BMJ Open

Multi-state Markov model application for blood pressure transition among Chinese elderly population

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-059805
Article Type:	Original research
Date Submitted by the Author:	28-Dec-2021

Complete List of Authors:	Zheng, Xujuan; Shenzhen University, Health Science Center Xiong, Juan; Shenzhen University, School of Public Health Zhang, Yiqin ; Xiamen Medical College Affiliated Second Hospital, Nephrology Xu, Liping; Xiamen Medical College Affiliated Second Hospital, Nephrology Zhou, Lina; Xiamen Medical College Affiliated Second Hospital, Nephrology Zhao, Bin; Affiliated Xiangan Hospital of Xiaman University, Department of medical laboratory Wang, Yuxin; Xiamen Medical College Affiliated Second Hospital, Nephrology

Keywords:	Hypertension < CARDIOLOGY, EPIDEMIOLOGY, PUBLIC HEALTH

Title page

• Short informative title

Multi-state Markov model application for blood pressure transition among Chinese elderly population

• Short running title

Multi-state Markov model for blood pressure

• List of all authors

Xujuan **Zheng**[1 $], Juan **Xiong**[1 $], Yiqin **Zhang**[2], Liping **Xu**[2], Lina **Zhou**[2], Bin **Zhao***[3], Yuxin **Wang***[2]

Affiliations

[1] Health Science Centre, Shenzhen University, Shenzhen, China

[2] Dept.Nephrology,the No.2 Affliated Hospital of Xiamen Medical College, Xiamen, China

[3] Department of medical laboratory, Xiang'an Hospital Affiliated to Xiamen University, Xiamen, China

Corresponding author:

* Bin Zhao, Department of medical laboratory, Xiang'an Hospital Affiliated to Xiamen University, Xiangan District, Xiamen, China, 361000.

email: 393603468@qq.com

* Yuxin Wang, Dept.Nephrology,the No.2 Affliated Hospital of Xiamen Medical College, Xiamen, China, 361000.

email: wyx_1000@126.com

Other author footnotes

$Xujuan Zheng and $Juan Xiong made equal contributions to this manuscrip

Additional emails

Xujuan Zheng email: zhengxujuan@szu.edu.cn

Juan Xiong email: jxiong@szu.edu.cn

Yiqin Zhang email: 553098786@qq.com

Liping Xu email: 469722875@qq.com

Lina Zhou email: zhoulina154@126.com

• Acknowledgments

We would like to thank all participants who voluntarily participated in this study.

• Funding Statement

YXW was supported by grants from Fujian Province planning project of science and technology (2019D015). JX was supported by the Medical Science and Technology Research Fund Project of Guangdong Province (grant no. A2020405).

Title page

• Short informative title

Multi-state Markov model application for blood pressure transition among Chinese elderly population

• Short running title

Multi-state Markov model for blood pressure

• List of all authors

Xujuan **Zheng**[1 $], Juan **Xiong**[1 $], Yiqin **Zhang**[2], Liping **Xu**[2], Lina **Zhou**[2], Bin **Zhao***[3], Yuxin **Wang***[2]

Affiliations

[1] Health Science Centre, Shenzhen University, Shenzhen, China

[2] Dept.Nephrology,the No.2 Affliated Hospital of Xiamen Medical College, Xiamen, China

[3] Department of medical laboratory, Xiang'an Hospital Affiliated to Xiamen University, Xiamen, China

Corresponding author:

* Bin Zhao, Department of medical laboratory, Xiang'an Hospital Affiliated to Xiamen University, Xiangan District, Xiamen, China, 361000.

email: 393603468@qq.com

* Yuxin Wang, Dept.Nephrology,the No.2 Affliated Hospital of Xiamen Medical College, Xiamen, China, 361000.

email: wyx_1000@126.com

Other author footnotes

[$]Xujuan Zheng and [$]Juan Xiong made equal contributions to this manuscrip

Additional emails

Xujuan Zheng email: zhengxujuan@szu.edu.cn

Juan Xiong email: jxiong@szu.edu.cn

Yiqin Zhang email: 553098786@qq.com

Liping Xu email: 469722875@qq.com

Lina Zhou email: zhoulina154@126.com

Multi-state Markov model application for blood pressure transition among Chinese elderly population: A longitudinal study

Abstract

Background: The natural process of hypertension is a dynamic evolution, and hypertensive individuals could experience different stages along its progression trajectory with the passage of time. It is imperative to investigate the transition patterns among different levels of blood pressure for early detection and prevention.

Objective: To explore the transitions of different blood pressure states based on multi-state Markov model among Chinese elderly population.

Methods: The multi-state Markov model was built based on 5001 blood pressure measurements in 1833 old people from 2015 to 2020. The research was conducted to explore hypertension progression process, providing information on the transition probability, hazard ratio, and the mean sojourn time in the three blood pressure states, namely normal state, elevated state, and hypertensive state.

Results: Probabilities from normal state to hypertensive state in first year were 16.97% (female) and 21.73% (male); and dramatically increased to 47.31% (female) and 51.70% (male) within 3-year follow-up. The sojourn time of normal state was 1.5±0.08 years. Old women in normal state have 16.97%, 33.30%, and 47.31% chance of progress to hypertension within 1, 2, 3 years, respectively. The corresponding probabilities of old men were 21.73%, 38.56%, and 51.70%, respectively. For old women starting in elevated state, the probabilities of developing hypertension were 25.07%, 43.03%, and 56.32% in next one, two, and three years, respectively; while the corresponding changes of old men were 20.96%, 37.65%, and 50.86%. The increasing age, BMI, and glucose were associated with the probabilities for developing into hypertension from normal state or elevated state (HR: 1.04-1.12).

Conclusions: The preventive actions on hypertension progressions should be conducted at the early stages, and at least one yearly checkup is strongly recommended for elderly population. More awareness should be paid for elderly women with elevated state or elderly men with normal state. The increasing age, BMI, and glucose were critical risk factors for developing hypertensions.

Keywords: Blood pressure; Hypertension; Probability; Health Services for the Aged; Chinese; Multi-state Markov model

Introduction

Hypertension, defined by Chinese and European guidelines as an office systolic blood pressure (SBP) of ≥140 mmHg and/or diastolic blood pressure (DBP) of ≥90 mmHg without any antihypertensive medication [1-2]. As a significantly increasing global health issue, hypertension is the leading cause of cardiovascular and cerebrovascular diseases, chronic kidney disease and cognitive dysfunction [4-8]. It is likewise regarded as the most frequent modifiable risk factor for cardiovascular-related mortality, morbidity, disability and health expense in the global population [9-14]. During the last decade, the prevalence of hypertension has rapidly increased [15-16]. At present, approximately 1.13 billion people worldwide live with hypertension, and the number is predicted to increase by 15-20% in 2025 [17]. In China, hypertension emerging as a major public health problem influences more than 270 million of population [18-19]; and its incidence increases with age, affecting more than sixty percentages of people older than 60 years [20].

Sound evidence has identified various risk factors of hypertension, ranging from the genetic, environmental, and social-demographic perspectives, such as family history, diet, stress, obesity, age, gender, and hypercholesterolemia [21-24]. However, the commonly used methods of logistic regression and Cox proportional models for these risk factors discovery in the previous research could not offer adequate information about the dynamitic process of blood pressure evolution [24-27]. Actually, the natural process of hypertension is a dynamic evolution, and hypertensive individuals could experience different stages along its progression trajectory with the passage of time [28]. According to the hypertension prevention guidelines in China, blood pressure can be divided into three categories: normal state, elevated state, and hypertensive state [1, 29]. Elevated state is the blood pressure range of prehypertension, with the value of 120–139mmHg for SBP and 80–89mmHg for DBP without antihypertensive medication; and means the transition from normal state to hypertension in clinical diagnosis [1]. In addition to hypertensive state, the elevated state is also related to a higher risk of fatal cardiovascular disease. Therefore, it is imperative to investigate the transition patterns among different levels of blood pressure for early detection and prevention [30].

It is noted that multi-state Markov modeling is a modeling technique that have been widely used in healthcare filed to analyze the progression of various chronic diseases, such as hepatitis [31], diabetes [32], chronic kidney disease [33], and

Alzheimer's disease [34]. It likewise can be used to analyze the transition from a normal (non-disease) state, through a mild state to a severe and/or death state [35]. As an effective method dealing with repeated measurement data, multi-state Markov model can provide information on inter-state transitions, transition probability, hazard ratio and the mean sojourn time of the transition in cohort population [28-29]. There have been two studies exploring the blood pressure states transition based on multi-state Markov model. One study focused on the US working population aged 18-54 years old [28]; and the other study focused on the Chinese population with mean age of 37.54±13.80 years. Compared with young working population, elderly people have a higher incidence of hypertension, being worthy more attention and investigation [29].

Therefore, our research contributed to explore the state transition dynamics of three blood pressure states via multi-state Markov model and investigate the risk factors could associate with the progression of hypertension among the Chinese elderly population, which has not explored in the existing literature. Furthermore, our study estimated the information for the special group of old person on the sojourn time in each blood pressure state and the transition probabilities from one state to other states that initially providing statistical foundations for early hypertension prevention, timely targeted interventions, and effectively geriatric nursing.

Methods

Aim and Design

A quantitative longitudinal study was conducted to explore the transitions of different blood pressure states based on multi-state Markov model among Chinese elderly population.

Participants

This research included individuals who volunteered to have a community-organized freely annual physical examination in a community health center of hospital funded by Chinese Government from 2015 to 2020. Inclusion criteria were participants aged 60 years or above, and participants attended at least two checkups, including at least one baseline data and one follow-up data. Exclusion criteria were individuals who had hypertension at baseline, or whose record with missing data on age, gender, blood pressure, BMI, or blood glucose. After preprocessing, a total of 1833 individuals were included in the study. The maximum follow-up time was 5.7 years, and the mean follow-up was approximately 2.5 years.

Data Collection

This study used data from the annual physical examination. During each checkup per year, the individual's height, weight, abdominal circumference, blood pressure, and electrocardiogram were measured, and a blood test was taken to identify their blood glucose. The socio-demographic data such as age, gender, and marriage status were collected by health professionals. This study was approved by the review committee of X hospital, Southeast of China. All participants provided their informed consent before data collection; and were informed of the purpose and process of the study and freedom to withdraw whenever they want.

Blood pressure was measured by professional medical staff via Omron electronic sphygmomanometer with appropriately-sized cuffs, measuring SBP and DBP in the resting, sitting position on the right and left upper arm, respectively [36-37]. All participants took at least two mandatory blood pressure measurements, with the interval of ten minutes [38], and the average of two measurements was used as the result. If the numerical difference of SBP or DBP readings between the two mandatory measurements was more than 10 mmHg, a third blood pressure measurement was conducted to avoid error. In order to improve the accuracy of measurement, participants were asked to relax for >5 min, avoid caffeine, exercise, and smoking for at least 30 min before measurement. Neither the participant nor the observer should talk during the rest period or during the measurement.

In the research, three blood pressure states were categorized via the Chinese Hypertension Prevention Guide 2010 Third Edition [1]: (1) normal state: SBP less than 120mmHg, DBP less than 80 mmHg, and not taking any antihypertensive medicine; (2) elevated state: SBP 120–139mmHg (DBP<90mmHg) or DBP 80–89mmHg (SBP<140 mmHg), and not taking any antihypertensive medicine; (3) hypertensive state: SBP at least 140mmHg or DBP at least 90mmHg or taking any antihypertensive medicine.

Body mass index (BMI) is the ratio of a person's weight (in kilograms) to the square of height (in meters). In this study, four BMI categories were defined by Chinese Center for Disease Control and Prevention (1) underweight: BMI less than 18.5

kg/m^2; (2) normal: BMI ranging from 18.5 to 24.0 kg/m^2; (3) overweight: BMI ranging from 24.0 kg/m^2 to 28.0 kg/m^2; (4) obese: BMI higher than 28.0 kg/m^2.

Statistical Analysis

Descriptive analysis was used to describe the social-demographic and clinical data. For continuous data, mean and standard deviation (SD) was used; and for categorical data, frequencies and percentages were used. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were used in the statistical analysis. The multi-state Markov model was built using msm package of R software [39]. X^2 was reported to compare differences in baseline characteristics between the male and female person. All the statistical analyses were conducted by R software (R Foundation, Vienna, Austria). A P value less than 0.05 was considered statistically significant.

