 to 2012 are shown in Figure 1. From 2008 to 2012, there was an increased trend for both hospitalization visits (from 250,354 to 322,676 per year) and total costs (from US $ 388.52 to 721.58 million per year). During this period (1827 days), a total of 1,459,172 hospital admissions for CVDs were recorded in Shanghai, a mean of 798.7 per day (range 76–2041). Admissions varied seasonally, with the peak in spring followed by autumn. A supplement table (see Table S1, Supplemental

FIGURE 1. Yearly cumulative visits and expenditures for patients hospitalized with cardiovascular diseases in Shanghai (2014 US $ million). The line with symbol “X” represents the yearly visits for patients hospitalized, and the black bars represent the yearly total expenditures for total population, while gray bars represent expenditures for employed population and white bars represent expenditures for unemployed population.
Content) was used to report the hospitalization visits of each demographical group of the participants.

Cost Estimation for 2012
Since individual cost data were not available, only total medical expenditures and average costs per year per visit could be determined. Annual medical expenditures and yearly health expenditures per visit for CVD hospitalizations in 2012 are shown in Table 1. Costs per visit for CVD hospitalization in 2012 averaged US $2236.29, with the cost per visit for chronic rheumatic heart disease being highest, US $4710.78. Sex, age, and employment affected expenditure for all CVDs and for each specific disease. Expenditures per visit for all CVDs were higher for males than females, and higher for employed than for unemployed individuals, except for stroke. For most diseases, the major expenditure was for patients aged over 65 years, although expenditures for chronic rheumatic heart diseases were higher in patients aged <45 years than in other age groups. Most direct medical costs were spent on medication (Table 2).

Time Series Analysis of Average Costs for CVDs
A sequence chart of data from 2008 to 2012 showed that hospitalization visits for all CVDs showed an upward trend and seasonal variations. Table 3 shows the models and their performance. The P-values of the Ljung–Box test were all over 0.05, indicating that the residuals from the models had no significant autocorrelation and that these models fit the data. The results of forecasting, including observed, fit and forecast values, and credibility intervals are shown in Figure 2. The costs for all CVDs, chronic rheumatic heart diseases, ischemic heart diseases, and stroke showed increasing trends. By the end of 2030, the average costs per visit per month were estimated to be US $4042.68 (95% CI: US $3795.04–4290.31) for all CVDs, US $7102.17 (95% CI: US $116,143.93–130,348.27) for acute rheumatic fever, US $25,874.4 (95% CI: US $21,759.97–29,988.85) for chronic rheumatic heart diseases, US $4379.28 (95% CI: US $13,777.39–22,535.95) for hypertensive diseases, US $414.71 (95% CI: US $392.36–490.06) for ischemic heart diseases, US $5497.20 (95% CI: US $1929.35–12,923.75) for cerebrovascular diseases, and US $21,236.76 (95% CI: US $7366.53–3506.98) for stroke. Based on the main scenario, the numbers of hospitalizations for CVDs would be 294,145, making the total expenditure US $1.17 billion (95% CI: US $1.09–1.24 billion) in 2030.

Sensitivity Analysis
Based on the low and high scenarios, the numbers of hospitalizations for CVDs would be 282,346 and 297,967, respectively, in 2030, making the total expenditure US $1.12 billion (95% CI: US $1.05–1.19 billion) and 1.18 billion (95% CI: US $1.11–1.26 billion), respectively. The projections of the main scenario and the sensitivity analysis were shown in Figure 3.

We also tried to estimate the impact of aging based on our result of projection. Since the prevalence of CVDs in people aged ≥65 years would be about twice that of people aged <65 years,28 we presumed that the hospitalization rate was correlated with the prevalence and was also twice of the hospitalization rate of people aged <65 years. Still according to the prediction of future population of Shanghai,27 there would be about 2.34 million residents over 65-years old in 2030 based on the main scenario. As the hospitalization rate of the whole population (17.70 million) was 24.5%, we calculated that the hospitalization rate of >65 years group was 43.28%, which was 18.78% more than the whole population. So, we presumed that there would be about 29,820 more hospitalization visits in this age group, which would cause an extra expense of at least US $118.29 million.