In the Markov model of this study, there are three blood pressure states of interest: state 1 (normal state), state 2 (elevated state), and state 3 (hypertensive state). A state change is regarded as a transition. If the state can continue to transition to another, it is classified as a transient state; otherwise, it is an absorbing state meaning a lifelong health condition [39]. In the research, both normal state and elevated state were transient states as the model assumed that both the two states could transit to each other as well as to the hypertensive state. By contrast, once an individual transited to the hypertension state, he or she could not re-transit to normal state or elevated state because the transitions from hypertension to other states were not a natural process [28].

Six possible transitions among the three states were illustrated in Figure 1. For example, the blood pressure of an individual can stay in the current state or transit to any of the other states, such as normal → normal, normal → elevated, normal → hypertensive, elevated → elevated, elevated → normal, elevated → hypertensive. The sojourn time means the average length of time staying in a transient state before transiting to a new state.

Results

Baseline Characteristics of Participants

In this study, 1833 subjects were included with the 5001 measurement records. At the baseline checkup, 443 (25.17%) participants were in normal state and 1390

(75.83%) participants were in elevated state. However, at the final checkup, 247 (13.48%) individuals were in normal state, 447 (24.39%) individuals were in elevated state and 1139 (62.14%) individuals were in hypertensive state (Table 1).

Table 1 The statistic of blood pressure state transition

Blood pressure state	Baseline checkup N(%)	Final checkup N(%)
Normal state	443 (24.17)	247 (13.48)
Elevated state	1390 (75.83)	447 (24.39)
Hypertensive state	0 (0.00)	1139 (62.14)
Total	1833 (100.00)	1833 (100.00)

Among these participants, the mean age was 65.5 (6.04) years, and 967 (52.76%) were female. The baseline characteristics of these participants, and their discrepancy between male and female participants were summarized in Table 2.

Table 2 Baseline characteristics of participants

Variable	**Overall**, N = 1,833[1]	**Male**, N = 866	**Female**, N = 967	***P*-value**[2]
Age Mean (SD)	65.5 (6.04)	65.7 (5.85)	65.4 (6.20)	0.031
Married	1,605(88%)	817(94%)	788 (82%)	<0.001
Blood pressure				0.002
Normal state	443(24%)	181 (21%)	262 (27%)	
Elevated state	1,390 (76%)	685 (79%)	705 (73%)	
Glucose Mean (SD)	5.6 (1.67)	5.5 (1.38)	5.8 (1.88)	<0.001
Diabetes	119 (6.5%)	51 (5.9%)	68 (7.0%)	0.300
BMI				<0.001
Normal	1,160 (63%)	579 (67%)	581 (60%)	
Obese	78(4.3%)	28 (3.2%)	50 (5.2%)	
Overweight	421 (23%)	170 (20%)	251 (26%)	
Underweight	174 (9.5%)	89 (10%)	85 (8.8%)	
Abnormal ECG	466 (28%)	248 (32%)	218 (25%)	0.001

Transition Frequency from One Checkup to the Following Checkup

Among 5001 blood pressure measurements in 1833 old people over the period of 2015-2020, 1833 measurements were conducted at the baseline checkup and 3168 measurements were conducted at follow-up checkups. The numbers of transitions from one checkup (given by the row state) to the next one (given by the column state) were shown in Table 3.

Table 3 Observed number of transitions from one checkup to the next checkup

From\To	Normal	Elevated	Hypertensive	Total
Normal	430(47.25%)	242(26.59%)	238(26.15%)	910(100%)
Elevated	284(12.58%)	1073(47.52%)	901(39.90%)	2258(100%)

Of the 3168 transitions, 26.59% showed deterioration from normal state to elevated state at the next checkup; 26.15% from normal state to hypertensive state, and 47.25% with normal state showed no change. Similarly, there were 1073 occurrences where participants remained in elevated state, 901 (39.90%) cases where participants progressed from elevated state to hypertension, while 284 (12.25%) cases showed alleviation from elevated state to normal state at the following visit.

The six possible blood pressure state transitions with the corresponding probabilities over one year, two years and three years period, stratified by gender were illustrated in Figure 2 and 3. Compared with male participants, female participants have lower probabilities from normal state to hypertensive state; but have higher probabilities from elevated state to hypertensive state over any periods of time. For instance, old women in normal state have 16.97%, 33.30%, and 47.31% chance of progress to hypertension if the next checkup was performed after the interval of one year, two years and three years, respectively. By contrast, the chances of old men moving from normal state to hypertensive state were 21.73%, 38.56%, and 51.70% within 1, 2, 3 years, respectively. For old women starting in elevated state, the probabilities of developing hypertension were 25.07%, 43.03%, and 56.32% in the next one, two, and three years, respectively; while the corresponding changes of old men between the two states transition were 20.96%, 37.65%, and 50.86%. As time went by, both female and male participants had a higher probability of developing hypertension. For example, the changes from normal state to hypertensive state over a 1-year follow-up were 16.97% (female) and 21.73% (male); and dramatically increased to 47.31% (female) and 51.70% (male) within the 3-year follow-up.

The sojourn time of normal state in the study cohort was 1.5±0.08 years, and the duration of elevated state was 2.0±0.07 years.

Covariate Effects on Blood Pressure States Transitions

The covariates included in the research were age, gender, marriage, BMI, glucose, and ECG. The effects of covariates on blood pressure state transition with statistical significance are summarized in Table 4. Gender, BMI, age and glucose had some significant associations with possible transitions. For example, the increasing age, BMI, and glucose were risk factors for developing into hypertension from the normal state or elevated state (HR: 1.04-1.12). Female participants and participants with higher glucose were less likely to alleviate from elevated state to normal state than male counterparts (HR: 0.61-0.83).

Table 4 Covariate effects on blood pressure states transitions

Covariate	Normal–Elevated HR (95% CI)	Normal-Hypertensive HR (95% CI)	Elevated–Normal HR (95% CI)	Elevated –Hypertensive HR (95% CI)
Gender	1.131 (0.807, 1.586)	0.544 (0.288, 1.028)	0.606 (0.412, 0.891)	1.461 (0.999, 2.136)
BMI	1.038 (0.992, 1.086)	1.124 (1.058, 1.195)	1.017 (0.963, 1.074)	1.019 (0.983, 1.057)
Age	1.016 (0.980, 1.054)	1.042 (1.010, 1.075)	1.018 (0.990, 1.047)	1.017 (0.997, 1.037)
Glucose	1.013 (0.947, 1.083)	0.876 (0.697, 1.102)	0.827 (0.715, 0.956)	1.054 (1.012, 1.097)

Survival Probability Based on Multi-state Markov Model

The multi-state Markov model can be used to infer the survival probability for each subgroup in the future, which may provide insightful information for the individuals. In this study, survival probability represents the probability of not transiting into the hypertensive state. Survival probability curves over 5 years for all subgroups stratified by female and male categories were given in Figure 4 and 5. The survival probability decreased significantly with increased time among all subgroups. As shown in Figure 4, the survival probability for female participants originating from the normal state was similar with the probability for male participants (no difference, P=0.70). Figure 5 illustrated that male participants starting from elevated state had a higher survival probability over 5 years than female participants (P=0.01).

Discussion

Hypertension is regarded as the leading cause of cardiovascular and cerebrovascular diseases; and the most frequent risk factor for cardiovascular-related mortality, morbidity, disability and health expense in the global population [9-14]. In addition to hypertensive state, the elevated state is also identified as a higher risk of fatal cardiovascular disease. Thus, it is of significance to investigate the transition patterns among different levels of blood pressure, and the factors influencing the progression and regression of blood pressure for early detection and prevention [30]. Sound evidence verified compared with young population, elderly people have a higher incidence of hypertension, being worthy more attention and investigation [29]. With the huge total population in China, there were 254 million people aged≥60 years accounting for 18.1% of the whole population in 2020 [40]. Therefore, in this study, we explore the state transition dynamics of three blood pressure states via multi-state Markov model and investigate the risk factors could associate with the progression of hypertension for elderly population in China, which has not explored in the existing literature.

There are some significant findings in the research. Firstly, our research found that of the 3168 transitions, 26.15% of participants showed deterioration from normal state to hypertensive state at the next checkup, much higher than the corresponding percentage of 16.98 and 9.18 in the previous studies for working population [28-29]. It further confirmed that older people should be caused much more attention on hypertension prevention and research. Secondly, we found that both female and male participants in normal state had a lower probability of developing hypertension in the first year; however, the probability substantially increased in the following thee year, which was consistent with the prior research for young people [28-29]. In the study, the changes from normal state to hypertensive state in the first year were 16.97% (female) and 21.73% (male); and dramatically increased to 47.31% (female) and 51.70% within the 3-year follow-up. Furthermore, the sojourn time of normal state was 1.5±0.08 years in the study cohort. These results indicated that the preventive actions and effective intervention on hypertension progression should be conducted at the early stages, and at least one yearly checkup is strongly recommended for elderly population. Thirdly, male participants were found to have high probabilities from normal state to hypertension, in comparison with female participants. For example, old women in normal state have 16.97%, 33.30%, and 47.31% chance of progress to hypertension within 1, 2, 3 years, respectively. By contrast, the corresponding chances of old men were 21.73%, 38.56%, and 51.70% respectively. The findings well align with the prior study that indicated that more attention should be paid to elderly men with normotension [28, 41, and 42]. However, we initially found that elderly female participants had higher probabilities developing from elevated state to hypertensive state than male participants. For instance, for old women starting in elevated state, the probabilities of developing hypertension were 25.07%, 43.03%, and 56.32% in the next one, two, and three years, respectively; while the corresponding changes of old men between the two states transition were 20.96%, 37.65%, and 50.86%. Female participants were less likely to alleviate from elevated state to normal state than male counterparts in the study (HR: 0.61, 95% CI: 0.41-0.89). Our survival probability pilot also illustrated that male participants starting from elevated state had a higher survival probability over 5 years than female participants (*P*=0.01). The above findings reminded that more attention should be paid at the progression from elevated state to hypertension in elderly women.

In addition to age and gender discussed above, the increasing BMI (HR: 1.12, 95% CI: 1.06-1.20) and glucose (HR: 1.05, 95% CI: 1.01-1.10) were identified to be risk factors for developing into hypertension from normal state or elevated state. The previous research also found that the hazard ratio for transitioning from normal state to hypertensive state improved with the higher BMI value [28, 29, and 43]; and the higher glucose value [44].

In summary, there are key contributions in the research. First of all, a multi-state Markov model was used to explore the state transition dynamics of three blood pressure states, and investigated how several important covariates affected the progression or alleviation of hypertension for Chinese elderly population. Furthermore, through the developed model, the sojourn time in each blood pressure state and the transition probabilities from one state to other state were estimated, therefore supplying statistical foundations for the preventive actions and effective intervention on hypertension progression for elderly people.

Limitations

By contrast, some limitations can be summarized as follows. (1) Owing to the time and financial limitation, we only focused on the cohort population over five years in one city; thus the study findings could not representative and fit for extrapolation.

(2) In this study, the hypertensive state was regarded as absorbing state, meaning that the reversed transition from hypertensive state to normal or elevated state could not be included. (3) Some significant covariates such as varied life habits of diet, exercise and psychological status were not covered in the current study, being worthy of investigating in the further research.

Conclusions

The results of three blood pressure state transition probabilities caused more awareness about the timely prevention for elderly women with elevated state and elderly men with normal state. The preventive actions and effective intervention on hypertension progression should be conducted at the early stages, and at least one yearly checkup is strongly recommended for elderly people. The increasing age, BMI, and glucose were risk factors for developing into hypertension from the normal state or elevated state. The derived transition probabilities and sojourn time can serve as a significant reference for health professionals to make proactive plans and targeted interventions for hypertension progression among Chinese elderly population.

Figure 1: Three blood pressure states transitions In the Markov model
Figure 2: Female participants' transition diagrams
Figure 3 Male participants' transition diagrams
Figure 4 The survival distribution starting from normal state
Figure 5 The survival distribution starting from elevated state

Acknowledgements

We would like to thank all participants who voluntarily participated in this study.

Contributorship statement

XZ and JX performed the statistical analysis, interpretation and wrote the manuscript. YZ, LX and LZ contributed to the conceptualization of the research process and critically reviewed the manuscript. BZ and YW are responsible for the overall content as guarantor. All authors read and approved the final manuscript.

Funding

YW was supported by grants from Fujian Province planning project of science and technology (2019D015). JX was supported by the Medical Science and Technology Research Fund Project of Guangdong Province (grant no. A2020405).

Ethics approval

This study was approved by the review committee of X hospital, Southeast of China. All participants provided their informed consent before data collection; and were informed of the purpose and process of the study and freedom to withdraw whenever they want.

Conflicts of Interest

None

References

1. Liu LS. 2010. Chinese guidelines for the management of hypertension. *Zhonghua Xin Xue Guan Bing Magazine* 2011; 39:579–615.
2. Williams B, Mancia G, Spiering W, *et al*. ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018;39(33):3021–3104. doi:10.1080/08037051.2018.1527177.
3. Herman WW, Konzelman JL, Prisant LM. Joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure bethesda (MD): National heart, lung, and blood institute (US) 2004.
4. Lawes CM, Hoorn SV, Rodgers A. Global burden of blood-pressure-related disease. *Lancet* 2008;371:1513–1518. doi: 10.1016/S0140-6736(08)60655-8.
5. Kokubo Y, Matsumoto C. Hypertension is a risk factor for several types of heart disease: review of prospective studies. *Adv Exp Med Biol* 2017;956:419–26. doi: 10.1007/5584_2016_99.
6. Oparil S, Acelajado MC, Bakris GL, *et al*. Hypertension. *Nat Rev Dis Primers* 2018;4(18014):1–21. doi: 10.1038/nrdp.2018.14.
7. Tackling G, Borhade MB, Tackling G, *et al*. Hypertensive heart disease. [Updated 2020 Jun 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing 2020. https://www.ncbi.nlm.nih.gov/books/NBK539800/

8. Jan YT, Tsai PS, Longenecker CT, *et al*. Thoracic aortic calcification and pre-clinical hypertension by new 2017 ACC/AHA hypertension guidelines. *Diagnostics* 2021;11:1027.
9. Ettehad D, Emdin CA, Kiran A, *et al*. Blood pressure lowering for prevention of cardiovascular disease and death: A systematic review and meta-analysis. *Lancet* 2016;387:957–967. doi: 10.1016/S0140-6736(15)01225-8.
10. Khaja SU, Mathias KC, Bode ED, *et al*. Hypertension in the United States fire service. *Int. J. Environ. Res. Public Health* 2021;18:5432. dio:10.3390/ijerph18105432.
11. GBD 2015 neurological disorders collaborator group. Global, regional, and national comparative risk assessment of 79 behavioral, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: A systematic analysis for the global burden of disease study 2015. *Lancet Neural* 2017;16(388):877–97.
12. Di Palo KE; Barone NJ. Hypertension and heart failure: Prevention, targets, and treatment. *Heart Fail. Clin.*2020;16:99–106. doi: 10.1016/j.hfc.2019.09.001.
13. Dominguez LJ, Veronese N, Barbagallo M. Magnesium and hypertension in old age. *Nutrients* 2021;13:139. dio: 10.3390/nu13010139.
14. Ye X, Yi Q, Shao J, *et al*. Trends in prevalence of hypertension and hypertension phenotypes among Chinese children and adolescents over two decades (1991–2015). *Front.* Cardiovasc*. Med* 2021;8:627741. dio: 10.3389/fcvm.2021.627741.
15. Kearney PM, Whelton M, Reynolds K, *et al*. Global burden of hypertension: analysis of worldwide data. *Lancet* 2005;365(9455):217–223.
16. Forouzanfar MH, Liu BP, Roth GA, *et al*. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990–2015. *JAMA* 2017;317(2):165–182. dio: 10.1001/jama.2016.19043.
17. WHO. Hypertension. World Health Organisation. https://www.who.int/newsroom/factsheets/detail/hypertension. Published 2019. Accessed 2 October 2020.
18. Griffin G. Antiplatelet therapy and anticoagulation in patients with hypertension. *Am Fam Physician* 2005;71:897–9. doi: 10.1001/jama.293.9.1123.

19. Xiong X, Yang X, Liu Y, *et al*. Chinese herbal formulas for treating hypertension in traditional Chinese medicine: perspective of modern science. *Hypertens Res* 2013;36:570–9. doi: 10.1038/hr.2013.18.
20. Chow CK, Teo KK, Rangarajan S, *et al*. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *JAMA* 2013;310(9):959–968. dio: 10.1001/jama.2013.184182.
21. Patel RS, Masi S and Taddei S. Understanding the role of genetics in hypertension. *Eur. Heart J* 2017;38(29): 2309–2312. dio: 10.1093/eurheartj/ehx273.
22. Li C, Sun DD, Liu JL, *et al*. A predictionmodel of essential hypertension based on genetic and environmental risk factors in northern han Chinese. *Int. J. Med. Sci* 2019;16(6):793–799. dio: 10.7150/ijms.33967.
23. Bigazzi R, Zagato L, Lanzani C, *et al*. Hypertension in high school students: Genetic and environmental factors: The HYGEF study. *Hypertension* 2020;75:71–78. dio: 10.1161/HYPERTENSIONAHA.119.13818.
24. Zhang YY, Yang H, Ren M, *et al*. Distribution of risk factors of hypertension patients in different age groups in Tianjin. *BMC Public Health* 2021;21:247. dio: 10.1186/s12889-021-10250-9.
25. Shihab HM, Meoni LA, Chu AY, *et al*. Body mass index and risk of incident hypertension over the life course: The Johns Hopkins precursors study. *Circulation* 2012;126(25):2983–2989. dio: 10.1161/CIRCULATIONAHA.112.117333.
26. Tohidi M, Hatami M, Hadaegh F, *et al*. Triglycerides and triglycerides to high-density lipoprotein cholesterol ratio are strong predictors of incident hypertension in middle eastern women. *J. Hum. Hypertens* 2012;26(9):525–532. dio: 10.1038/jhh.2011.70.
27. Zhang W, Wang L, Chen Y, *et al*. Identification of hypertension predictors and application to hypertension prediction in an urban han Chinese population: A longitudinal study, 2005–2010. *Preventing Chronic Disease* 2015;12:E184. dio: 10.5888/pcd12.150192.
28. Yang JM, Liu F, Wang B, *et al*. Blood pressure states transition inference based on multi-state Markov model. *IEEE J Biomed Health* 2021;25(1):237-246. dio: 10.1109/JBHI.2020.3006217.

29. Wang YF, Ma ZM, Xu CN, *et al.* Prediction of transfer among multiple states of blood pressure based on Markov model: an 18-year cohort study. *J. Hypertens* 2018;36:15061513. dio:10.1097/HJH.0000000000001722.
30. Mills KT, Obst KM, Wei S, *et al*. Comparative effectiveness of implementation strategies for blood pressure control in hypertensive patients: A systematic review and meta-analysis. *Ann. Internal Med* 2018;168(2):110–120. dio: 10.7326/M17-1805.
31. Tada T, Kumada T, Toyoda H, *et al*. Longterm natural history of liver disease in patients with chronic hepatitis b virus infection: An analysis using the Markov chain model. *J. Gastroenterol* 2018;53(11):1196–1205. dio: 10.1007/s00535-018-1467-x.
32. Wong LY, Toh MPHS and Tham LWC. Projection of prediabetes and diabetes population size in singapore using a dynamic Markov model. *J. Diabetes* 2017;9(1):65–75. dio: 10.1111/1753-0407.12384. 10.1111/1753-0407.12384
33. Grover G, Sabharwal A, Kumar S, *et al*. A multi-state Markov model for the progression of chronic kidney disease. *Türkiye Klinikleri Biyoistatistik* 2019;11(1):1–14. dio: 10.5336/biostatic.2018-62156.
34. Brookmeyer R and Abdalla N. Multistate models and lifetime risk estimation: Application to Alzheimer's disease. *Statist. Med* 2019;38(9):1558–1565. dio: 10.1002/sim.8056.
35. Srikanth P. Using Markov chains to predict the natural progression of diabetic retinopathy. *Int. J. Ophthalmol* 2015;8(1):383 132–137. dio: CNKI:SUN:GYZZ.0.2015-01-026.
36. Attard SM, Herring AH, Zhang B, *et al*. Associations between age, cohort, and urbanization with SBP and DBP in China: a population based study across 18 years. *J Hypertens* 2015;33:948–956.
37. Guo J, Zhu YC, Chen YP, *et al*. The dynamics of hypertension prevalence, awareness, treatment, control and associated factors in Chinese adults: results from CHNS 1991-2011. *J Hypertens* 2015;33:1688–1696.
38. Cuddy MLS. The Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 2004;55:17–21.
39. Jackson CH. Multi-state models for panel data: the msm package for R. *J Stat Soft* 2011;38:1–28. dio: 10.18637/jss.v038.i08.

40. China development research foundation, 2020. China development report-aging population in 2020: Development trend and policy options. Available from URL: http://www.199it.com/archives/1068230.html

41. Singh S, Shankar R, and Singh GP. Prevalence and associated risk factors of hypertension: A cross-sectional study in urban Varanasi. *Int. J.Hypertens* 2017;2017:5491838. dio: 10.1155/2017/5491838.

42. Faulkner JL and de Chantemèle EJB. Sex differences in mechanisms of hypertension associated with obesity. *Hypertension* 2018;71(1):15–21. dio: 10.1161/HYPERTENSIONAHA.117.09980.

43. Davis J, Juarez D, and Hodges K. Relationship of ethnicity and body mass index with the development of hypertension and hyperlipidemia. *Ethnicity Disease* 2013;23(1):65–70. dio: 10.1111/jphd.12008.

44. Huang Z, Wang GD, Jonas JB, *et al*. Blood pressure control and progression of arteriosclerosis in hypertension. *J. Hypertens* 2021;39(6):1221-1229. dio: 10.1097/HJH.0000000000002758.

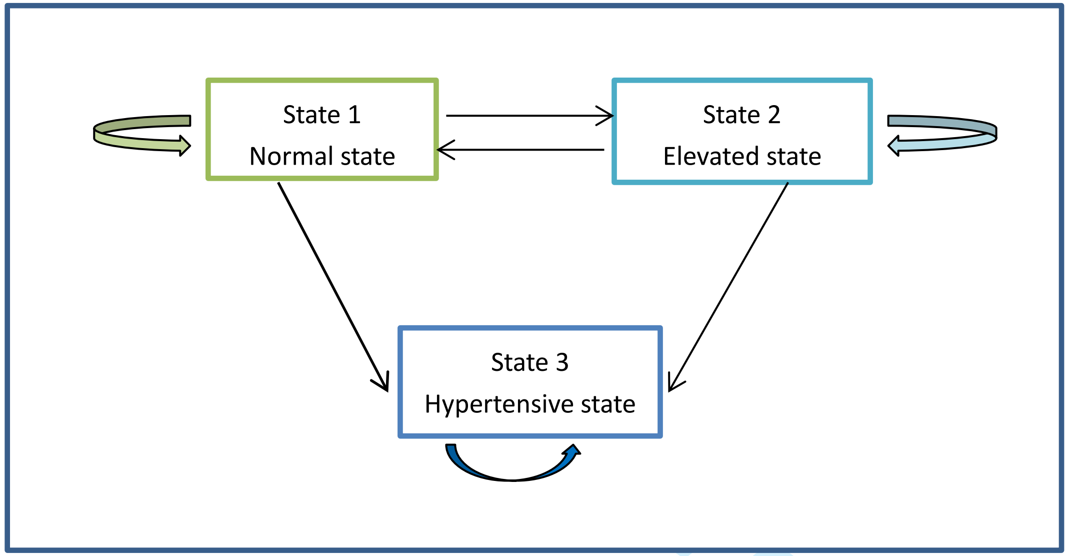
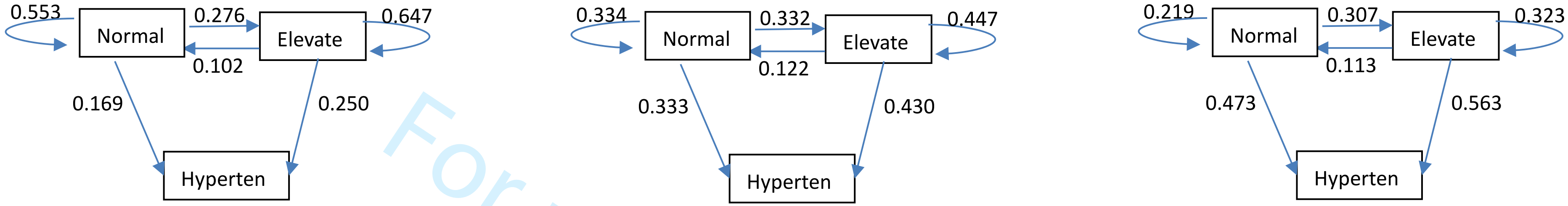
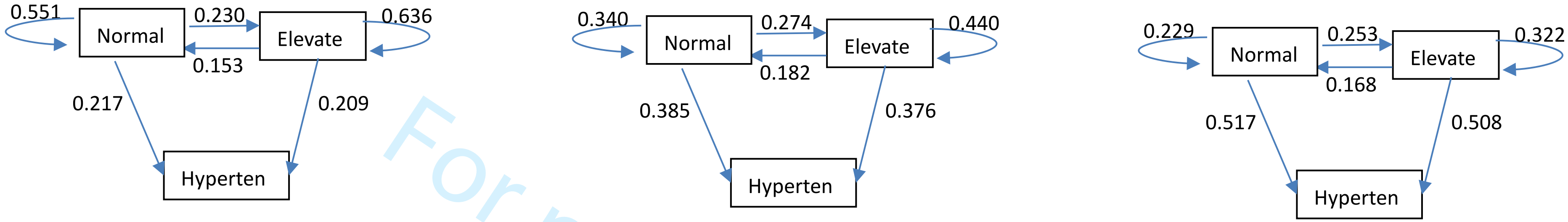