DISCUSSION
This study showed that the burden of CVDs is likely to increase in Shanghai over the next 15 years. Both the incidence of CVDs and expenses associated with hospitalization for these diseases were increasing trends. By the end of 2030, the average costs per visit per month were estimated to be US $4042.68 (95% CI: US $3795.04–4290.31) for all CVDs, US $7102.17 (95% CI: US $116,143.93–130,348.27) for acute rheumatic fever, US $25,874.4 (95% CI: US $21,759.97–29,988.85) for chronic rheumatic heart diseases, US $4379.28 (95% CI: US $13,777.39–22,535.95) for hypertensive diseases, US $414.71 (95% CI: US $392.36–490.06) for ischemic heart diseases, US $5497.20 (95% CI: US $1929.35–12,923.75) for cerebrovascular diseases, and US $21,236.76 (95% CI: US $7366.53–3506.98) for stroke. Based on the main scenario, the numbers of hospitalizations for CVDs would be 294,145, making the total expenditure US $1.17 billion (95% CI: US $1.09–1.24 billion) in 2030.

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TABLE 1. Annual Medical Expenditures for Cardiovascular Disease Hospitalizations in Shanghai, 2012 (2014 US Dollar)
diseases increased from 2008 to 2012, constituting 0.16% of national health expenditure in 2012. According to the predictive model, the total health expenditures for CVDs will continue to increase, to over 1.71 billion US $ in 2030, if there are no additional government interventions. About two-thirds of hospitalization expenditures for CVDs in Shanghai City were due to ischemic heart diseases and cerebrovascular diseases.

Most previously published economic studies on CVD have utilized incidence-based cost estimates or specific demographic and clinical characteristics. One study used an exponential curve fitting method to predict average costs and estimated total hospitalization expenditures for cerebrovascular diseases and CHD.30 Since information on individual patients was not available in our study, an ARIMA model was used to predict expenditures for most CVDs. An exponential smoothing method was applied to ischemic heart diseases as the Ljung–Box Q value of the ARIMA model was not statistically significant. The BIC value was also smaller and showed better fitness than the ARIMA model. Although the average costs of hospitalizations for acute rheumatic fever and hypertensive diseases increased from 2008 to 2012, constituting 0.16% of national health expenditure in 2012, an ARIMA model was used to predict average costs and estimated total hospitalization expenditures for CVDs in Shanghai City were due to ischemic heart diseases and cerebrovascular diseases.

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Most costs-of-illness studies regarding CVDs, focusing on the burden of one or several specific diseases, involved developed countries.30–34 The global cost of CVD has been estimated to be US $863 billion in 2010, or an average per capita cost of US $125, with this amount estimated to rise to US $1044 billion in 2030.35 CVDs account for about one quarter of current annual health expenditures in the United States. The American Heart Association has projected that, between 2012 and 2030, national total direct medical costs of CVDs will approximately triple, from $309 to $834 billion.36 Our results, which showed that the hospitalization expenditure would increase from $721.58 million in 2012 to $1.71 billion in 2030, had a similar trend with this estimation.

Although it is sometimes difficult to assess the total burden of CVDs in the developing world because of the scarce epidemiological data,37 there are some studies estimating burden for the developing countries. The economic burden study carried out by the WHO and World Economic Forum indicated that the CVDs-related cumulative lost was projected to be more than US$ 2.52 trillion in upper–middle-income countries over the period 2011 to 2025, while in lower–middle-income countries it would be US$ 1.07 trillion.38 According to Institute of Medicine (US) Committee on Preventing the Global Epidemic of Cardiovascular Disease, estimates ranged from an annual US$ 3 billion in China to US$ 72 billion in Brazil.39 In China, it has been predicted that, in 2020, hospitalization costs per visit for CVDs will increase to CNY 11,992.87 (US $1900.61), with the total expenditure reaching CNY 2.2 trillion (US $348.65 billion),40 which was much lower as compared with our projection. Since our study was conducted in urban Shanghai, which is the most populous area with the highest level of consumption in China, which may partly explains the inconsistence.