Figure 1 Three blood pressure states transitions In the Markov model



1 year transition diagram 2 year transition diagram 3 year transition diagram

Figure 2 Female participants' transition diagrams



1 year transition diagram 2 year transition diagram 3 year transition diagram

Figure 3 Male participants' transition diagrams

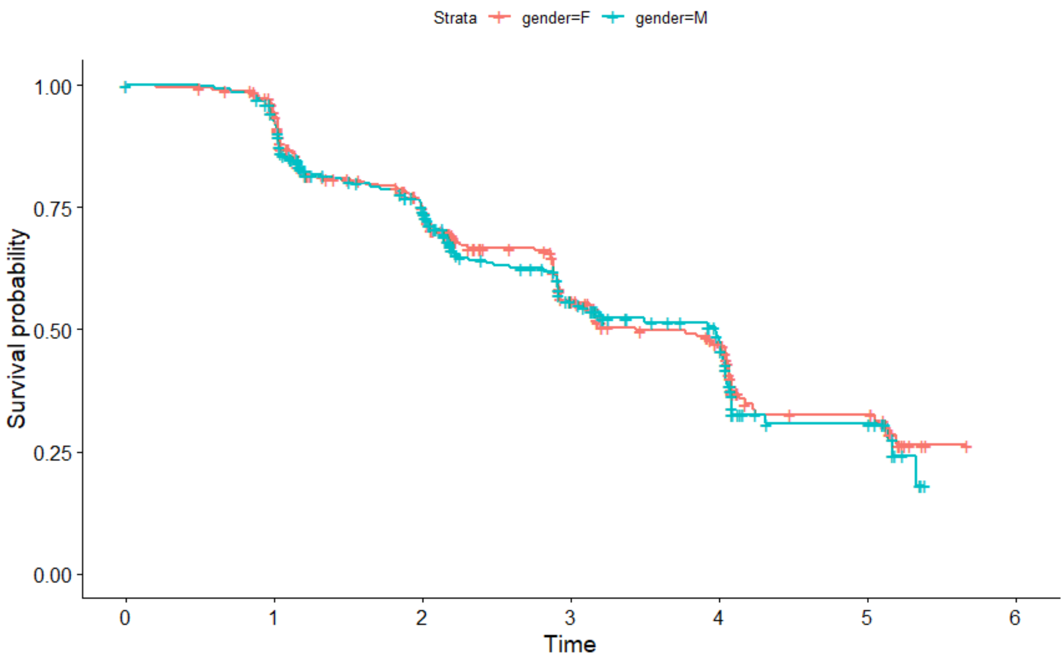


Figure 4 The survival distribution starting from normal state

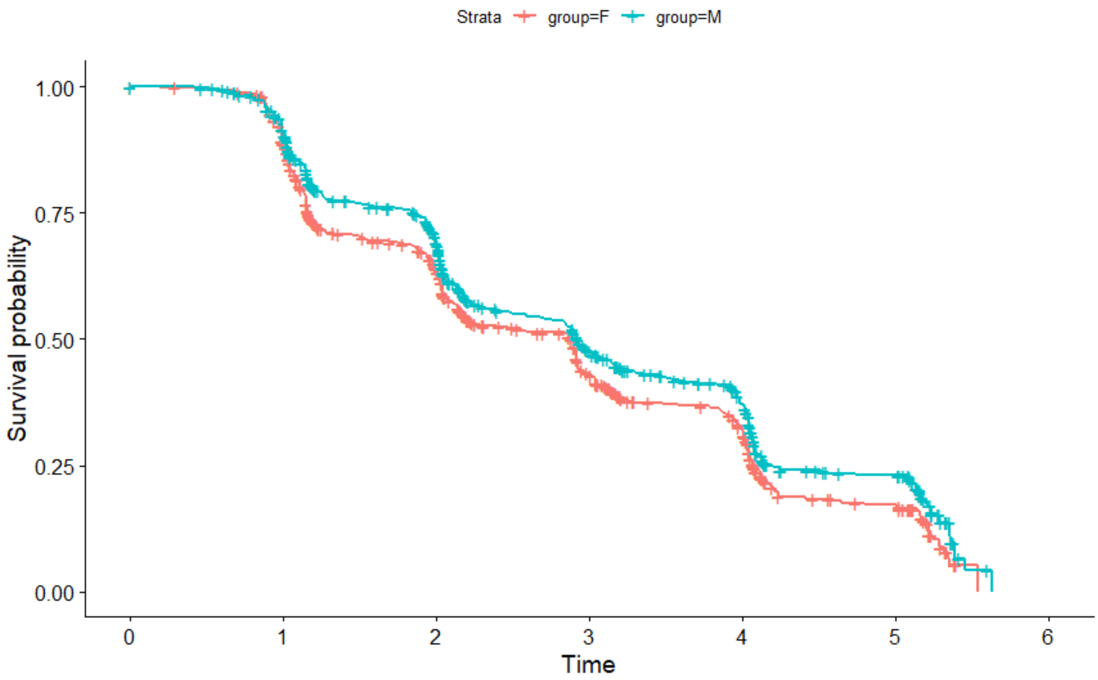


Figure 5 The survival distribution starting from elevated state

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
✓		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
✓ Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
✓ Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
✓ Study design	4	Present key elements of study design early in the paper
✓ Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
✓ Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
✓ Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
✓ Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
✓ Bias	9	Describe any efforts to address potential sources of bias
✓ Study size	10	Explain how the study size was arrived at
✓ Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
✓ Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
✓ Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
✓ Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
✓ Outcome data	15*	Report numbers of outcome events or summary measures over time
✓ Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

✓	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
	Discussion		
✓	Key results	18	Summarise key results with reference to study objectives
✓	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
✓	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
✓	Generalisability	21	Discuss the generalisability (external validity) of the study results
	Other information		
✓	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Multi-state Markov model application for blood pressure transition among the Chinese elderly population: A quantitative longitudinal study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-059805.R1
Article Type:	Original research
Date Submitted by the Author:	20-Apr-2022
Complete List of Authors:	Zheng, Xujuan; Shenzhen University, Health Science Center Xiong, Juan; Shenzhen University, School of Public Health Zhang, Yiqin ; the No.2 Affiliated Hospital of Xiamen Medical College, Nephrology Xu, Liping; the No.2 Affiliated Hospital of Xiamen Medical College, Nephrology Zhou, Lina; the No.2 Affiliated Hospital of Xiamen Medical College, Nephrology Zhao, Bin; Affiliated Xiangan Hospital of Xiaman University, Department of medical laboratory Wang, Yuxin; the No.2 Affiliated Hospital of Xiamen Medical College, Nephrology
Primary Subject Heading:	Health services research
Secondary Subject Heading:	Health services research, Public health, Cardiovascular medicine
Keywords:	Hypertension < CARDIOLOGY, EPIDEMIOLOGY, PUBLIC HEALTH

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title page

• Short informative title

Multi-state Markov model application for blood pressure transition among the Chinese elderly population: A quantitative longitudinal study

• Short running title

Multi-state Markov model for blood pressure

• List of all authors

Xujuan **Zheng**[1 $], Juan **Xiong**[1 $], Yiqin **Zhang**[2], Liping **Xu**[2], Lina **Zhou**[2], Bin **Zhao***[3], Yuxin **Wang***[2]

Affiliations

[1] Health Science Centre, Shenzhen University, Shenzhen, China

[2] Dept. Nephrology, the No.2 Affiliated Hospital of Xiamen Medical College, Xiamen, China

[3] Department of medical laboratory, Xiang'an Hospital Affiliated to Xiamen University, Xiamen, China

Corresponding author:

* Bin Zhao, Department of medical laboratory, Xiang'an Hospital Affiliated to Xiamen University, Xiangan District, Xiamen, China, 361000.

email: 393603468@qq.com

* Yuxin Wang, Dept. Nephrology, the No.2 Affiliated Hospital of Xiamen Medical College, Xiamen, China, 361000.

email: wyx_1000@126.com

Other author footnotes:

[$]Xujuan Zheng and Juan Xiong made **equal contributions** to this manuscript

Additional emails

Xujuan Zheng email: zhengxujuan@szu.edu.cn

Juan Xiong email: jxiong@szu.edu.cn

Yiqin Zhang email: 553098786@qq.com

Liping Xu email: 469722875@qq.com

Lina Zhou email: zhoulina154@126.com

Keywords: Blood pressure; Hypertension; Probability; Health services for the elderly; Chinese; Multi-state Markov model.

Word count: 3541

Abstract count: 299

Number of Reference: 44

Multi-state Markov model application for blood pressure transition among the Chinese elderly population: A quantitative longitudinal study

Abstract

Objective: To explore the transitions of different blood pressure states based on a multi-state Markov model among the Chinese elderly population.

Setting: A community health center in Xiamen, China.

Participants: 1833 elderly Chinese people.

Methods: A multi-state Markov model was built based on 5001 blood pressure measurements from 2015 to 2020. Research was conducted to explore the process of hypertension progression, providing information on the transition probability, hazard ratio, and the mean sojourn time in three blood pressure states, namely normal state, elevated state, and hypertensive state.

Results: Probabilities of moving from the normal state to the hypertensive state in the first year were 16.97% (female) and 21.73% (male); they increased dramatically to 47.31% (female) and 51.70% (male) within a 3-year follow-up period. The sojourn time in the normal state was 1.5±0.08 years. Elderly women in the normal state had a 16.97%, 33.30%, and 47.31% chance of progressing to hypertension within 1, 2, and 3 years, respectively. The corresponding probabilities for elderly men were 21.73%, 38.56%, and 51.70%, respectively. For elderly women starting in the elevated state, the probabilities of developing hypertension were 25.07%, 43.03%, and 56.32% in the next one, two, and three years, respectively; while the corresponding changes for elderly men were 20.96%, 37.65%, and 50.86%. Increasing age, body mass index (BMI), and glucose were associated with the probability of developing hypertension from the normal state or elevated state.

Conclusions: Preventive actions against progression to hypertension should be conducted at an early stage. More awareness should be paid to elderly women with elevated state and elderly men with normal state. Increasing age, BMI, and glucose were critical risk factors for developing hypertension. The derived transition probabilities and sojourn time can serve as a significant reference for making targeted interventions for hypertension progression among the Chinese elderly population.

Keywords: Blood pressure; Hypertension; Probability; Health services for the elderly; Chinese; Multi-state Markov model

Strengths and limitations of this study

► A multi-state Markov model was used to explore the state transition dynamics of three blood pressure states, and to investigate the risk factors affecting the progression of hypertension in the Chinese elderly population.

► The derived transition probabilities and sojourn time can serve as a significant reference for the development of proactive and targeted interventions for hypertension progression among the Chinese elderly population.

► Owing to time and financial limitations, the research only focused on the cohort population over five years in one city.

► The hypertensive state was regarded as an absorbing state, meaning that the reverse transition from the hypertensive state to the normal or elevated state was not considered.

► Some significant covariates such as various life habits of diet, smoking, exercise, and psychological status were not covered, but are worthy of investigation in further research.

Introduction

Hypertension is defined by Chinese and European guidelines as an office systolic blood pressure (SBP) of ≥140 mmHg and/or diastolic blood pressure (DBP) of ≥90 mmHg without any antihypertensive medication [1-2]. As a significantly increasing global health issue, hypertension is the leading cause of cardiovascular and cerebrovascular diseases, chronic kidney disease, and cognitive dysfunction [3-8]. It is likewise regarded as the most frequent modifiable risk factor for cardiovascular-related mortality, morbidity, disability, and health expense in the global population [9-14]. During the last decade, the prevalence of hypertension has rapidly increased [15-16]. At present, approximately 1.13 billion people worldwide live with hypertension, and the number is predicted to increase by 15–20% by 2025 [17]. In China, hypertension is emerging as a major public health problem and influences more than 270 million people [18-19]; its incidence increases with age, affecting more than 60% of people older than 60 years [20].

Sound evidence has identified various risk factors for hypertension, including genetic, environmental, and social-demographic perspectives, such as family history, diet, stress, obesity, age, gender, and hypercholesterolemia [21-24]. However, the methods commonly used to discover these risk factors in previous research, namely, logistic regression and Cox proportional models, do not provide adequate information about the dynamitic process of blood pressure evolution [24-27]. Indeed, the natural process of hypertension involves dynamic evolution, and hypertensive individuals experience different stages along its progression trajectory with the passage of time [28]. According to the hypertension prevention guidelines in China, blood pressure can be divided into three categories: the normal state, elevated state, and hypertensive state [1, 29]. The elevated state is the blood pressure range of prehypertension, with a value of 120–139 mmHg for SBP and 80–89 mmHg for DBP without antihypertensive medication; it represents the transition from a normal state to hypertension in clinical diagnosis [1]. In addition to the hypertensive state, the elevated state is also related to a higher risk of fatal cardiovascular disease. Therefore, it is imperative to investigate the transition patterns among different levels of blood pressure for early detection and prevention [30].

Multi-state Markov modeling has been widely used in healthcare research to analyze the progression of various chronic diseases, such as hepatitis [31], diabetes [32], chronic kidney disease [33], and Alzheimer's disease [34]. It likewise can be used to analyze the transition from a normal (non-disease) state, through a mild state to a severe and/or death state [35]. As an effective method for dealing with repeated measurement data, multi-state Markov modeling can provide information on inter-state transitions, transition probability, hazard ratio, and the mean sojourn time of the transition in the cohort population [28-29]. There have been two studies exploring transition of the blood pressure states based on multi-state Markov models. One study focused on the US working population aged 18–54 years [28]; the other study focused on the Chinese population with a mean age of 37.54±13.80 years. Compared with the young working population, elderly people have a higher incidence of hypertension, and are worthy of more attention and investigation [29].

Therefore, our research contributed to exploring the state transition dynamics of three blood pressure states via multi-state Markov modeling and investigating the risk factors associated with the progression of hypertension among the Chinese elderly population, which have not been explored in the existing literature. Furthermore, our study estimated, for this group of elderly persons, the sojourn time in each blood pressure state and the transition probabilities from one state to other states, to provide initial statistical foundations for early hypertension prevention, timely targeted interventions, and effective geriatric nursing.

Methods

Aim and Design

A quantitative longitudinal study was conducted to explore the transitions of different blood pressure states based on a multi-state Markov model among the Chinese elderly population.

Participants

This research included individuals who volunteered to have a community-organized free annual physical examination in a community health center of a hospital funded by the Chinese Government from 2015 to 2020. The inclusion criteria were participants aged 60 years or above, who attended at least two checkups, including at least one for baseline data and one for follow-up data. The exclusion criteria were individuals who had hypertension at baseline, or whose record had missing data on age, gender, blood pressure, BMI, or blood glucose. After preprocessing, a total of 1833 individuals were included in the study. The maximum follow-up time was 5.7 years, and the mean follow-up was approximately 2.5 years.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research. Patients or the public were not invited to contribute to the writing or editing of this article for readability or accuracy.

Data Collection

This study used data from the annual physical examination. During each annual checkup, the individual's height, weight, abdominal circumference, blood pressure, and electrocardiogram were assessed, and a blood test was taken to measure their blood glucose. Socio-demographic data such as age, gender, and marital status were collected by health professionals. This study was approved by the ethics committee of the No. 2 Affiliated Hospital of Xiamen Medical College, Xiamen City, southeast China. All participants provided their written informed consent before data collection, and were informed of the purpose and process of the study and their freedom to withdraw whenever they chose.

Blood pressure was measured by professional medical staff using an Omron electronic sphygmomanometer with appropriately sized cuffs, measuring SBP and DBP in the resting, sitting position on the right and left upper arm, respectively [36-37]. All participants gave at least two mandatory blood pressure measurements, with an interval of ten minutes [38], and the average of two measurements was used as the result. If the numerical difference of the SBP or DBP readings between the two mandatory measurements was more than 10 mmHg, a third blood pressure measurement was conducted to avoid error. In order to improve the accuracy of measurement, participants were asked to relax for >5 min, and avoid caffeine, exercise, and smoking for at least 30 min before measurement. Neither the participant nor the observer was allowed to talk during the rest period or during the measurement.

In the research, three blood pressure states were categorized according to the Chinese Hypertension Prevention Guide 2010 Third Edition [1]: (1) normal state: SBP less than 120 mmHg, DBP less than 80 mmHg, and not taking any antihypertensive medicine; (2) elevated state: SBP 120–139 mmHg (DBP <90 mmHg) or DBP 80–89 mmHg (SBP <140 mmHg), and not taking any antihypertensive medicine; (3) hypertensive state: SBP at least 140 mmHg or DBP at least 90 mmHg or taking any antihypertensive medicine.

The body mass index (BMI) is the ratio of a person's weight (in kilograms) to the square of their height (in meters). In this study, four BMI categories were defined by the Chinese Center for Disease Control and Prevention: (1) underweight: BMI less than 18.5 kg/m^2; (2) normal: BMI ranging from 18.5 to 24.0 kg/m^2; (3) overweight: BMI ranging from 24.0 kg/m^2 to 28.0 kg/m^2; (4) obese: BMI higher than 28.0 kg/m^2.

Statistical Analysis

Descriptive analysis was used to describe the social-demographic and clinical data. For continuous data, the mean and standard deviation (SD) were used, and for categorical data, frequencies and percentages were used. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were used in the statistical analysis. The multi-state Markov model was built using the "msm" package of R software [39]. The X^2 test was used to compare differences in baseline characteristics between the male and female participants. All the statistical analyses were conducted using R software (R Foundation, Vienna, Austria). A *P*-value less than 0.05 was considered statistically significant.

In the Markov model of this study, there are three blood pressure states of interest: state 1 (normal state), state 2 (elevated state), and state 3 (hypertensive state). A state change is regarded as a transition. If a state can continue to transition to another, it is classified as a transient state; otherwise, it is an absorbing state, meaning a lifelong health condition [39]. In the research, both the normal state and the elevated state were transient states as the model assumed that the two states could transition to each other as well as to the hypertensive state. By contrast, once an individual transitioned to the hypertension state, he or she could not return to the normal state or elevated state because the transitions from hypertension to the other states were not natural processes [28].

Six possible transitions among the three states are illustrated in Figure 1. For example, the blood pressure of an individual can stay in the current state or transition to any of the other states, such as normal → normal, normal → elevated, normal → hypertensive, elevated → elevated, elevated → normal, elevated → hypertensive. The sojourn time means the average length of time the blood pressure remained in a transient state before transitioning to a new state.

Results

Baseline Characteristics of Participants

In this study, 1833 participants were included, with 5001 measurement records. At the baseline checkup, 443 (25.17%) participants were in the normal state and 1390 (75.83%) participants were in the elevated state. However, at the final checkup, 247 (13.48%) individuals were in the normal state, 447 (24.39%) individuals were in the elevated state, and 1139 (62.14%) individuals were in the hypertensive state (Table 1).

Table 1 The statistic of blood pressure state transition

Blood pressure state	Baseline checkup N(%)	Final checkup N(%)
Normal state	443 (24.17)	247 (13.48)
Elevated state	1390 (75.83)	447 (24.39)
Hypertensive state	0 (0.00)	1139 (62.14)
Total	1833 (100.00)	1833 (100.00)

Among these participants, the mean age was 65.5 (6.04) years, and 967 (52.76%) were female. The baseline characteristics of these participants, and their discrepancies between male and female participants, are summarized in Table 2.

Table 2 Baseline characteristics of participants

Variable	Overall, N = 1,833[1]	Male, N = 866	Female, N = 967	p-value[2]
Age Mean (SD)	65.5 (6.04)	65.7 (5.85)	65.4 (6.20)	0.031
Married	1,605/1,830 (88%)	817/865 (94%)	788/965 (82%)	<0.001
Blood pressure				0.002
Normal state	443/1,833 (24%)	181/866 (21%)	262/967 (27%)	
Elevated state	1,390/1,833 (76%)	685/866 (79%)	705/967 (73%)	
Glucose Mean (SD)	5.6 (1.67)	5.5 (1.38)	5.8 (1.88)	<0.001
Diabetes	119/1,833 (6.5%)	51/866 (5.9%)	68/967 (7.0%)	0.300
BMI				<0.001
Normal	1,160/1,833 (63%)	579/866 (67%)	581/967 (60%)	
Obese	78/1,833 (4.3%)	28/866 (3.2%)	50/967 (5.2%)	
Overweight	421/1,833 (23%)	170/866 (20%)	251/967 (26%)	
Underweight	174/1,833 (9.5%)	89/866 (10%)	85/967 (8.8%)	
Abnormal ECG	466/1,662 (28%)	248/779 (32%)	218/883 (25%)	0.001

[1]Mean (SD), n/N (%); [2]Wilcoxon rank sum test; Pearson's chi-squared test
BMI: Body mass index, ECG: Electrocardiogram

Transition Frequency from One Checkup to the Following Checkup

Among 5001 blood pressure measurements in 1833 elderly people over the period 2015–2020, 1833 measurements were conducted at the baseline checkup and 3168 measurements were conducted at follow-up checkups. The numbers of transitions from one checkup (given by the row state) to the next one (given by the column state) are shown in Table 3.

Table 3 Observed number of transitions from one checkup to the next checkup

From\To	Normal	Elevated	Hypertensive	Total
Normal	430(47.25%)	242(26.59%)	238(26.15%)	910(100%)
Elevated	284(12.58%)	1073(47.52%)	901(39.90%)	2258(100%)

Of the 3168 transitions, 26.59% showed deterioration from the normal state to the elevated state at the next checkup, 26.15% from the normal state to the hypertensive state, and 47.25% with the normal state showed no change. Similarly, there were 1073 occurrences where participants remained in the elevated state, 901 (39.90%) cases where participants progressed from the elevated state to hypertension, while

284 (12.25%) cases showed alleviation from the elevated state to the normal state at the following visit.

The six possible blood pressure state transitions with the corresponding probabilities over 1-year, 2-year, and 3-year periods, stratified by gender, are illustrated in Figures 2 and 3. Compared with male participants, female participants have lower probabilities of transitioning from the normal state to the hypertensive state, but have higher probabilities of moving from the elevated state to the hypertensive state over any period of time. For instance, elderly women in the normal state had a 16.97%, 33.30%, and 47.31% chance of progressing to hypertension if the next checkup was performed after an interval of 1 year, 2 years, and 3 years, respectively. By contrast, the chances of elderly men moving from the normal state to the hypertensive state were 21.73%, 38.56%, and 51.70% within 1, 2, and 3 years, respectively. For elderly women starting in the elevated state, the probabilities of developing hypertension were 25.07%, 43.03%, and 56.32% in the next 1, 2, and 3 years, respectively; while the corresponding probabilities for elderly men transitioning between the two states were 20.96%, 37.65%, and 50.86%. As time went by, both female and male participants had a higher probability of developing hypertension. For example, the probabilities of changing from the normal state to the hypertensive state over a 1-year follow-up period were 16.97% (female) and 21.73% (male), which increased dramatically to 47.31% (female) and 51.70% (male) within the 3-year follow-up period.

We further stratified the study individuals by gender and age group, and the transition probabilities in the 3rd year originating from the normal state or the elevated state at baseline are illustrated in Figure 4 and Figure 5, respectively. The detailed corresponding numerical values are described in Table S1 (see Supplementary material). As shown, both female and male participants with age ≧65 years were more likely to progress to hypertension whether starting from the normal state or the elevated state within the next 3 years, in comparison with the corresponding participants who were <65 years old.

The sojourn time for the normal state in the study cohort was 1.5±0.08 years, and the duration of the elevated state was 2.0±0.07 years.