There are many researches that focused on the influencing factors of CVD prevalence and expenditure.41,42 Rapid increases in some risk factors (eg, diabetes mellitus and obesity) may result in a greater increase in CVD prevalence and its associated costs. Conversely, most CVDs can be prevented by

| Model | Ljung–Box P | MAE | MAPE |
|-------|-------------|-----|------|
| All cardiovascular diseases | ARIMA (1,0,1) × (1,1,0)_{12} | 0.16 | 33.426 | 1.529 |
| Acute rheumatic fever | ARIMA (1,0,0) × (0,1,1)_{12} | 0.94 | 775.452 | 167.08 |
| Chronic rheumatic heart diseases | ARIMA (0,1,1) × (1,0,1)_{12} | 0.69 | 628.871 | 13.917 |
| Hypertensive diseases | Winters’ Additive | 0.17 | 37.663 | 6.79 |
| Ischemic heart diseases | Winters’ Additive | 0.15 | 39.264 | 6.79 |
| Cerebrovascular diseases | ARIMA (0,1,1) × (1,0,1)_{12} | 0.38 | 35.336 | 3.936 |
| Stroke | ARIMA (2,1,0) × (0,1,1)_{12} | 0.33 | 180.555 | 10.222 |

For the measures of MAE and MAPE, a smaller value indicates better model performance. However, there is no absolute standard to which these values can be compared directly. ARIMA = autoregressive integrated moving average, MAE = mean absolute error, MAPE = mean absolute percentage error.
addressing risk factors such as tobacco use, unhealthy diet and obesity, physical inactivity, high blood pressure, diabetes, and increased lipids. Also, the prevalence as well as expenditures of CVD will increase as a result of the aging of population and continued declines in mortality from CVD, such as in the United States. Developing countries would also enter the phase of delayed degenerative disease soon due to the rapid health transition. For example, it was also reported that there was recent decline in CVDs mortality in South Korea because of the fall in the contribution from hemorrhagic strokes, while thrombotic stroke and CHD burdens have just begun to rise. A study has demonstrated that population ageing was a considerable factor, contributing to more than 20% of the rise in the total hospitalization costs for CVD. In addition to control costs by providing more effective and economic medical treatment therefore, it is also important to provide interventions targeting the prevention of high blood pressure and cholesterol especially and obesity to curb the soaring trend of expenditure of CVD.

This study had several limitations. First, our projections assumed no change in policy over the period, and the economic growth of China till 2030 keeps the same trend with the period 2008 to 2012. Moreover, policy was not considered influential.

FIGURE 2. Forecasted costs for cardiovascular diseases per month per visit (2014 US $). The gray solid lines show observed values, while the black solid lines show fit values (before the reference line) and projected values (after the reference line), and the dotted lines show 95% confidence intervals of the series: (A) all cardiovascular diseases; (B) acute rheumatic fever; (C) chronic rheumatic heart diseases; (D) hypertensive diseases; (E) ischemic heart diseases; (F) cerebrovascular diseases; and (G) stroke.
in the models since the effects of policy changes are hard to quantify. This, however, may not reflect the demographics of an aging population. Another limitation was that the expenditure data were for urban residents who had social health insurance, while the hospitalization visits and expenditures of private hospitals were unavailable, thus possibly introducing a selection bias. However, since the number of private hospitals was very limited in China, the prediction result would still be credible.

Also, the study focused on only one city, Shanghai, one of the most populous and advanced cities in China, thereby possibly affecting the effectiveness of extrapolation. At last, the expenditure would likely be corresponding to the changes of treatment patterns (eg, advance of technology, new medicine, etc.) in a longer period that unfortunately is difficult to be quantified at this stage, which brings an uncertainty for a long-term projection. However, we have checked the newest Chinese Guidelines for Prevention of Cardiovascular Diseases (2011 updated version), the recommended treatment patterns for CVDs did not change substantially, and therefore we assume that hospitalization expenditure would not be influenced significantly by the change of treatment pattern in the next several years.

In conclusion, this study analyzed medical expenditures for several CVDs in Shanghai and found increasing trends in costs of hospitalization, both for employed and unemployed individuals. Moreover, our model predicted that these costs will continue to increase in the following decades. These findings suggest that the burden of CVDs will be higher in the future. People who follow a healthy lifestyle experience a comparably reduced risk of CHD and stroke. Therefore, a greater focus on prevention may alter these future CVD projections. These results should be a valuable future resource to both researchers on economic effects of CVDs and policy makers.

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FIGURE 3. Sensitivity analysis of predicted hospitalization expenditure based on different population scheme (2014 US $ billion). This figure showed the results of sensitivity analysis, which was calculated by multiplying the projected average costs with different population schemes. The line with the symbol “X” represents the annual total hospitalization expenditure of the high population scheme, while the line with the symbol “Δ” represents the expenditure of middle scheme and the line with the symbol “■” represents the expenditure of the low scheme.
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