Covariate Effects on Blood Pressure State Transitions

The covariates included in the research were age, gender, marriage, BMI, glucose, and ECG. The effects of the covariates on blood pressure state transition with statistical significance are summarized in Table 4. Gender, BMI, age and glucose had some significant associations with possible transitions. For example, increasing age, BMI, and glucose were risk factors for developing hypertension from the normal state or elevated state (HR: 1.04–1.12). Female participants and participants with higher glucose levels were less likely to return from the elevated state to the normal state than their male counterparts (HR: 0.61–0.83).

Table 4 Covariate effects on blood pressure state transitions

Covariate	Normal–Elevated HR (95% CI)	Normal-Hypertensive HR (95% CI)	Elevated–Normal HR (95% CI)	Elevated –Hypertensive HR (95% CI)
Gender	1.131 (0.807, 1.586)	0.544 (0.288, 1.028)	0.606 (0.412, 0.891)	1.461 (0.999, 2.136)
BMI	1.038 (0.992, 1.086)	1.124 (1.058, 1.195)	1.017 (0.963, 1.074)	1.019 (0.983, 1.057)
Age	1.016 (0.980, 1.054)	1.042 (1.010, 1.075)	1.018 (0.990, 1.047)	1.017 (0.997, 1.037)
Glucose	1.013 (0.947, 1.083)	0.876 (0.697, 1.102)	0.827 (0.715, 0.956)	1.054 (1.012, 1.097)
Marriage	0.989 (0.574, 1.702)	0.961 (0.347, 2.665)	1.073 (0.607, 1.897)	0.866 (0.630, 1.189)
Abnormal ECG	0.737 (0.516, 1.052)	0.920 (0.479, 1.767)	0.794 (0.545, 1.155)	1.026 (0.825, 1.275)

Reference categories of covariates: gender, ref=male; marriage, ref=single/divorced/widowed; abnormal ECG, ref=normal.

Survival Probability Based on the Multi-state Markov Model

The multi-state Markov model can be used to infer the survival probability for each subgroup in the future, which may provide insightful information for individuals. In this study, the survival probability represents the probability of not transitioning into the hypertensive state. Survival probability curves over 5 years for all subgroups stratified by female and male categories are given in Figures 6 and 7. The survival probability decreased significantly with increased time among all subgroups. As shown in Figure 6, the survival probability for female participants originating from the normal state was similar to the probability for male participants (no difference, P=0.70). Figure 7 illustrates that male participants starting from the elevated state had a higher survival probability over 5 years than female participants (P=0.01).

Discussion

Sound evidence has verified that, when compared with the young population, elderly people have a higher incidence of hypertension, which is worthy of more attention and investigation [29]. In 2020, there were 254 million people aged ≥60 years in China, accounting for 18.1% of the population [40]. Therefore, in this study, we explored the state transition dynamics of three blood pressure states via multi-state Markov models and investigated the risk factors associated with the progression of hypertension in the elderly population in China, which has not been explored in the existing literature.

There are some significant findings in the research. First, our study found that, of the 3168 transitions, 26.15% of participants showed deterioration from the normal state to the hypertensive state at the next checkup, much higher than the corresponding 16.98% and 9.18% reported in previous studies of the working population [28-29]. This further confirmed that older people should be given much more attention in hypertension prevention and research. Second, we found that both female and male participants in the normal state had a low probability of developing hypertension in the first year; however, this probability increased substantially in the following 3 years, which is consistent with the prior research on young people [28-29]. In this study, the percentage changes from the normal state to the hypertensive state in the first year were 16.97% (female) and 21.73% (male), which increased dramatically to 47.31% (female) and 51.70% (male) within the 3-year follow-up period. Furthermore, the sojourn time in the normal state was 1.5±0.08 years in the study cohort. These results indicate that preventive actions and effective intervention on hypertension progression should be conducted at an early stage, and at least one yearly checkup is strongly recommended for the elderly population. Third, male participants were found to have high probabilities of transitioning from the normal state to hypertension, in comparison with female participants. For example, elderly women in the normal state have a 16.97%, 33.30%, and 47.31% chance of progressing to hypertension within 1, 2, and 3 years, respectively. By contrast, the corresponding probabilities for elderly men were 21.73%, 38.56%, and 51.70%, respectively. The findings align with those of a prior study that indicated that more attention should be paid to elderly men with normotension [28, 41, and 42].

However, we also found that elderly female participants had higher probabilities of developing from the elevated state to the hypertensive state than male participants. For instance, for elderly women starting in the elevated state, the probabilities of developing hypertension were 25.07%, 43.03%, and 56.32% in the next 1, 2, and 3 years, respectively; the corresponding probabilities for elderly men were 20.96%, 37.65%, and 50.86%, respectively. Female participants were less likely to return from the elevated state to the normal state than their male counterparts in the study (HR: 0.61, 95% CI: 0.41–0.89). Our survival probability pilot also illustrated that male participants starting from the elevated state had a higher survival probability over 5 years than female participants (P=0.01). The above findings show that more attention should be paid to the progression from the elevated state to hypertension in elderly women. In this study, if an elderly individual was diagnosed with elevated blood pressure, health professionals in the community health center provided a face-to-face health education session and sent text messages to the patient describing how to prevent hypertension through diet, exercise, daily blood pressure testing, etc.

In addition to age and gender, as discussed above, higher BMI (HR: 1.12, 95% CI: 1.06–1.20) and blood glucose levels (HR: 1.05, 95% CI: 1.01–1.10) were identified to be risk factors for developing hypertension from the normal state or elevated state. Previous research has also found that the HR for transitioning from the normal state to the hypertensive state increases with higher BMI values [28, 29, and 43] and higher glucose levels [44].

In summary, the research has made key contributions. First, a multi-state Markov model was used to explore the state transition dynamics of three blood pressure states, and to investigate how several important covariates affected the progression or alleviation of hypertension in the Chinese elderly population. Furthermore, through the developed model, the sojourn time in each blood pressure state and the transition probabilities from one state to another state were estimated, thereby supplying statistical foundations for preventive actions and effective intervention in the progression of hypertension for elderly people.

Limitations

The limitations of the study can be summarized as follows. (1) Owing to time and financial limitations, we only focused on a cohort population for five years in one city; thus the study findings may not be representative and fit for extrapolation. (2) In this study, the hypertensive state was regarded as an absorbing state, meaning that the reverse transition from a hypertensive state to a normal or elevated state was not considered. (3) Some significant covariates, such as various lifestyle habits of diet, smoking, exercise, other medical conditions, and psychological status, were not covered in the current study, and are worthy of investigation in further research.

Conclusions

The findings regarding the three blood pressure state transition probabilities should increase awareness of the timely prevention for elderly women with elevated blood pressure and elderly men with normal blood pressure. Preventive actions and effective intervention on hypertension progression should be conducted at an early stage, and at least one yearly checkup is strongly recommended for elderly people. Increasing age, BMI, and blood glucose were risk factors for developing hypertension from the normal state or elevated state. The derived transition probabilities and sojourn time can serve as a significant reference for health professionals when developing proactive and targeted interventions for hypertension progression among the Chinese elderly population.

Figure 1: The three blood pressure state transitions in the Markov model

Figure 2: State transition diagrams for female participants

Figure 3: State transition diagrams for male participants

Figure 4: Transition probabilities from the normal state in the 3rd year, stratified by gender and age group

Figure 5: Transition probabilities from the elevated state in the 3rd year, stratified by gender and age group

Figure 6 Survival distribution starting from the normal state

Figure 7 Survival distribution starting from the elevated state

Table S1 Shown in the supplementary material

Acknowledgements

We would like to thank all participants who voluntarily participated in this study. We thank International Science Editing (http://www.internationalscienceediting.com) for editing this manuscript.

Contributor

XZ and JX performed the statistical analysis and interpretation and wrote the manuscript. YZ, LX, and LZ contributed to the conceptualization of the research process and critically reviewed the manuscript. BZ and YW were responsible for the overall content as guarantors. All authors read and approved the final manuscript.

Funding

YW was supported by grants from the Fujian Province Planning Project of Science and Technology (2019D015). JX was supported by the Medical Science and Technology Research Fund Project of Guangdong Province (grant no. A2020405).

Ethics approval

This study was approved by the review committee of the No. 2 Affiliated Hospital of Xiamen Medical College. All participants provided their informed consent before data collection, and were informed of the purpose and process of the study and their freedom to withdraw whenever they chose.

Data availability statement

The data presented in this study are available from the corresponding author up on a reasonable request.

Conflicts of Interest

None

References

1. Liu LS. 2010. Chinese guidelines for the management of hypertension. *Zhonghua Xin Xue Guan Bing Magazine* 2011; 39:579–615.
2. Williams B, Mancia G, Spiering W, *et al*. ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018;39(33):3021–3104. doi:10.1080/08037051.2018.1527177.
3. Herman WW, Konzelman JL, Prisant LM. Joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure bethesda (MD): National heart, lung, and blood institute (US) 2004.
4. Lawes CM, Hoorn SV, Rodgers A. Global burden of blood-pressure-related disease. *Lancet* 2008;371:1513–1518. doi: 10.1016/S0140-6736(08)60655-8.
5. Kokubo Y, Matsumoto C. Hypertension is a risk factor for several types of heart disease: review of prospective studies. *Adv Exp Med Biol* 2017;956:419–26. doi: 10.1007/5584_2016_99.
6. Oparil S, Acelajado MC, Bakris GL, *et al*. Hypertension. *Nat Rev Dis Primers* 2018;4(18014):1–21. doi: 10.1038/nrdp.2018.14.

7. Tackling G, Borhade MB, Tackling G, *et al*. Hypertensive heart disease. [Updated 2020 Jun 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing 2020. https://www.ncbi.nlm.nih.gov/books/NBK539800/
8. Jan YT, Tsai PS, Longenecker CT, *et al*. Thoracic aortic calcification and pre-clinical hypertension by new 2017 ACC/AHA hypertension guidelines. *Diagnostics* 2021;11:1027.
9. Ettehad D, Emdin CA, Kiran A, *et al*. Blood pressure lowering for prevention of cardiovascular disease and death: A systematic review and meta-analysis. *Lancet* 2016;387:957–967. doi: 10.1016/S0140-6736(15)01225-8.
10. Khaja SU, Mathias KC, Bode ED, *et al*. Hypertension in the United States fire service. *Int. J. Environ. Res. Public Health* 2021;18:5432. dio:10.3390/ijerph18105432.
11. GBD 2015 neurological disorders collaborator group. Global, regional, and national comparative risk assessment of 79 behavioral, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: A systematic analysis for the global burden of disease study 2015. *Lancet Neural* 2017;16(388):877–97.
12. Di Palo KE; Barone NJ. Hypertension and heart failure: Prevention, targets, and treatment. *Heart Fail. Clin.*2020;16:99–106. doi: 10.1016/j.hfc.2019.09.001.
13. Dominguez LJ, Veronese N, Barbagallo M. Magnesium and hypertension in old age. *Nutrients* 2021;13:139. dio: 10.3390/nu13010139.
14. Ye X, Yi Q, Shao J, *et al*. Trends in prevalence of hypertension and hypertension phenotypes among Chinese children and adolescents over two decades (1991–2015). *Front.* Cardiovasc*.* *Med* 2021;8:627741. dio: 10.3389/fcvm.2021.627741.
15. Kearney PM, Whelton M, Reynolds K, *et al*. Global burden of hypertension: analysis of worldwide data. *Lancet* 2005;365(9455):217–223.
16. Forouzanfar MH, Liu BP, Roth GA, *et al*. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990–2015. *JAMA* 2017;317(2):165–182. dio: 10.1001/jama.2016.19043.
17. WHO. Hypertension. World Health Organisation. https://www.who.int/newsroom/factsheets/detail/hypertension. Published 2019. Accessed 2 October 2020.

18. Griffin G. Antiplatelet therapy and anticoagulation in patients with hypertension. *Am Fam Physician* 2005;71:897–9. doi: 10.1001/jama.293.9.1123.
19. Xiong X, Yang X, Liu Y, *et al*. Chinese herbal formulas for treating hypertension in traditional Chinese medicine: perspective of modern science. *Hypertens Res* 2013;36:570–9. doi: 10.1038/hr.2013.18.
20. Chow CK, Teo KK, Rangarajan S, *et al*. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *JAMA* 2013;310(9):959–968. dio: 10.1001/jama.2013.184182.
21. Patel RS, Masi S and Taddei S. Understanding the role of genetics in hypertension. *Eur. Heart J* 2017;38(29): 2309–2312. dio: 10.1093/eurheartj/ehx273.
22. Li C, Sun DD, Liu JL, *et al*. A predictionmodel of essential hypertension based on genetic and environmental risk factors in northern han Chinese. *Int. J. Med. Sci* 2019;16(6):793–799. dio: 10.7150/ijms.33967.
23. Bigazzi R, Zagato L, Lanzani C, *et al*. Hypertension in high school students: Genetic and environmental factors: The HYGEF study. *Hypertension* 2020;75:71–78. dio: 10.1161/HYPERTENSIONAHA.119.13818.
24. Zhang YY, Yang H, Ren M, *et al*. Distribution of risk factors of hypertension patients in different age groups in Tianjin. *BMC Public Health* 2021;21:247. dio: 10.1186/s12889-021-10250-9.
25. Shihab HM, Meoni LA, Chu AY, *et al*. Body mass index and risk of incident hypertension over the life course: The Johns Hopkins precursors study. *Circulation* 2012;126(25):2983–2989. dio: 10.1161/CIRCULATIONAHA.112.117333.
26. Tohidi M, Hatami M, Hadaegh F, *et al*. Triglycerides and triglycerides to high-density lipoprotein cholesterol ratio are strong predictors of incident hypertension in middle eastern women. *J. Hum. Hypertens* 2012;26(9):525–532. dio: 10.1038/jhh.2011.70.
27. Zhang W, Wang L, Chen Y, *et al*. Identification of hypertension predictors and application to hypertension prediction in an urban han Chinese population: A longitudinal study, 2005–2010. *Preventing Chronic Disease* 2015;12:E184. dio: 10.5888/pcd12.150192.

28. Yang JM, Liu F, Wang B, *et al*. Blood pressure states transition inference based on multi-state Markov model. *IEEE J Biomed Health* 2021;25(1):237-246. dio: 10.1109/JBHI.2020.3006217.
29. Wang YF, Ma ZM, Xu CN, *et al.* Prediction of transfer among multiple states of blood pressure based on Markov model: an 18-year cohort study. *J. Hypertens* 2018;36:15061513. dio:10.1097/HJH.0000000000001722.
30. Mills KT, Obst KM, Wei S, *et al*. Comparative effectiveness of implementation strategies for blood pressure control in hypertensive patients: A systematic review and meta-analysis. *Ann. Internal Med* 2018;168(2):110–120. dio: 10.7326/M17-1805.
31. Tada T, Kumada T, Toyoda H, *et al*. Longterm natural history of liver disease in patients with chronic hepatitis b virus infection: An analysis using the Markov chain model. *J. Gastroenterol* 2018;53(11):1196–1205. dio: 10.1007/s00535-018-1467-x.
32. Wong LY, Toh MPHS and Tham LWC. Projection of prediabetes and diabetes population size in singapore using a dynamic Markov model. *J. Diabetes* 2017;9(1):65–75. dio: 10.1111/1753-0407.12384. 10.1111/1753-0407.12384
33. Grover G, Sabharwal A, Kumar S, *et al*. A multi-state Markov model for the progression of chronic kidney disease. *Türkiye Klinikleri Biyoistatistik* 2019;11(1):1–14. dio: 10.5336/biostatic.2018-62156.
34. Brookmeyer R and Abdalla N. Multistate models and lifetime risk estimation: Application to Alzheimer's disease. *Statist. Med* 2019;38(9):1558–1565. dio: 10.1002/sim.8056.
35. Srikanth P. Using Markov chains to predict the natural progression of diabetic retinopathy. *Int. J. Ophthalmol* 2015;8(1):383 132–137. dio: CNKI:SUN:GYZZ.0.2015-01-026.
36. Attard SM, Herring AH, Zhang B, *et al*. Associations between age, cohort, and urbanization with SBP and DBP in China: a population based study across 18 years. *J Hypertens* 2015;33:948–956.
37. Guo J, Zhu YC, Chen YP, *et al*. The dynamics of hypertension prevalence, awareness, treatment, control and associated factors in Chinese adults: results from CHNS 1991-2011. *J Hypertens* 2015;33:1688–1696.

38. Cuddy MLS. The Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 2004;55:17–21.
39. Jackson CH. Multi-state models for panel data: the msm package for R. *J Stat Soft* 2011;38:1–28. dio: 10.18637/jss.v038.i08.
40. China development research foundation, 2020. China development report-aging population in 2020: Development trend and policy options. Available from URL: http://www.199it.com/archives/1068230.html
41. Singh S, Shankar R, and Singh GP. Prevalence and associated risk factors of hypertension: A cross-sectional study in urban Varanasi. *Int. J.Hypertens* 2017;2017:5491838. dio: 10.1155/2017/5491838.
42. Faulkner JL and de Chantemèle EJB. Sex differences in mechanisms of hypertension associated with obesity. *Hypertension* 2018;71(1):15–21. dio: 10.1161/HYPERTENSIONAHA.117.09980.
43. Davis J, Juarez D, and Hodges K. Relationship of ethnicity and body mass index with the development of hypertension and hyperlipidemia. *Ethnicity Disease* 2013;23(1):65–70. dio: 10.1111/jphd.12008.
44. Huang Z, Wang GD, Jonas JB, *et al*. Blood pressure control and progression of arteriosclerosis in hypertension. *J. Hypertens* 2021;39(6):1221-1229. dio: 10.1097/HJH.0000000000002758.

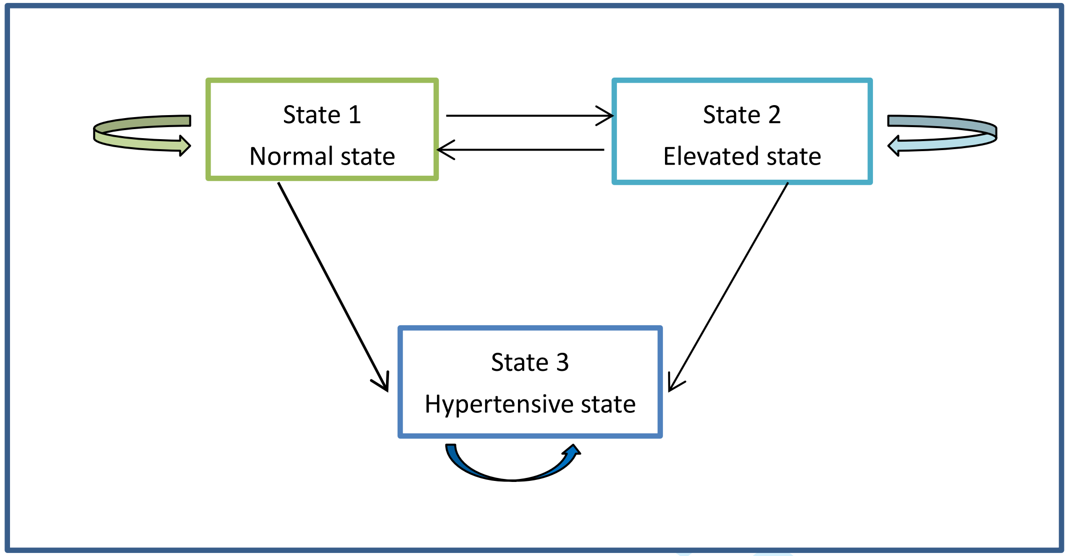


Figure 1: Three blood pressure states transitions In the Markov model

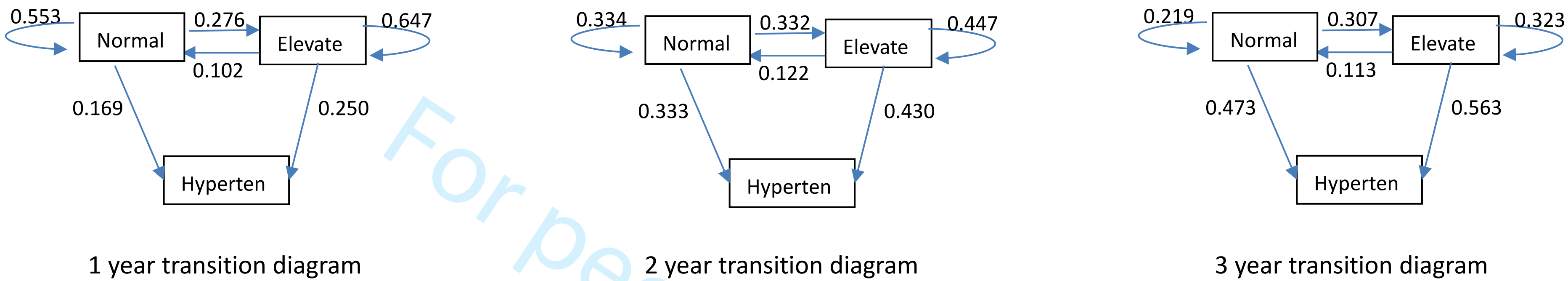
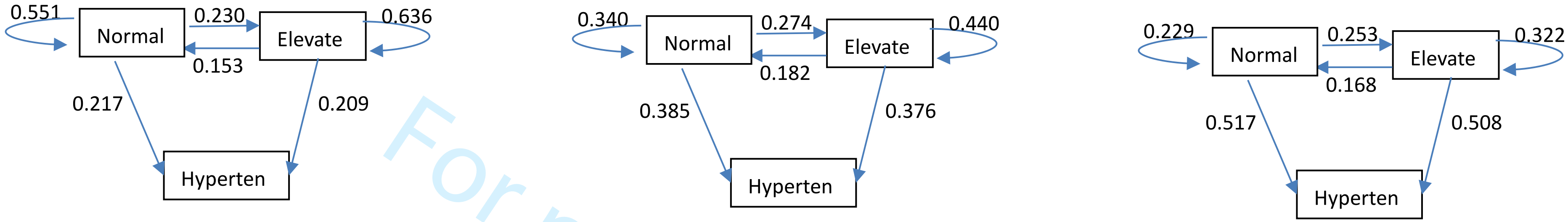


Figure 2: State transition diagrams for female participants

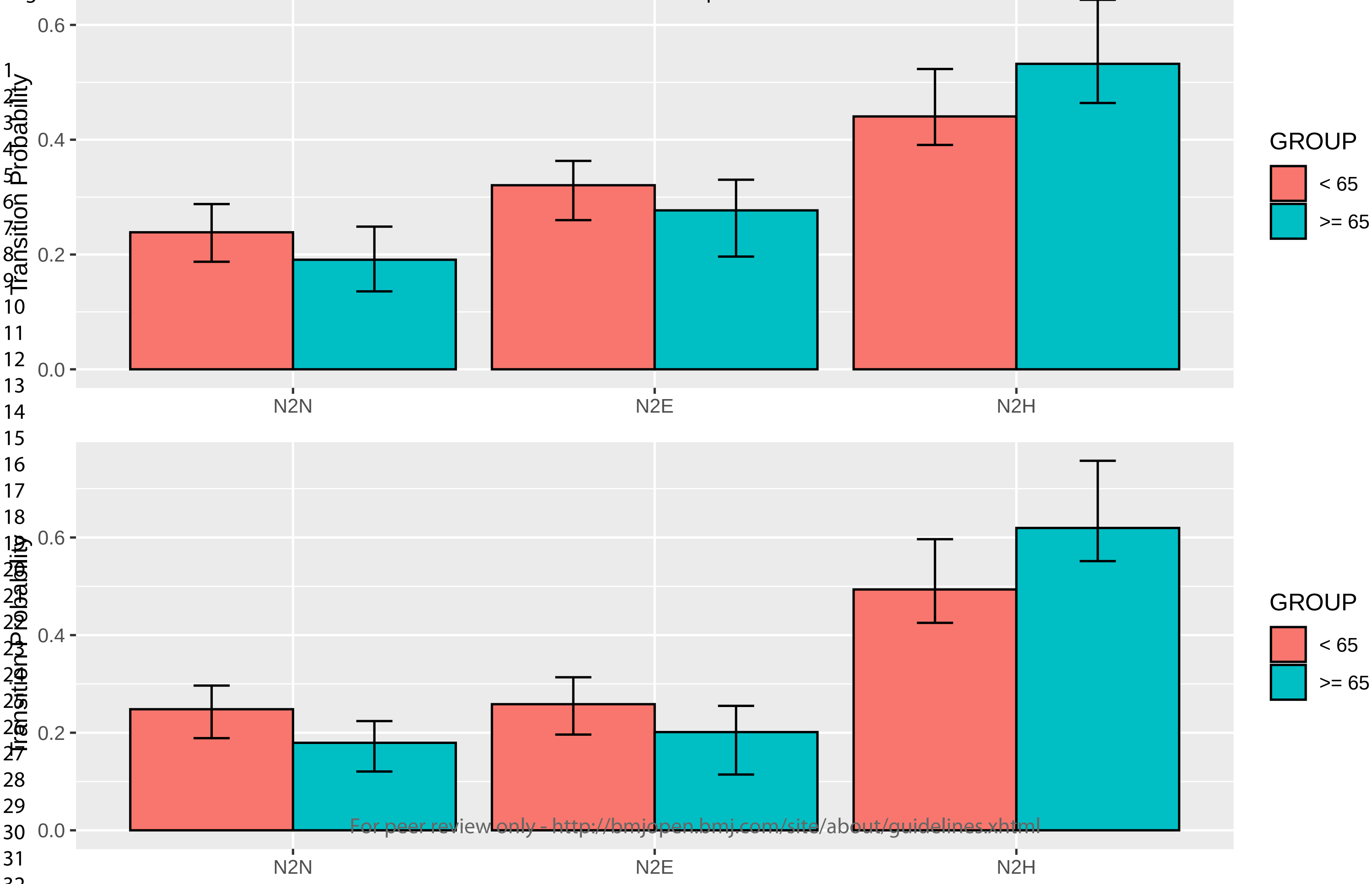


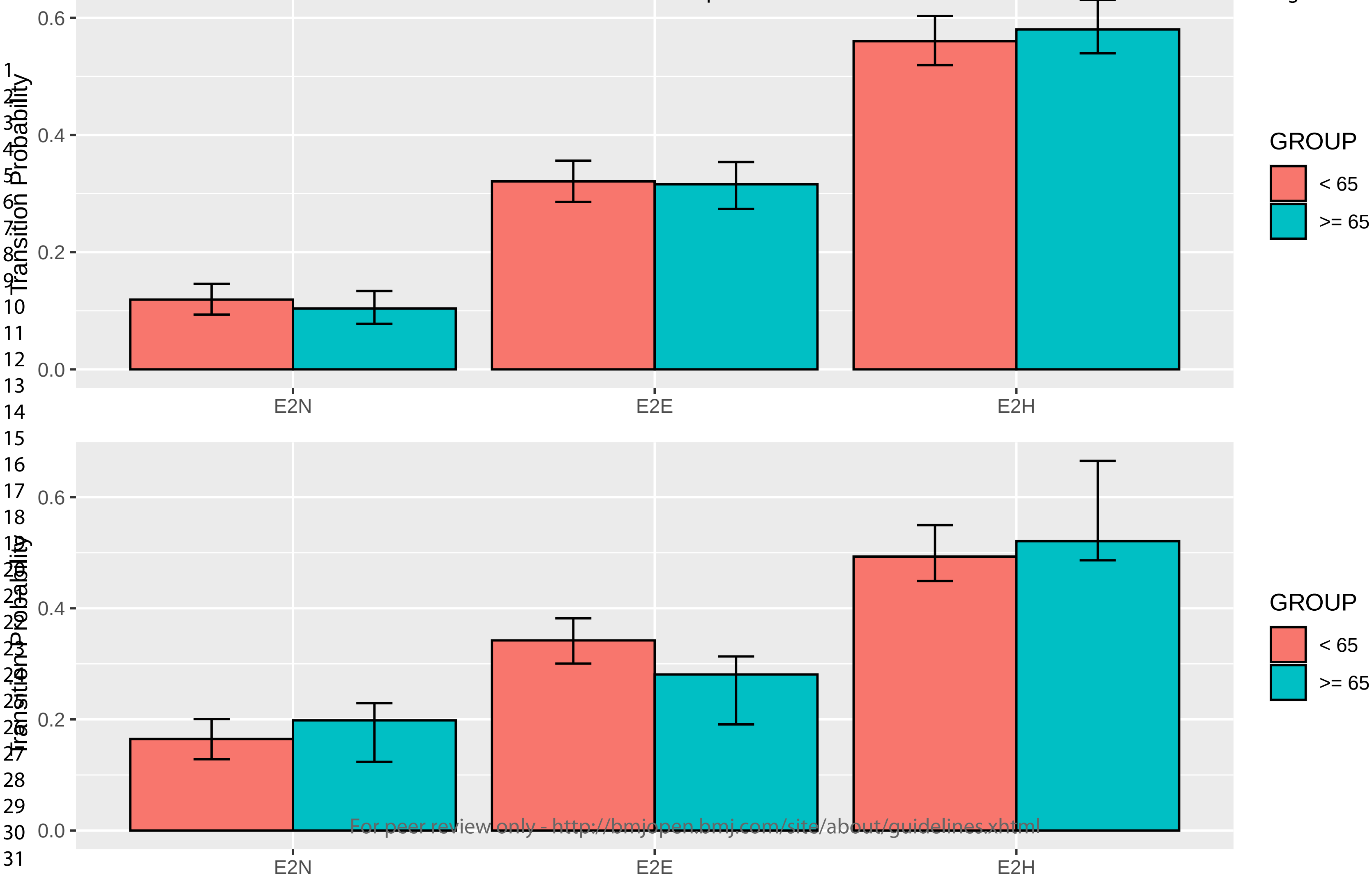
1 year transition diagram

2 year transition diagram

3 year transition diagram

Figure 3: State transition diagrams for male participants


Transition Probability
0.6
0.4
0.2
0.0
N2N
N2E
N2H
GROUP
< 65
>= 65
Transition Probability
0.6
0.4
0.2
0.0
N2N
N2E
N2H
GROUP
< 65
>= 65


Transition Probability
0.6
0.4
0.2
0.0
E2N
E2E
E2H
GROUP
< 65
>= 65
Transition Probability
0.6
0.4
0.2
0.0
E2N
E2E
E2H
GROUP
< 65
>= 65

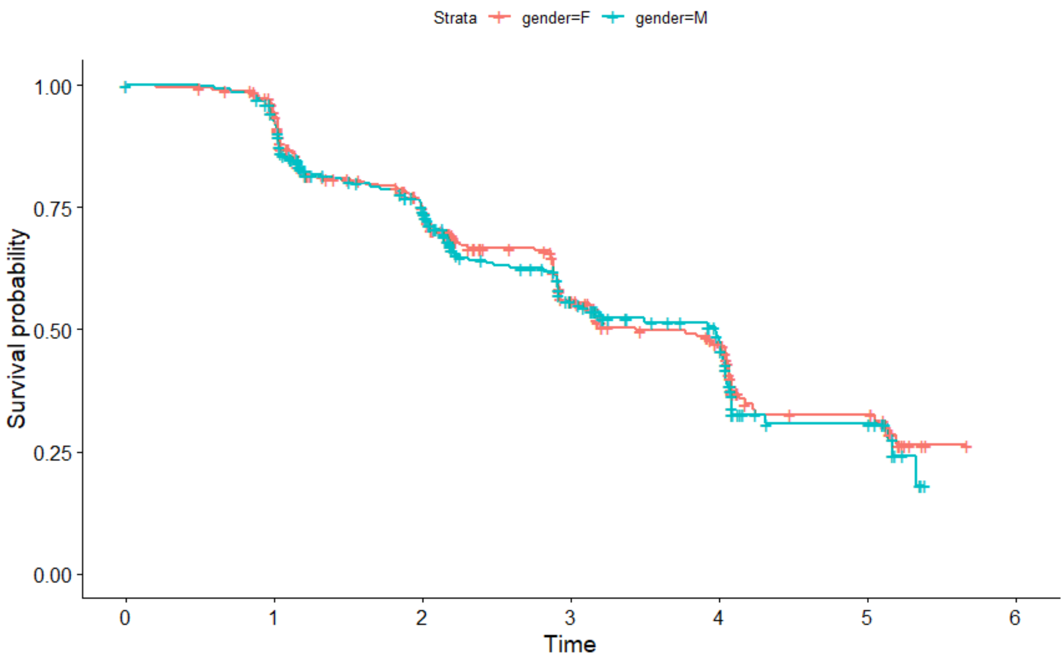


Figure 6: Survival distribution starting from normal state

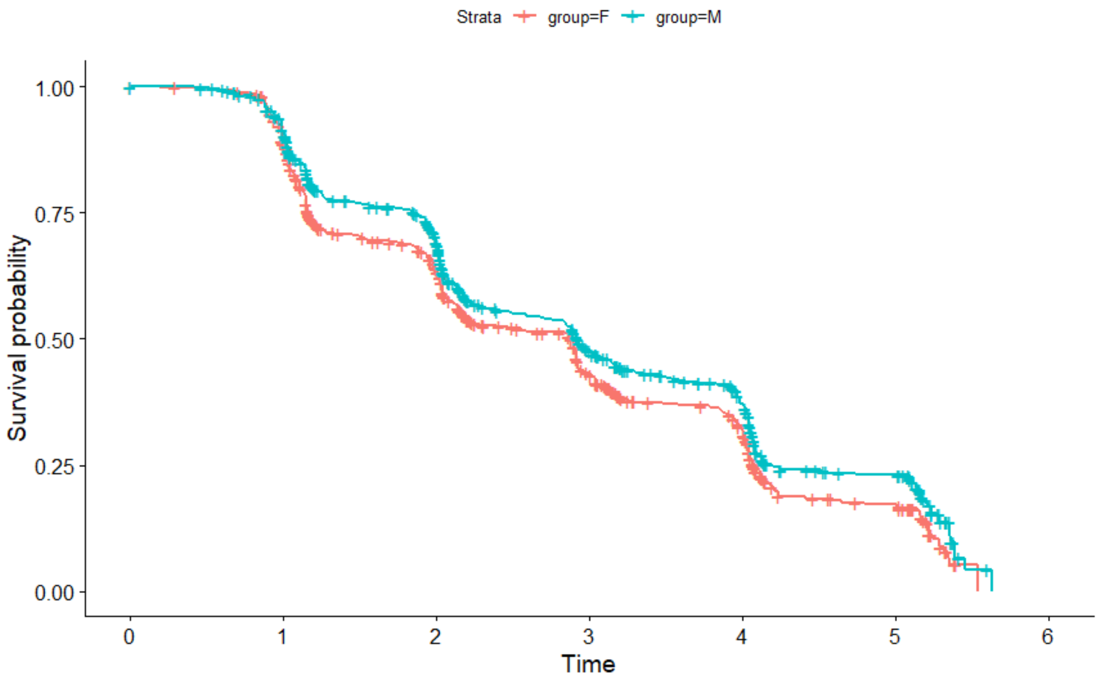


Figure 7: Survival distribution starting from the elevated state

Table S1: The six possible blood pressure state transitions with the corresponding probabilities in the 3rd year, stratified by gender and age group

Gender	Group	States transition	Transition probability
Female	<65	N2N	0.2387 (0.1874, 0.2879)
Female	>=65	N2N	0.1909 (0.1358, 0.2486)
Male	<65	N2N	0.2481 (0.1888, 0.2966)
Male	>=65	N2N	0.1793 (0.1205, 0.2238)
Female	<65	N2E	0.3207 (0.2599, 0.3631)
Female	>=65	N2E	0.2769 (0.1964, 0.3303)
Male	<65	N2E	0.2584 (0.1962, 0.3136)
Male	>=65	N2E	0.2013 (0.1143, 0.2550)
Female	<65	N2H	0.4405 (0.3909, 0.5232)
Female	>=65	N2H	0.5322 (0.4640, 0.6438)
Male	<65	N2H	0.4935 (0.4251, 0.5965)
Male	>=65	N2H	0.6195 (0.5516, 0.7572)
Female	<65	E2N	0.1192 (0.0935, 0.1460)
Female	>=65	E2N	0.1040 (0.0778, 0.1338)
Male	<65	E2N	0.1647 (0.1283, 0.2004)
Male	>=65	E2N	0.1983 (0.1236, 0.2291)
Female	<65	E2E	0.3208 (0.2858, 0.3562)
Female	>=65	E2E	0.3159 (0.2739, 0.3539)
Male	<65	E2E	0.3422 (0.3004, 0.3819)
Male	>=65	E2E	0.2809 (0.1910, 0.3133)
Female	<65	E2H	0.5600 (0.5193, 0.6032)
Female	>=65	E2H	0.5801 (0.5395, 0.6308)
Male	<65	E2H	0.4931 (0.4491, 0.5497)
Male	>=65	E2H	0.5208 (0.4863, 0.6653)

N2N: normal state to normal state; N2E: normal state to elevated state; N2H: normal state to hypertensive state; E2N: normal state to normal state; E2E: elevated state to elevated state; E2H: elevated state to hypertensive state;

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2-3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	4-5
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	5
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	Report numbers of outcome events or summary measures over time	7

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.